N,N-Dialkylhydrazones in Organic Synthesis. From Simple *N,N*-Dimethylhydrazones to Supported Chiral Auxiliaries

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1. Introduction

The well-known properties of the carbonyl group render aldehydes and ketones prominent substrates in both C−C and C−heteroatom bond forming methodologies of organic synthesis. In practical syntheses, nitrogen analogues of aldehydes and ketones such as enamines, imines, or hydrazones, acting as synthetic equivalents of the carbonyl

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Ryszard Lazny was born in Olsztyn, Poland. He received his M.Sc. degree in chemistry in 1990 from the University of Warsaw, Bialystok Branch. His thesis supervisor was Prof. J. W. Morzycki. After one year as a research assistant at the University, he began postgraduate studies at the University of Saskatchewan, Canada, working under the supervision of Prof. M. Majewski. He completed his Ph.D. in 1996. Following graduation, he worked with Prof. D. E. Ward at the University of Saskatchewan and then with Prof. D. Enders at the Institute of Organic Chemistry, RWTH-Aachen University, Germany. After returning to Poland, he researched and lectured at the University of Bialystok and received his habilitation (D.Sc.) in 2005 from the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw. He is presently a Professor at the University of Bialystok. Professor Lazny has wide-ranging research experience that includes asymmetric synthesis with chiral reagents (enantioselective deprotonation) and chiral auxiliaries (SAMP/RAMP-methods), synthesis of cyclic depsipeptides (destruxin B), synthesis of chiral phosphinoalcohol ligands (asymmetric phosphinylation), synthesis of tropane alkaloids, and development of solid-phase synthesis methodologies based on triazene and hydrazone linkers. His current research interests extend to polymer-supported reagents and catalysts, reactions in the presence of water, and organocatalytic processes. In addition to research papers, he is the author/coauthor of several review articles and has made a contribution to Science of Synthesis and a chapter in Linker Strategies in Solid-Phase Organic Synthesis. His most rewarding role, thus far, has been that of father to his six year old son, Patryk.

Aneta Nodzewska was born in Monki near Bialystok, Poland. She graduated from the University of Bialystok in 2002 (M.Sc. thesis under the supervision of Prof. R. Lazny). Her graduate thesis concerned polymer supported reactions and the preparation of polymers with triazene linkers. After graduation, she started work as an assistant at the Institute of Chemistry, University of Bialystok. Currently, she is carrying out research on the development and synthetic applications of *N,N*-dialkylhydrazone linkers and reactions of polymer supported *N,N*-dialkylhydrazones. Her time is skillfully divided between research, teaching, and raising her two daughters: 6 year old Emilia and 1 year old Izabela.

compounds, are often preferred. From a synthesis point of view, *N,N*-dialkylhydrazones offer many advantages: high nucleophilicity of their metalated species, regioselectivity, controlled α-monoalkylation, and the possibility of using the hydrazone moiety as a chiral auxiliary or a multifunctional linker in solid-phase synthesis.

Even though *N,N*-dialkylhydrazones show very diverse reactivity and can participate in polar, free radical, pericyclic, and organometallic catalytic reactions, it is their reactivity as aldehyde and ketone synthetic equivalents, where they participate in nucleophile−electrophile interactions, that has found major uses in synthesis. The goal of this review is to bring the reader up to date regarding the synthetic utility of these important and versatile reagents.

In this review, both early achiral and later chiral hydrazone methods prominent in synthesis will be recalled. Since excellent reviews[1−4] have already been published on the subject, the reactivity, cleavage, and formation of hydrazones will be presented only in brief. The short overview of reactivity and typical (classical) synthetic applications is intended to help an unfamiliar reader gain an appreciation of synthetic applications of hydrazones prior to 2000. The 20th century scientific literature is host to a number of reviews on the hydrazones, and thus, only the most important concepts that set the stage for later development will be presented. Reference to the published reviews, as well as selected landmark primary literature, will be made for the convenience of the reader. In the main part of the paper, recent synthetic applications (2000−2009) of aldehyde and ketone *N,N*-dialkylhydrazones, including novel catalytic and solid-phase methodologies, will be described comprehensively. Reactivity and applications of *N*-acylhydrazones have been reviewed[5,6] and are outside the scope of this review, although they parallel to some extent those of *N,N*-dialkylhydrazones.[7]

2. General Reactivity Characteristics of N,N-Dialkylhydrazones and Their Azaenolates

The usefulness of *N,N*-dialkylhydrazones in synthetic organic chemistry arises mostly from the rich reactivity of the hydrazones and the high reactivity of hydrazone-derived organometallic species, particularly organolithium derivatives. Hydrazones have two bonds susceptible to cleavage, yet usually are stable enough to allow problem-free transformations in other parts of the hydrazone molecule. The C═N bond is susceptible to hydrolytic, oxidative, and reductive cleavage, restoring the carbonyl group,[8] and the N−N bond is predisposed to reductive cleavage to produce primary amines (Figure 1). The carbon atom of the C═N bond (the azomethine carbon atom) is prone to nucleophilic addition of organometallic nucleophiles such as organolithiums, organomagnesiums, and organoceriums or organoytterbiums. On the other hand, the same carbon atom of formaldehyde hydrazone and some aromatic hydrazones, demonstrating the azaenamine character of the hydrazones, may be attacked under suitable conditions by electrophiles such as Michael acceptors.[9] These reactions may take place on either the nitrogen or carbon atom of the azaenamine ambident nucleophile. However, for the *N,N*-disubstituted hydrazones the reaction on the nitrogen atom despite higher nitrogen nucleophilicity is a reversible process, contrary to the reaction on the azomethine carbon, which, in effect, is the prevailing pathway for the azaenamine hydrazone reactivity.

The acidity of hydrogens at the α-carbon atom of the hydrazone group is deemed to be lowered by ca. 10 orders of magnitude compared to the C−H acidity of the parent carbonyl compound; the evaluated pK_a of the hydrazone is ca. 30 compared to the pK_a of the corresponding ketone of ca. 20. The lower C−H acidity grants higher reactivity of

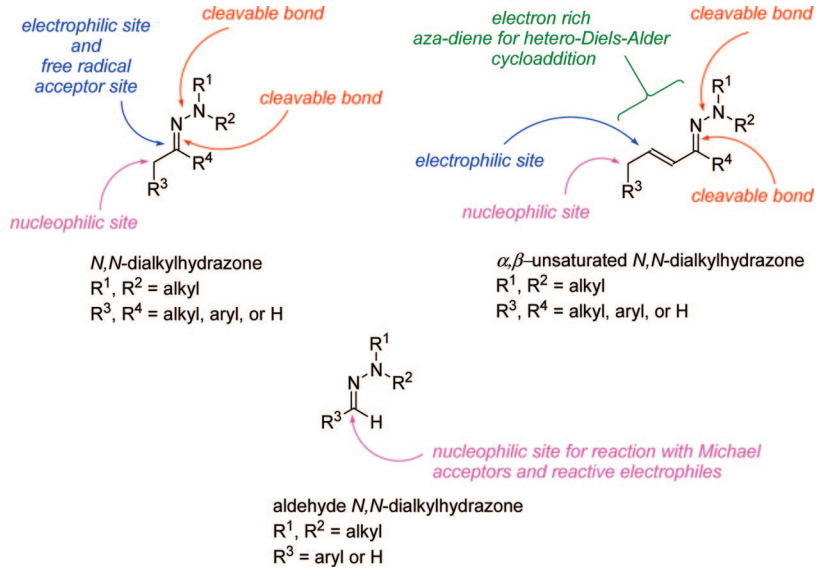


Figure 1. Typical reactivity sites of *N*,*N*-dialkylhydrazones.

the hydrazone conjugate bases toward electrophiles, an advantage compared to synthetically equivalent carbonyl compounds. The hydrazone C−H acidity and the stability of the metalated hydrazones (owing to coordination of the metal with the hydrazone nitrogen atoms) are high enough to allow, usually, α-metalation of the hydrazones with alkali-metal amides such as LDA,[10,11] LTMP[12] (at 0 °C in 2−4 h), and KDA[13] or with alkyllithium bases such as *n*-BuLi and *t*-BuLi (at −78 °C in 15−120 min).[11,14] Other possible metalating bases for the formation of stabilized azaenolates are NaH in the presence of HMPA, potassium amide, KH, and NaHMDS.[4] On the other hand, the C−H acidity of hydrazones is low enough to prevent any racemization of stereogenic α-centers of chiral hydrazones by typical bases (basic glass, carbonates, hydroxides, alkoxides), which is in sharp contrast to high racemization rates of analogous ketones and especially aldehydes (silylation of laboratory glassware is often needed to prevent enolizable α-stereocenters of aldehydes or ketones from racemization caused by the basic glass surface).[15] The deprotonation regioselectivity of hydrazones is typically high and predictable.[16,17] It takes place at the less substituted carbon atom unless there is an anion-stabilizing group present at the competing site.

Subsequent alkylation of the formed azaenolates gives, as a result, regioselectively functionalized or branched hydrazones. It is worth noting that alkylation of hydrazones occurs selectively at the α-carbon unlike ketones or aldehydes, where *O*-alkylation often competes with *C*-alkylation. *N*,*N*-Dialkylhydrazones offer other advantages: greater nucleophilicity of the corresponding metalated species, selective monoalkylation (no problems with polyalkylation), and the possibility of using the hydrazone moiety as a chiral auxiliary. In addition, alkylation of the aldehyde hydrazones has a major advantage over alkylation of the corresponding aldehydes, since aldehydes cannot be easily α-alkylated with strong bases and alkylating agents. It is not widely known that the problem of aldehyde deprotonation/alkylation arises not so much from self-aldolization but from aldehyde complexation and reduction by lithium amides, e.g., LDA.[18,19]

Moreover, alkylations (and likely other electrophilic reactions) of azaenolates of simple cyclic ketones (e.g., substituted cyclohexanones) are diastereoselective and show preference for the product with the new alkyl substituent in the α-axial position. The diastereoselectivity for axial methylation (LDA, MeI) was reported as high as 97:3 (*trans*:*cis*) for 2-methylcyclohexanone *N*,*N*-dimethylhydrazone[10] and quantitative for 4-*tert*-butylcyclohexanone DMH-hydrazone.[11] The C═N bond of the *N*,*N*-dialkylhydrazone group can act as a radical acceptor, typically in intramolecular reactions, leading to cyclized hydrazine products.[20,21] Besides radical additions and consecutive fragmentation reactions, the Eschenmoser hydrazones (*N*-aziridinylimines such as (2-phenylaziridinyl)- and (*trans*-2,3-diphenylaziridinyl)imine)[22,23] can undergo thermal and photochemical decomposition to diazo compounds and alkenes. Owing to their special structural features, reactivity of the *N*-aziridinylimines provides entry into carbene or carbenoid chemistry and cabanionic Shapiro-type reactions.[24,25]

By the virtue of vinylogy, the α,*β*-unsaturated aldehyde or ketone hydrazones can react with nucleophiles in the *β* position or be metalated and reacted with electrophiles in the *γ* position of the hydrazone group (Figure 1). By analogy to enamines, hydrazones (azaenamines) have the azadiene structure enriched in electrons through electron-donating properties of the tertiary amine nitrogen atom and as such can react with electron-poor dienophiles in Diels−Alder and related cycloaddition reactions (Figure 1).

Lithiated chiral *N*,*N*-dialkylhydrazones developed and propagated by the Enders research team (corresponding hydrazines SAMP, RAMP, SADP, SAEP, SAPP, and RAMBO, Figure 2) undergo metalation and react in many useful asymmetric transformations.[1] Stereoselectivities of the reactions in the case of the most often used species, i.e., SAMP/RAMP-hydrazones, were thoroughly studied.[2,26] Cryoscopic[27] and X-ray studies[28] of lithiated SAMP-hydrazone of methyl 2-naphthyl ketone (Scheme 1) suggest that the lithiohydrazones form monomers in THF solution. However, simple lithio-*N*,*N*-dimethylhydrazones show aggregation in solution (suggested as high as tetramer for lithiated cyclohexanone DMH-hydrazone).[29] Fast aggregate dissociation may precede slow alkylation reaction. In general, complex homonuclear and heteronuclear (with a lithium amide such as LDA) aggregation and metal coordination may be expected for metalo-*N*,*N*-dimethylhydrazones and related simple hydrazones.[30] On the basis of the investigation of configurations of lithiated SAMP-hydrazone species in

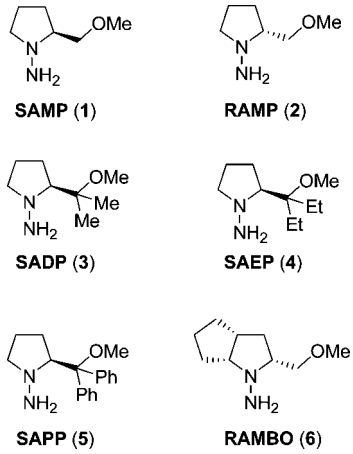


Figure 2. Chiral hydrazine auxiliaries used for the formation of hydrazones for asymmetric synthesis.

solution (NMR of DMH- and SAMP-hydrazone)[26,31] and in crystals,[28] it was concluded that they form four possible rotational isomers.[16,26] The preferred configuration is **7** ($E_{CC}Z_{CN}$, Figure 3). The configuration of the C−C and C−N bonds of lithiated *N,N*-dialkylhydrazones in the presence of HMPA is changed to $Z_{CC}E_{CN}$ (**10**).[26] The absolute configuration of the products produced by cleavage of the SAMP chiral auxiliary results from the diastereoselective (more precisely diastereotopic face selective) attack of the electrophilic reagent on one of the sides of the SAMP-hydrazone azaenolate (Scheme 1). The diastereoselectivity in the reaction with an electrophilic reagent (typically an alkyl halide) is rationalized by the so-called metalloretentive, S_E2'-front mechanism of electrophilic substitution (Scheme 2, electrophilic attack from the chelated metal side). As a consequence the hydrazone products, analogous to **12**, have the usually less thermodynamically favored Z_{CN} configuration and isomerize spontaneously to the more stable E_{CN} configuration. The reversal of configuration of C−C and C−N bonds in Li-SAMP-hydrazone, in the presence of HMPA, results in reversal of the configuration of the stereocenter formed newly by alkylation reaction, albeit with low stereoselectivity.[26]

The stereoselectivity of asymmetric reactions with chiral hydrazones has been thoroughly studied since the late 1970s. Generalized conclusions, based on observations of electrophilic alkylations by Enders, and other reactions (e.g., nucleophilic 1,2-addition by Denmark)[32] with chiral SAMP-hydrazones, suggest that the highest diastereoselectivity is observed in ethereal solvents such as Et_2O and THF, at very low temperatures, without chelating cosolvents or additives, and with judiciously chosen electrophilic reagents (e.g., Me_2SO_4 is better than MeI in some cases although iodides

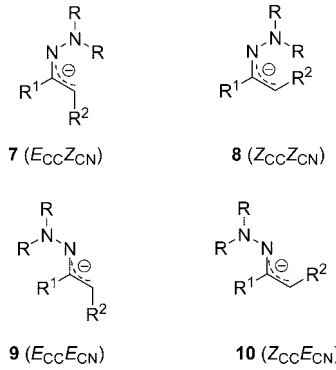


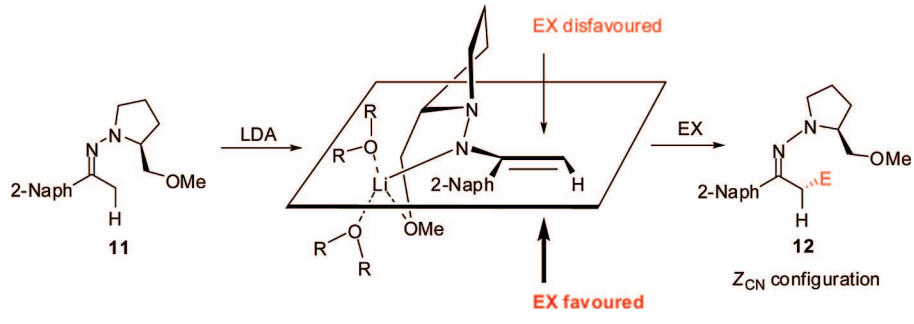
Figure 3. Configurations of lithiated *N,N*-dialkylhydrazones.

are usually preferred). The methoxy group in the SAMP-like chiral auxiliaries is essential because a change to other more bulky groups, such as TMS, trityl, or TBDMS,[33] or a change to NEt_2 or removal of O (change of OMe to Me) leads to a medium to very high drop in diastereoselectivity.[2] Substitution of the methyl group in SAMP with CH_2OMe or $CH_2OCH_2CH_2OMe$ retains virtually the same level of selectivity tested on methylation of cyclohexanone.[2] Interestingly, slightly higher diastereoselectivity than for SAMP-hydrazone was reported for the SAMP analogue hydrazone with the methyl group exchanged for $CH_2OCH_2CH_2OMe$ in the 1,2-addition of organoceriums.[32]

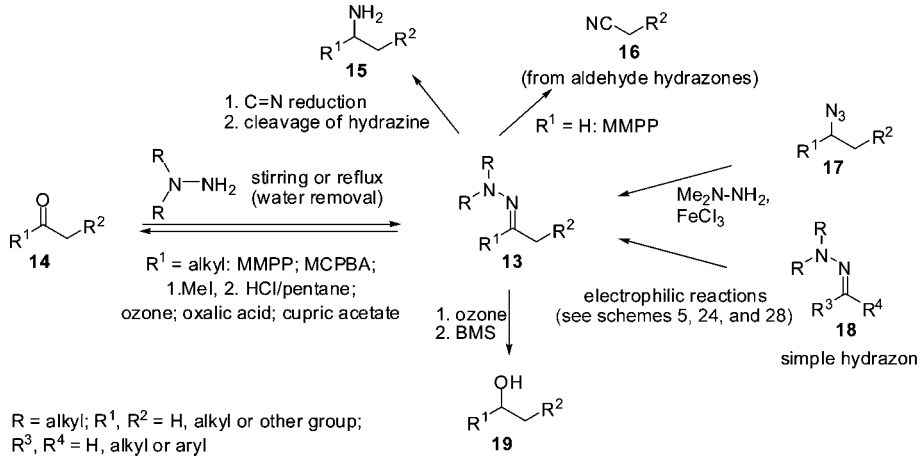
3. Preparation and Cleavage of *N,N*-Dialkylhydrazones

Preparation of *N,N*-dialkylhydrazones **13** from simple aldehydes and ketones **14** (Scheme 2) is often a spontaneous reaction, where fast separation of water from immiscible organics is observed when reagents are mixed neat or in benzene, dichloromethane, or hexane solutions. Hindered, or less reactive, aldehydes and especially ketones may require acidic catalysts (AcOH, TFA, *p*-TsOH), heating, and removal of forming water (azeotropic, by molecular sieves or other water scavengers) to achieve high conversions or reasonable reaction times.[1,3,4] In difficult cases of hydrazone formation, special reagents can be used such as trimethylsilyl chloride[34] or trimethylaluminum (forming reactive $[Me_2AlNHNR_2]_n$ with *N,N*-dialkylhydrazines).[35] Trimethylsilyl chloride was used for the formation of a *N,N*-dimethylhydrazone of a hindered ketone with an α-quaternary carbon atom,[34] while the trimethylaluminum reagent was successful for planar ferrocenyl ketones.[36] Besides direct formation from hydrazines, the ketone and aldehyde hydrazones can be synthesized from alkyl azides **17** ($NH_2NMe_2/FeCl_3 \cdot 6H_2O$, MeCN/reflux),[37] from ketimines by transamination,[38] or from other hydrazones **18** by α-alkylation and other hydrazone reactions. The polyfunctional hydrazones, in particular, can be formed

Scheme 1



Scheme 2



by many hydrazone reactions (vide infra) at the α-carbon atom and by reactions of aldehyde hydrazones at the azomethine carbon (Michael-type addition to the activated C═C bond, electrophilic Vilsmeier-type formylation, or acylation with reactive acylating reagents). In addition to the rather typical methods mentioned above, some special routes can also provide hydrazones. For example, alkynes can be hydrohydrazinated with *N*,*N*-disubstituted hydrazines using the titanium catalyst $Ti(dap)_2(NMe_2)_2$ to give hydrazones.[39] A special family of hydrazones, the *N*-aziridinylimines, known as Eschenmoser hydrazones, can be prepared by direct reaction of 1-aminoaziridines (1-amino-2-phenylaziridine and 1-amino-*trans*-2,3-diphenylaziridine) with reactive carbonyl compounds at temperatures below 40 °C or with imines (substitutes for less reactive carbonyl compounds).[24,40]

Cleavage of the *N*,*N*-dialkylhydrazones (Scheme 2) can be effected by a multitude of methods.[41] Methods for recovery of carbonyl compounds from *N,N*-dimethyl- and SAMP/RAMP-hydrazones were thoroughly reviewed in the Enders' account.[8] General uses in preparative practice have a few methods, including oxidative, hydrolytic, and reductive protocols. In the typical laboratory practice, carbonyl compounds **14** are obtained from their *N*,*N*-dialkylhydrazones **13** by oxidative cleavage with magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$; ketones only),[42,43] *m*-chloroperbenzoic acid (ketones only),[44a] recently reported peroxyselenous acid (ketones only),[44b] and ozonolysis (O_3, −78 °C).[2,45] In contrast to ketone *N*,*N*-dialkylhydrazones, the aldehyde hydrazones give nitriles **16** when oxidized with MMPP or *m*-CPBA.[46] A one-pot ozonolytic cleavage combined with reductive workup is a practical method that provides alcohols **19** and may be desired when racemization-susceptible α-chiral carbonyl compounds[47] (e.g., aldehydes, α-phosphino ketones, etc.) produced by ozonolysis cannot be isolated without loss of enantiomeric purity. Owing to its mild conditions and low temperature, ozonolysis is the oxidative protocol most broadly used for regeneration of carbonyl compounds from the corresponding hydrazones. One should however be conscious of a toxic *N*-nitrosoamine byproduct forming during ozonolytic cleavage of hydrazones and take proper care during the reaction workup.

The hydrolytic cleavage methods are broadly used for polyfunctional hydrazones possessing other functionalities that react with oxidants. Typical hydrolytic cleavage is often conducted through methylation and acidic hydrolysis of SAMP/RAMP-hydrazones in a two-phase system (MeI, 3 M HCl, *n*-pentane),[48,49] which prevents racemization of α-chiral carbonyl products **14**. The use of an aqueous oxalic acid solution in a two-phase system[50] is currently quite a popular method for the cleavage of sensitive products. This also allows for the recovery of the precious SAMP chiral auxiliary. Copper(II)-induced hydrolytic cleavage (aqueous cupric acetate or dichloride) may also provide good results in most cases[51,52] including α,β-unsaturated aldehyde *N*,*N*-dimethylhydrazones.[53] Hydrolysis of *N*,*N*-dimethylhydrazones, and RAMP-hydrazones containing an olefin or acetal group, to ketones was reported using ammonium dihydrogen phosphate buffer solutions.[54] Interestingly, enzymatic hydrolytic cleavage to the carbonyl group is possible with porcine pancreatic lipase (PPL).[55] An attractive, racemization-free cleavage using $BF_3 \cdot Et_2O$, paraformaldehyde, and acetone/water was recently reported,[56] as was a study on the hydrolytic stability of *N*,*N*-dimethylhydrazones and related compounds.[57]

The most commonly used reductive cleavage methods involve N−N bond cleavage and as a result give primary amines **15**. The hydrazone may be reduced (e.g., with catecholborane,[58] DIBAL,[59] or DMAB/*p*-TsOH[60]) to hydrazine, cleavage of which is effected by Raney nickel[58] or borane/THF.[61] The whole hydrazone reduction−cleavage is also possible in one step with borane/THF itself.[62]

4. Short History of Synthetic Applications

Although simple *N*,*N*-dialkylhydrazones such as dimethyl- and diethylhydrazones of benzaldehyde, *p*-nitrobenzaldehyde,[63] aromatic aldehydes, and cyclohexanone[64] were known in the early times of modern organic chemistry, the record of synthetic applications of *N*,*N*-dialkylhydrazones starts in the 1960s, when piperazine-derived hydrazones of type **20** (Figure 4) and dimethylhydrazones of aldehydes were prepared and used in sodium borohydride reductions to hydrazines.[65] In the same decade, oxidation of hydrazones of aliphatic and aromatic aldehydes to nitriles with hydrogen peroxide was reported.[66] Oxidation of hydrazones to parent carbonyl compounds was also observed by Horner.[67] *N*,*N*-

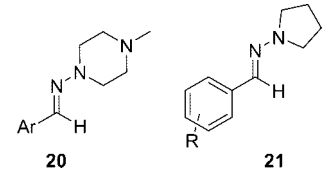
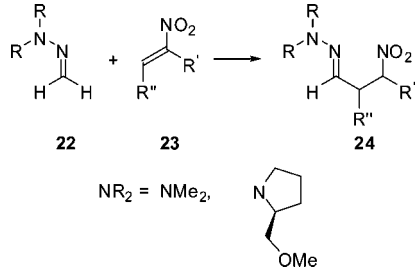


Figure 4. The earliest *N*,*N*-dialkylhydrazones.

Scheme 3



Dialkylhydrazones were described in 1969 as possible protecting groups for ketones, furnishing under hydrolytic or oxidative cleavage the parent carbonyl compounds.[68] The 1,2-addition of phenyl- and butyllithiums to C═N bonds of *N,N*-dimethylhydrazones of 4-pyridinealdehyde and 4-acetylpyridine was described in 1964 (the reaction with cyclohexanone or nicotinaldehyde was not successful).[69] Nucleophilic, azaenamine character of *N*-aminopyrrolidine-derived benzaldehyde hydrazones **21** was recognized and demonstrated through Vilsmeier formylation[70] and reactions with electrophilic sulfonyl isocyanates[71] as early as 1968. *N,N*-Dialkylhydrazones of α,*β*-unsaturated aldehydes and ketones can be viewed as aza analogues of electron-rich dienes (Figure 1). The synthetic applications of such hydrazones in hetero-Diels−Alder[72−74] and [2 + 2] cycloaddition[75] reactions have been known at least since the 1980s.

Despite the early reports, *N,N*-dialkylhydrazones did not gain widespread application in synthesis until the landmark papers on alkylation of metalated *N,N*-dimethylhydrazones (described also as metal azaenolates) were published by Corey and Enders in the years 1976−1978.[10,11,51,76−80] It was shown that hydrazones, acting like aza analogues of the parent carbonyl compounds, could be α-deprotonated (lithiated with LDA or *n*-BuLi) and reacted with a number of electrophiles (in particular alkyl halides). The pioneering studies have shown that *N,N*-dialkylhydrazones (mostly *N,N*-dimethylhydrazones) could be important intermediates in the synthesis of α-substituted aldehydes and ketones, and also in other C−C bond forming reactions. Shortly thereafter, Enders developed a very successful approach to the synthesis of enantiomerically pure compounds based on the reactions of chiral *N,N*-dialkylhydrazones made from carbonyl compounds and prolinol-derived chiral hydrazines known as SAMP and its enantiomer RAMP (Figure 2).[1,2,48,49,81−84] Other chiral hydrazines shown in Figure 2 were developed later for specific purposes.

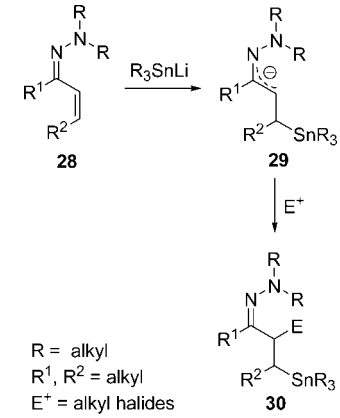
The free radical acceptor character of the hydrazone functional group was demonstrated in a cyclization of *N*-aziridinylimines by Kim in 1991.[85]

High nucleophilic reactivity of formaldehyde *N,N*-dimethylhydrazones (FDMHs) **22** toward nitroolefins **23** was exploited in a Michael addition for the first time by Lassaletta[86,87] and Enders[88] (Scheme 3) in both achiral and chiral versions based on formaldehyde SAMP-hydrazone (FSAMPH).

5. Formation of Azaenolates

Metalated hydrazones can be prepared via several methods. The most commonly used metalated hydrazones **25** (Scheme 5) are lithium and potassium azaenolates (also known as azaallyllithiums and -potassiums)[4,89] which are made via deprotonation of hydrazones with LDA (sometimes with additives such as HMPA, LiBr, and TMEDA), *n*-BuLi (sometimes with additives such as HMPA, TMEDA, and DMPU), *t*-BuLi, LTMP, *t*-BuOK, NDA,[2,90] KDA (potassium diisopropylamide made from diisopropylamine, *t*-BuOK, and *n*-BuLi),[91] and the Lochmann−Schlosser superbase, i.e., *t*-BuOK/*n*-BuLi.[92]

Scheme 4



Transition-metal azaenolates such as zinc and copper are typically made by transmetalation of the lithium enolate. Zinc azaenolates, made through a reaction of a hydrazone with LDA, $ZnCl_2$, and 1 equiv of BuLi, were successful reagents in the addition to unactivated olefins.[93] Lithium−copper mixed azaenolates, which are presumably formed through Li−Cu transmetalation reaction of lithiated hydrazones (*n*-BuLi), with copper(I) iodide in *i*-Pr_2S solution, undergo conjugate addition to α,*β*-unsaturated ketones or esters (adducts **26**).[77] Titanium azaenolates (titanated hydrazone) made by the action of $TiCl_4$ and NEt-*i*-Pr_2 on a SAMP-hydrazone have been used in *syn*-selective aldol reaction (products **27**).[94]

An interesting case constitutes the formation of a lithium azaenolate of a *β*-stannane (**29**) through 1,4-addition of R_3SnLi (R_3 = Me, *n*-Bu) or $Li_2[CuMeCN(SnBu_3)]$ to the hydrazone of an α,*β*-unsaturated ketone (**28**) (Scheme 4), which after typical α-alkylation provides access to *β*-stannylketones.[95]

6. Reactions of Azaenolates with Electrophiles: Carbon−Carbon Bond Formation

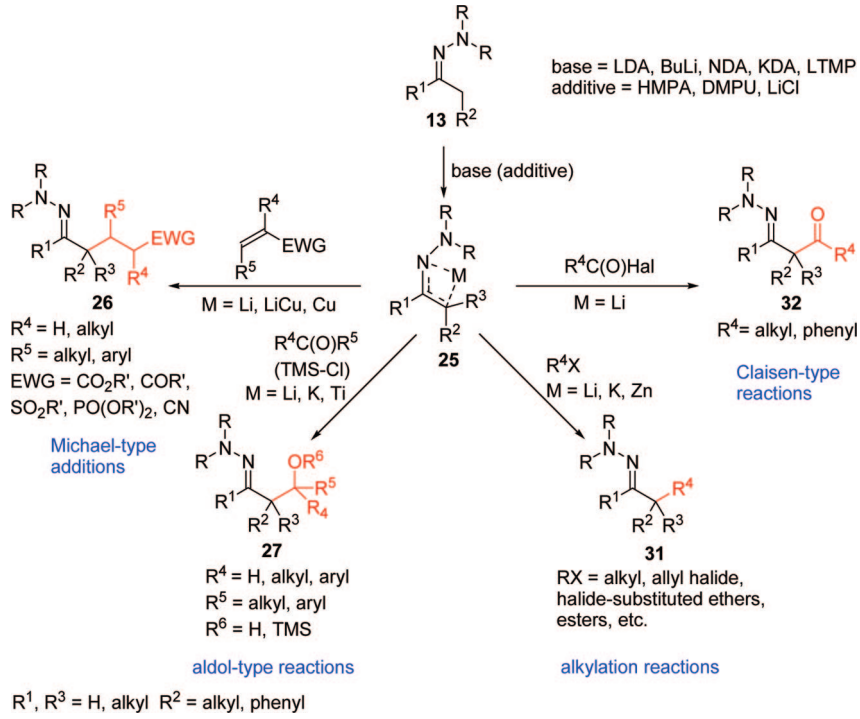
The typical electrophilic reactions on the α-carbon of a hydrazone require prior deprotonation (metalation) of the hydrazone C−H acid. As a result of the above-discussed reactivity of hydrazones and their metalated derivatives, several synthetically useful transformations based on electrophilic reactions are known, many of them belonging already to the classical organic synthesis literature (Scheme 5).

Once the azaenolates are formed they can react with a number of electrophiles. The known synthetically useful C−C bond forming reactions (Scheme 5) of α-metalated hydrazones include Michael-type additions (**26**), aldol-type reactions (**27**), α-alkylation (**31**), and Claisen-type acylations (**32**).[4]

6.1. Typical Electrophilic Reactions of Azaenolates (Prior to 2000)

α-Alkylation. The reaction having the most synthetic uses is α-alkylation (Scheme 5). The reaction was used, for

Scheme 5



example, in the synthesis of α-branched aldehydes including intermediates in the epothilone synthesis,[96] α-branched acyclic and cyclic ketones,[2] dioxanones,[97] lactones,[98] and β-keto esters.[2] The alkylating agents used are alkyl, allyl, and benzyl halides (Br, I), bromo or iodo ethers (halide-substituted ethers) especially BOM-Cl, bromo or iodo esters (halide-substituted esters), protected bromo or iodo alcohols, oxiranes, tosylaziridines, methyl sulfate, and even trialkylsilyl triflate-activated THF.[99] The asymmetric syntheses of branched ketones and aldehydes through alkylation of SAMP/RAMP-hydrazones,[48,49,81,100] including many natural products, published up to the year 2000 have been reviewed by Enders.[1,2]

Aldol-Type, Michael-Type, and Other Addition Reactions.[4] Typical 1,2-addition of azaenolates to the carbonyl group of ketones and aldehydes provides access to azaaldol-type products (Scheme 5) which can further be hydrolyzed to carbonyl derivatives.[76,77] The hydroxyls of the azaaldols are often silylated in "one pot" to protect the aldols from hydrazone cleavage conditions. Related addition to carbon disulfide gives lithium hydrazonoalkanedithiolates that can be further *S*-alkylated.[101] 1,4-Addition of hydrazone anions to α,β-unsaturated carbonyl compounds, esters, nitriles, alkenyl sulfones, and alkenyl phosphonates results in various Michael-type adducts (Scheme 5).[77] Claisen-type substitution on sp^2 carbon atoms of acid chlorides by azaenolates followed by hydrazone hydrolysis provides an access to 1,3-diketones.[80,102]

Various applications of hydrazone azaenolates (1-azaallylic anions) toward the synthesis of heterocyclic structures have previously been reviewed.[103]

6.2. Alkylations

Electrophilic alkylations were among the first synthetically useful transformations of hydrazones and remain still the most frequently used reactions of hydrazones. The alkylations of DMH-hydrazones and SAMP/RAMP-hydrazones are often employed as key steps in the synthesis of complex targets which are typically natural products.

6.2.1. Alkylation of *N,N*-Dimethylhydrazones

Alkylation of DMH-hydrazones was used in recent years as the major C−C bond forming reaction in the synthesis of spiroketals (Scheme 6).

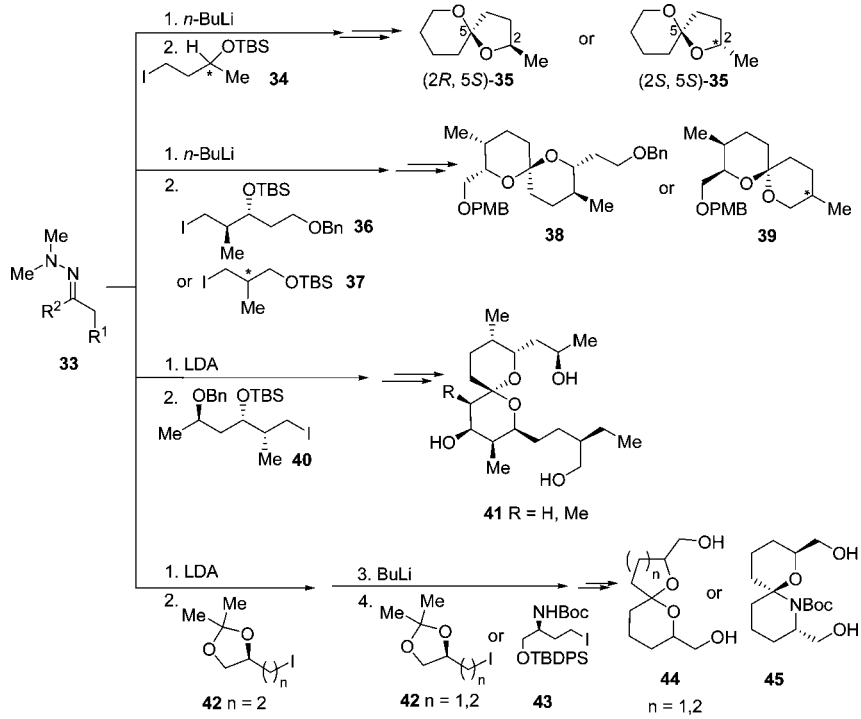
Spiroketal **35** was synthesized starting with alkylation of cyclopentanone *N,N*-dimethylhydrazone **33** (R^1, $R^2 = (CH_2)_3$) with the chiral iodide **34** (either the (*R*)- or (*S*)-enantiomer), derived from enantiomerically pure ethyl β-hydroxybutyrate. The alkylation served as a method for introducing the stereocenter at C2 of the target molecule **35**. The alkylation products were transformed into a diastereomeric mixture (2:1) of compound (2*R*,5*S*)-**35** or compound (2*S*,5*S*)-**35** in five synthetic steps including stereoselective spiroketalization in acidic media.[104]

A very efficient alkylation of a lithiated *N,N*-dimethylhydrazone of a chiral ketone (**33**, R^2 = Me, R^1 = $CH_2CH(Me)$-$CH(O(TBS))CH_2O(PMB)$) followed by spiroketal formation under acidic conditions was also used in a short synthesis of the 6,6-spiroketal fragments **38** and **39** useful for synthesis of the antifungal antibiotics spirofungins A and B.[105]

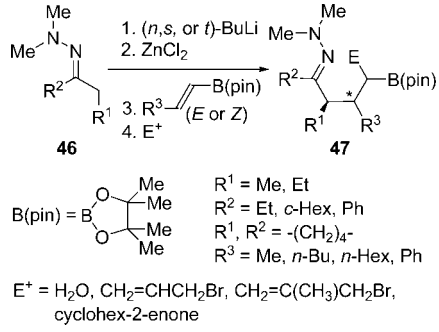
Another alkylation reaction of the lithiated *N,N*-dimethylhydrazones of elaborate methyl ketones **33** (R^1 = H, R^2 = chiral *O*-protected substituted trihydroxynonyl) with suitable, protected iodide **40** afforded linear spiroketal intermediates. After functional group adjustment, these advanced intermediates were cyclized to their respective spiroketals **41** (R = H, R = Me), which constituted subunits in the asymmetric synthesis of the macrolide antibiotics (+)-rutamycin B and (+)-oligomycin.[106]

Several chiral spiroketal skeletons were obtained by sequential α- and α′-alkylations of acetone *N,N*-dimethylhydrazone with acetonide-protected dihydroxy iodides **42**. A one-pot acidic deprotection/spirocyclization sequence (Amberlyst 15, MeOH) provided spiroketal **44**.[107] The same convergent approach via a double alkylation of acetone *N,N*-dimethylhydrazone was also used for synthesis of a spiroheterocycle, 1-oxa-7-azaspiro[5.5]undecane (**45**).[108]

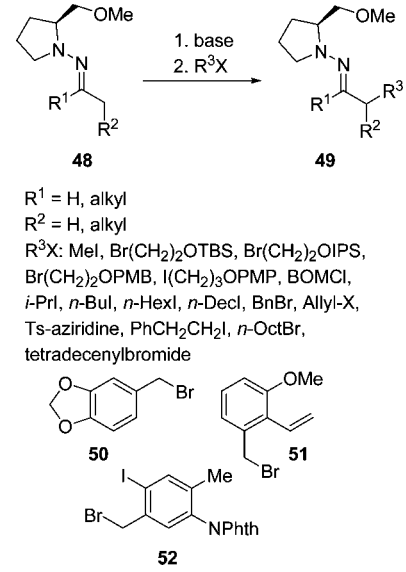
Scheme 6



Scheme 7



Scheme 8



6.2.2. Alkylation of Zincated N,N-Dialkylhydrazones

Zincated *N*,*N*-dimethylhydrazones of ketones, prepared by transmetalation of lithium azaenolates with zinc chloride, underwent stereospecific *syn*-addition to both (*E*)- and (*Z*)-alkenylboronates to give zinc intermediates, which reacted with subsequently added electrophiles (Scheme 7) to give γ-borylhydrazones **47** in yields from 48% to 93% and with good to excellent diastereoselectivities (up to 99%).[109] It is noteworthy that the method (three-component coupling) allowed the generation of two to four contiguous stereogenic centers in a one-pot reaction. Recently, an asymmetric version of the process with zincated SAMP-hydrazones, along with thorough experimental and theoretical study, was reported.[110] The SAMP-hydrazone adducts corresponding to **47** were obtained with a diastereoselectivity of 95% (after recrystallization the reported ds was >99% and the ee was >99%).

6.2.3. Alkylations of Chiral N,N-Dialkylhydrazones

The well-known alkylation of chiral hydrazones, notably SAMP/RAMP-hydrazones (Scheme 8), is often used as a key step in the asymmetric synthesis of natural products. The alkylation of the diethyl ketone SAMP-hydrazone (*S*)-**48** with *p*-MePhO$(CH_2)_3$I (yield 80%, de > 98%, Scheme 8), followed by titanium-mediated *syn*-diastereoselective aldol reaction and other transformations, allowed for the first highly diastereo- and enantioselective total synthesis of stigmatellin A (**53**; Figure 5), a powerful inhibitor of electron transport in mitochondria and chloroplasts isolated from the myxobacterium *Stigmatella aurantiaca*.[94]

Similar asymmetric α-alkylation of an *O*-protected derivative of 4-hydroxybutanal with methyl iodide via the SAMP/RAMP-hydrazone method (de 72% to >95%) was exploited for the preparation of intermediates in the synthesis of the potent cytotoxic marine natural product (−)-callystatin A (**54**; Figure 5)[111,112] and its 20-*epi* analogue (overall yield 18% and 17%, respectively). The synthesis also required a diastereoselective *syn*-aldol reaction of an α-substituted chiral ethyl ketone and an α-substituted chiral aldehyde, both prepared in enantiomerically pure form, again by means of the asymmetric alkylation of corresponding RAMP-hydra-

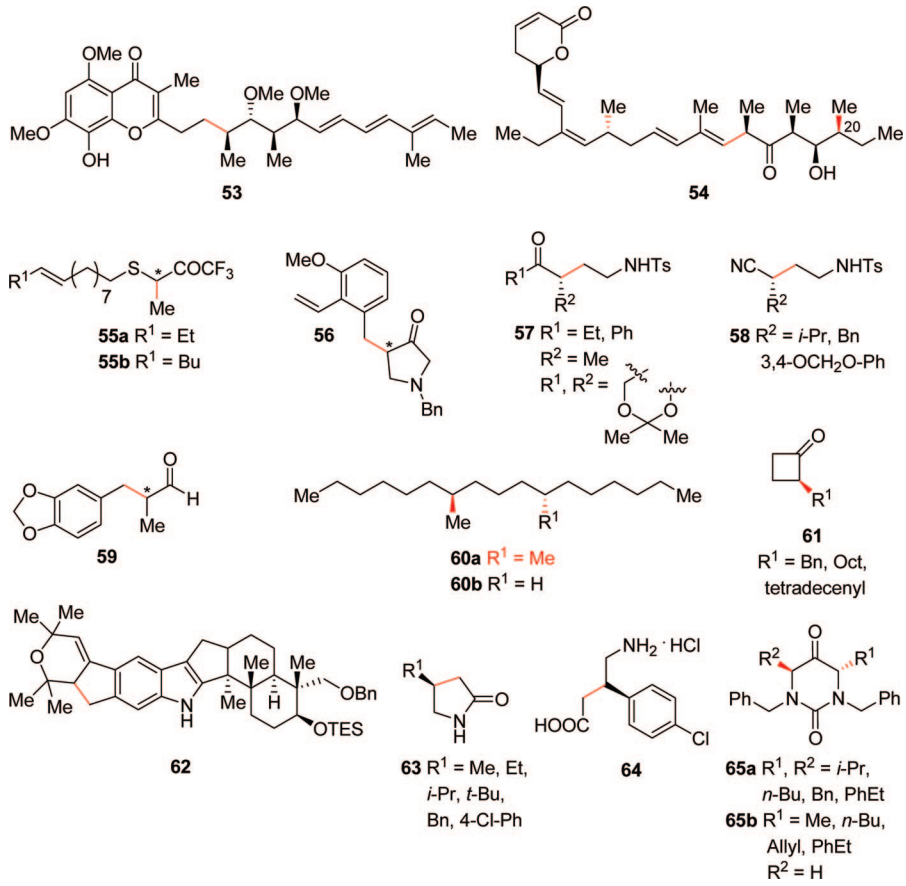


Figure 5. Products synthesized via hydrazone alkylation as key steps (bonds formed are shown in red).

zones (reactions of diethyl ketone with BOM-Cl and butyraldehyde with MeI, respectively).[112]

Both enantiomers of (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-hexadecen-2-one (**55a**; Figure 5) and (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-octadecen-2-one (**55b**; Figure 5), potential inhibitors of the pheromone action of two major maize pests, *Sesamia nonagrioides* and *Ostrinia nubilalis*, were synthesized via alkylation of SAMP/RAMP-hydrazones with methyl iodide as the key step (79−86% yield, de 92−94%). Specific hydrazone cleavage under racemization-free conditions ($BF_3 \cdot Et_2O$, paraformaldehyde, acetone/water) gave the target ketones **55** (ee ≥ 90%).[56]

The synthesis of *C*4-alkylated pyrrolidin-3-ones of type **56** (Figure 5) by regio- and diastereoselective (de 38% to >95%) alkylation of SAMP-, SAPP-, and SADP-hydrazones of *N*-protected pyrrolidine-3-ones was also reported (LDA or LHDMS, THF, MeI or BnBr, −78 or −100 °C).[113] The pyrrolidin-3-one **56** was prepared by the alkylation of SADP-hydrazone (63% yield, de > 95%) and subsequent cleavage with aqueous $CuCl_2$ (67% yield, ee > 95%).

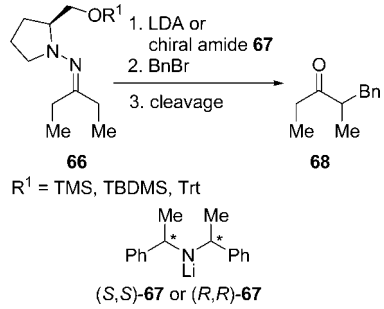
An interesting approach to asymmetric synthesis of tosyl-protected γ-amino ketones **57** (Figure 5) and γ-amino nitriles **58** through reactions of lithiated SAMP- and RAMP-hydrazones with tosylaziridine is worth noting. The key step was the highly diastereoselective (de ≥ 98%) α-aminoethylation of the hydrazones. Cleavage of the hydrazones with magnesium monoperoxyphthalate (MMPP) provided γ-amino nitriles **58** in good yields and excellent enantiomeric excesses (ee ≥ 98%). Likewise, γ-amino ketones **57** were obtained in good overall yields by cleavage of the hydrazones with aqueous copper(II) chloride (ee ≥ 98%).[114]

The first asymmetric synthesis of both enantiomers of Tropional **59** (Figure 5) was also realized by alkylation (LDA, THF, −100 °C) of the SAMP- and RAMP-hydrazones of propanal with 5-(bromomethyl)-1,3-benzodioxole (**50**; Scheme 8). The resulting alkylated hydrazones had to be oxidatively cleaved with MMPP to nitriles, and via subsequent reduction with diisobutylaluminum hydride (DIBAL-H), transformed to the desired enantiomers of Tropional (overall yields 52−53%, ee 90%).[115]

The asymmetric synthesis of all stereoisomers of 7,11-dimethylheptadecane (**60a**) and 7-methylheptadecane (**60b**; Figure 5) was possible owing to highly diastereoselective SAMP/RAMP-hydrazone alkylation. A mixture of (7*S*,11*R*)-**60a** and its demethylated analogue (*S*)-**60b** is the female sex pheromone of the spring hemlock looper moth (*Lambdina athasaria*) and the pitch pine looper moth (*Lambdina pellucidaria*); both are forest pests of northeastern North America.[116] The two stereogenic centers of the first component of the pheromone mixture were assembled by α-alkylation of propanal SAMP-hydrazone with *n*-hexyl iodide (lithiation with LiTMP and THF at 0 °C, alkylation at −100 °C) in an effective and highly diastereoselective way (de ≥ 96%). Under standard conditions at −78 °C lower selectivity was observed (de 90%). The other component, (*S*)-**60b**, was put together employing alkylation of *n*-octanal SAMP-hydrazone with decyl iodide under somewhat unusual conditions (LiTMP and THF at 0 °C, alkylation at −100 °C followed by warming to rt and refluxing), necessary to increase the yield to 68% (de ≥ 96%).

The RAMP-hydrazone auxiliary was essential for the asymmetric synthesis (67−87% ee) of (*R*)-2-benzyl-, (*S*)-2-octyl-, and (*S*)-2-tetradec-5′-enylcyclobutanones **61** by alkylation of cyclobutanone respectively with benzyl bromide,

Scheme 9



n-octyl bromide, or tetradec-5-enyl bromide. The hydrazone hydrolysis to the ketone products was effected by oxalic acid cleavage.[117]

The SAMP-hydrazone alkylation of 2,2,6,6-tetramethyltetrahydropyran-4-one with functionalized benzylic bromide **52** (72% yield, single diastereomer) was again a key step in a synthesis of the heptacyclic core of (−)-nodulisporic acid D (**62**), a member of a class of architecturally complex, ectoparasiticidal indole alkaloids.[118]

The α-alkylation of aldehyde SAMP-hydrazones **48** (Scheme 8, R^1 = H, R^2 = Me, Et, *i*-Pr, *t*-Bu, Bn, 4-ClPh) with alkyl (methyl or *tert*-butyl) bromoacetates, combined with MMPP oxidation to nitriles and a reductive cyclization with Raney Ni or nickel boride, provided the pyrrolidin-2-ones **63**. They were prepared in good overall yields (27−78%) and ee (93−99%). The method was applicable for an asymmetric synthesis of GABAs (γ-aminobutyric acids) as was demonstrated for (*R*)-(−)-baclofen hydrochloride (**64**; four steps, 55% yield and 94% ee).[119]

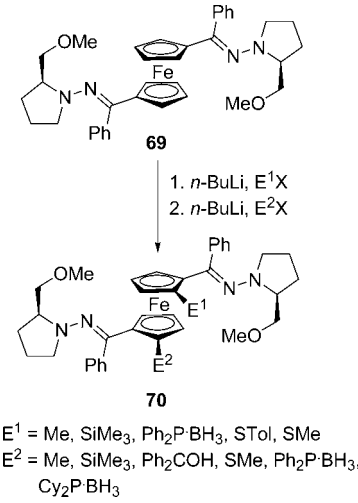
The same SAMP/RAMP-hydrazone alkylation method also allowed for the first asymmetric synthesis of potential HIV protease inhibitors of types II, III, and IV starting from a derivative of pyrimidine-2,5-dione which is a readily available building block.[120,121] The α- or α,α′-alkylation of 1,3-dibenzyltetrahydropyrimidine-2,5-dione hydrazones (metalation, LiTMP; alkylation, *i*-PrI, *n*-BuI, BnBr, $PhCH_2CH_2I$, allyl halide) followed by cleavage (ozone, dimethyldioxirane, or aqueous $CuCl_2$,) gave carbonyl compounds **65**. Monoalkylated tetrahydropyrimidine-2,5-diones were obtained with excellent de's (>96%) and good ee's (76% to >96%), while the bisalkylated products were prepared with good de's (80% to >96%) and ee's (76% to >96%). The potential HIV protease inhibitors (5-hydroxy derivative isomers of **65**) were prepared by stereoselective reduction of **65** (LAH, $NaBH_4$, L-Selectride, Super-Hydride, catecholborane, or BH_3/dimethyl sulfide) in good yields (71−92%) and with good diastereo- and enantiomeric purities.

The SAMP/RAMP-hydrazone alkylation method was investigated as one of the approaches to the unusual [5.3.2]-bicyclic structure of the insecticidal Amaryllidaceae alkaloids cripowellin A and B.[122]

Alkylation of diethyl ketone via the SAMP-hydrazone method also allowed the construction of three stereogenic centers of serricornin, a sex pheromone of the cigarette beetle (*Lasioderma serricorne*), and provided material for the determination of its absolute configuration by CD spectroscopy.[123,124]

Three prolinol-derived hydrazones, analogues of SAMP-hydrazone with alternative *O*-substituents, **66** (R^1 = TBDMS, TMS, and trityl, Scheme 9) were produced, and their effectiveness in directing alkylation of diethyl ketone hydrazone azaenolate with benzyl bromide was studied.[33] The

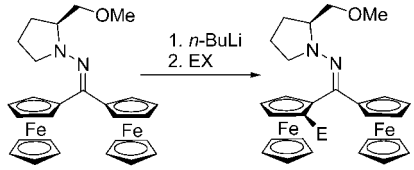
Scheme 10



substituent on the oxygen of the prolinol had a significant effect on both the stereoselectivity and the configuration of the asymmetric alkylation. The *tert*-butyldimethylsilyl hydrazones, lithiated with LDA in THF, gave the expected (*S*)-enantiomer of the benzylation product in good yield and moderate enantiomeric purity (61% yield, 61% ee). The sense of diastereoselection was in agreement with the known SAMP-hydrazone (R^1 = Me) performance where the (*S*)-enantiomer is also preferred. Changing the substituent on the oxygen atom to the trityl group caused a reversal of configuration of the major alkylation products and rather low stereoselectivity (7−64% depending on the solvent, (*R*)-enantiomer). The change was rationalized by the large $-CPh_3$ group hindering chelation of the oxygen to the lithium, thus disrupting the configuration of the transition state. Solvents also had a substantial effect on the reaction. Toluene gave the best yields and ee's, while both pentane and hexane were inferior. Additives (HMPA and TMEDA) caused a lowering of yields and dramatic decrease of the ee, contrary to lithium chloride, which increased the yield to 90%. The best performance was observed for the hydrazone with the least sterically demanding TMS substituent (R^1 = TMS) in toluene (65% yield, ee 86%, (*S*)-enantiomer). The effect of the oxygen substituents on the described asymmetric benzylation of SAMP-type hydrazones matches observations previously reported by Enders.[2] An interesting observation was made while testing chiral lithium amides (*S*,*S*)-**67** and (*R*,*R*)-**67** as deprotonating/lithiating bases. They have the potential to form a matched and mismatched pair of diastereomeric transition states; however, both enantiomers gave a diminished enantiomeric purity of **68** (R^1 = TMS, reaction in hexane 55% and 74% ee compared to 86% ee with LDA). The authors suggest that the reaction diastereoselectivity was governed entirely by the chiral auxiliary but do not comment on possible causes of observed ee reduction.

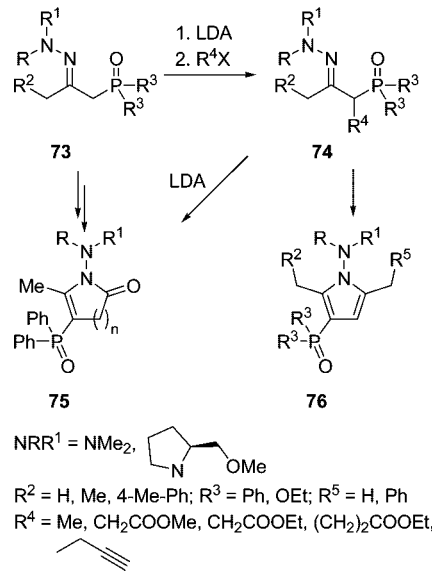
An interesting approach to the asymmetric synthesis of planarly chiral 2-mono- and 2,2′-disubstituted 1,1′-bisbenzoylferrocenes is based on the highly diastereoselective *ortho*-metalation of 1,1′-bisbenzoylferrocene via the corresponding bis(SAMP-hydrazone) **69** (Scheme 10, yield 85−100%, de ≥ 96%). This illustrates yet another extension of the SAMP-hydrazone methodology to new reactions. The lithiated ferrocenes were trapped with several carbon, silicon, phosphorus, and sulfur electrophiles. Cleavage of the monosubstituted hydrazones led to monosubstituted ketones (ee ≥ 98%). Further *ortho*-substitution of the monohydrazone

Scheme 11



E = Me, $SiMe_3$, Ph_2COH, Ph_2CH, SMe, STol, Si-Pr, Ph_2P, i-Pr_2P

Scheme 12



R^2 = H, Me, 4-Me-Ph; R^3 = Ph, OEt; R^5 = H, Ph
R^4 = Me, CH_2COOMe, CH_2COOEt, $(CH_2)_2COOEt$,

afforded 2,2′-disubstituted hydrazones **70** (yield 45−89%, de 92% to ≥96%), cleavage of which gave disubstituted ferrocenyl diketones (ee ≥ 99%). The cleavage of the auxiliary was effected by ozonolysis or reduction using $TiCl_3$ or $SnCl_2$ (yield 58−99%, de 98% to ≥99%).[125]

The same diastereoselective *ortho*-metalation of diferrocenyl ketone SAMP-hydrazone **71** was applied to the preparation of planar chiral 2-monosubstituted diferrocenyl ketones (yields 88−99%, de ≥ 96%, Scheme 11). The racemization-free cleavage of the resulting hydrazones **72** afforded the corresponding ketones in good to very good overall yields (21−97%, depending on the cleavage method) and high enantiomeric excesses (97−99%).[126] The monosubstituted diferrocenyl ketones **72** (E = SMe, PPh_2/BH_3, $C(OH)Ph_2$) have been subjected to *ortho*-metalation and reactions with electrophiles MeI, $(i\text{-PrS})_2$, $(MeS)_2$, Me_3SiCl. The reactions gave chiral disubstituted bisferrocenes in low to moderate yields (20−54%) and excellent stereoselectivities (97% to >99% ee, >96% de), however with poor regioselectivities in several cases.[127]

Phosphorus-controlled regioselective α-alkylation of α-phosphorylated hydrazones derived from phosphine oxides or phosphonates allowed for synthesis of 1-aminopyrrol-2-ones, 1-amino-3,4-dihydropyridin-2-ones **75** (n = 1, 2) or 1-aminopyrroles containing phosphinyl or phosphoryl substituents, **76** (Scheme 12). The azaenolates of **73**, of DMH-, SAMP-, and RAMP-hydrazones (obtained with LDA and THF at −78 °C or n-Bu_2CuLi and THF/Et_2O at −50 °C), were alkylated with alkyl halides (yield 42−89%). Diastereoselectivity of SAMP/RAMP-hydrazone alkylation was low (de 0−50%).[128] Alkylation product **74** (R^4 = $(CH_2)_nCOOEt$) underwent cyclocondensation on addition of LDA to form **75**. A palladium-catalyzed cyclization to form **76** was effective for the propargylic product **74** (R^4 = propargyl).

6.2.4. Alkylation of Dioxanone Hydrazones

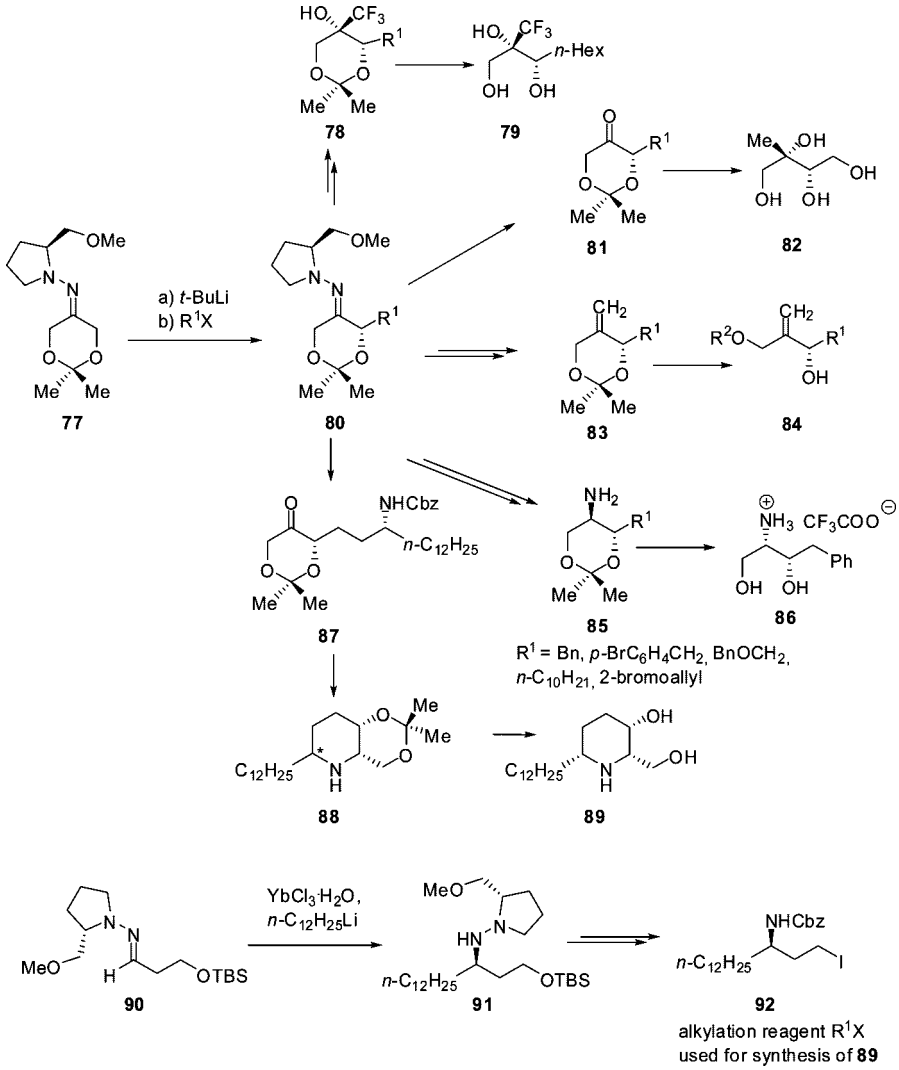
The *N*,*N*-dialkylhydrazone alkylation reaction is certainly the hydrazone transformation, most widely used in the synthesis of complex natural products. 1,3-Dioxanones (cyclic acetals of 1,3-dihydroxyacetone) are a group of synthetically versatile building blocks. *N*,*N*-Dialkylhydrazones of these synthetic equivalents of dihydroxyacetone (DHA) can be used by synthetic chemists in the same way that dihydroxyacetone phosphate (DHAP) is used by nature, i.e., as donors in important C−C bond forming reactions. The power of dioxanones as C_3 donor reagents has been demonstrated convincingly in many asymmetric electrophilic substitution reactions (including stereoselective alkylations and aldol reactions) in target-oriented syntheses. Synthetic applications of 1,3-dioxanones have been summarized in excellent reviews.[97,129]

Currently reliable procedures for the preparation of chiral and achiral 2,2-dimethyl-1,3-dioxan-5-one hydrazones,[130] their α- and α,α′-alkylation[130] and mild, selective hydrazone cleavage[97,130] to afford substituted dioxanones, are available. Dioxanone hydrolysis to 1,3-diols has been effected with PPTS/acetone/water,[131] Dowex 50/ethanol,[132] TFA/water/THF,[133] and aqueous HCl.[134,135] In recent years, a number of synthetic applications of dioxanone alkylation that deserve particular mention have been reported.

α-Alkylation of Dioxanone Hydrazones. The α-alkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP- or RAMP-hydrazones, followed by trifluoromethylation of the resulting enantiomerically pure, alkylated dioxanones, was used for the asymmetric synthesis of the 2-trifluoromethylated 1,2,3-triols **79** (Scheme 13). The nucleophilic trifluoromethylation of the monoalkylated dioxanones with (trifluoromethyl)trimethylsilane in the presence of TBAF gave the 2-trifluoromethylated acetonide-protected triols **78** in high diastereo- and enantiomeric excesses (de 96%, ee 92−98%) and good overall yields (52−97%, depending on R^1 = Me, Et, *i*-Pr, *n*-Bu, and *n*-Hex). Deprotection of the acetonide-protected triol under acidic conditions afforded trifluorotriol **79** and *ent*-**79** (de 96%, ee 95%, 96%, R^1 = *n*-Hex) chosen as typical examples. Extension of the methodology to the trialkylated dioxanone led to the analogous α-trifluoromethylated alcohol with tertiary and quaternary α-stereocenters in good yield (77%) and very good diastereo- and enantiomeric excesses (de 96%, ee 98%).[132]

An analogous approach was used for the asymmetric synthesis of (*S*,*S*)- and (*R*,*R*)-2-methylthreitol (**82** and *ent*-**82**; Scheme 13). Starting from the alkylation of the SAMP- or RAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one with BOM-Cl, as a key step, a benzyl-protected α-hydroxymethyldioxanone (**81**, R^1 = $BnOCH_2$) was prepared. The second stereogenic center was assembled by nucleophilic 1,2-addition of methyllithium or alternatively by the diastereoselective, bis(acetylacetonato)oxovanadium(IV) [$VO(acac)_2$] catalyzed epoxidation of the exocyclic methylene group (made from dioxanone carbonyl by Wittig reaction). After acidic methanolysis of the acetonide protection (Dowex 50X2-200) the enantiomeric methylthreitols **82** were obtained in excellent diastereo- and enantiomeric excesses (≥98% de, 98% ee) and in good overall yields (40−61% depending on the method used).[134]

Scheme 13

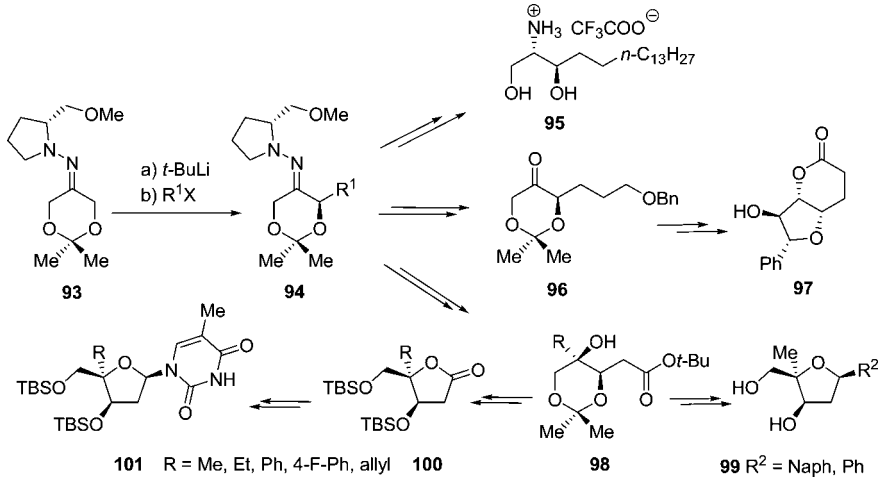


The SAMP/RAMP-hydrazone methodology was also employed in the enantioselective synthesis of mono-TBS-protected, allylic diols **84** (R^2 = TBS, ee 90−94%). Alkylation (R^1 = Bn, *i*-Pr, *n*-Bu, $(CH_2)_2Ph$, 4-*t*-$BuC_6H_4CH_2$) of dioxanone SAMP-hydrazone followed by hydrazone ozonolysis gave the acetonide-protected, α-substituted ketodiols (90−94% ee), which in turn were converted to exocyclic olefins **83** by Wittig reaction without racemization. Acidic acetal cleavage with TFA/water (room temperature) to give **84** (R^2 = H) and subsequent, selective, TBS protection of the primary hydroxyl group, furnished **84** (R^2 = TBS) in very good overall yields (54−99%) and enantiomeric excesses.[133]

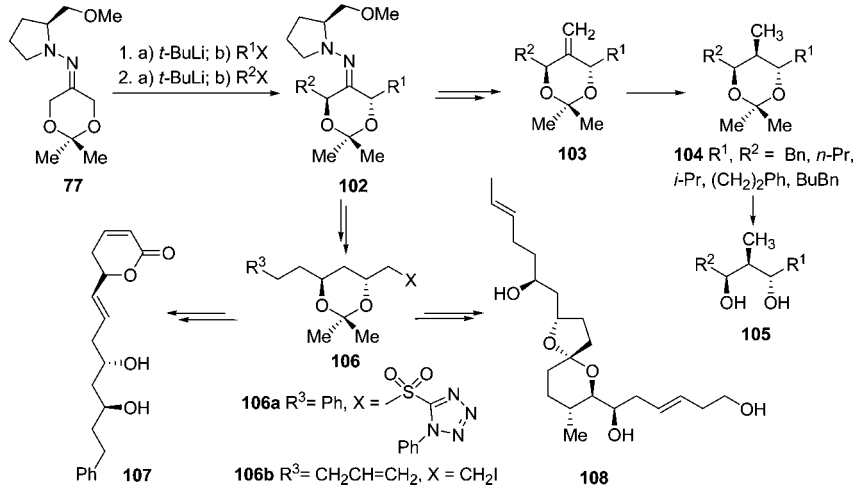
The asymmetric synthesis of protected 2-amino 1,3-diols (*S,R*)-**85** starting from 2,2-dimethyl-1,3-dioxan-5-one via SAMP/RAMP-hydrazone methodology could be extended to the synthesis of **86**. The two adjacent stereogenic centers were built up by α-alkylation using the SAMP-hydrazone method followed by oxalic acid hydrazone cleavage and diastereoselective reduction of the resulting ketones with L-Selectride. The resulting (*S,S*)-alcohol products were further transformed into the amines (*S,R*)-**85** by nucleophilic substitution with an azide and subsequent reduction of the azide with lithium aluminum hydride to the amine. The amine products were obtained in high diastereomeric and enantiomeric excesses (de ≥ 96%, ee 90−94%). By employing this approach and starting from RAMP-hydrazone, the ammonium salt of D-*erythro*-sphinganine, (*R,S*)-**95** (Scheme 14), was synthesized in 47% overall yield and with diastereomeric and enantiomeric excesses of ≥96%.[136]

The 11-step asymmetric synthesis of (+)-2-*epi*-deoxoprosopinine [(*S,S,R*)-**89**] (Scheme 13) based on the α-alkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazone with a Cbz-protected alkylation reagent is also noteworthy.[137] The alkylation reagent **92** was also obtained via the SAMP-hydrazone methodology (Scheme 13). First, the 1,2-addition of a dodecyl nucleophile ($YbCl_3 \cdot H_2O/C_{12}H_{25}Li$) to TBS-protected 3-hydroxypropanal SAMP-hydrazone (**90**) gave a hydrazine, **91**, which in turn was cleaved with borane/THF to the amine. Further protection−deprotection and functional group manipulation gave the protected 3-amino-1-pentadecyl iodide (**92**). Oxalic acid cleavage of the alkylated hydrazone **80**, followed by deprotection of the amine **87** (hydrogenolysis on Pd/C) combined in one step with cyclization to the imine, and imine hydrogenation, provided a mixture of acetonide-protected epimers *S,S,R*/*S,S,S*-**88** (98:2). Chromatographic purification and hydrolytic cleavage (acidic ion-exchange resin Lewatit S 100) of the acetonide protecting group afforded (*S,S,R*)-**89** in excellent diastereomeric and enantiomeric purity (de, ee ≥ 96%). It is noteworthy that the SAMP-hydrazone methodology was employed in two key steps of the synthesis, generating two of the three stereogenic centers.

Scheme 14



Scheme 15



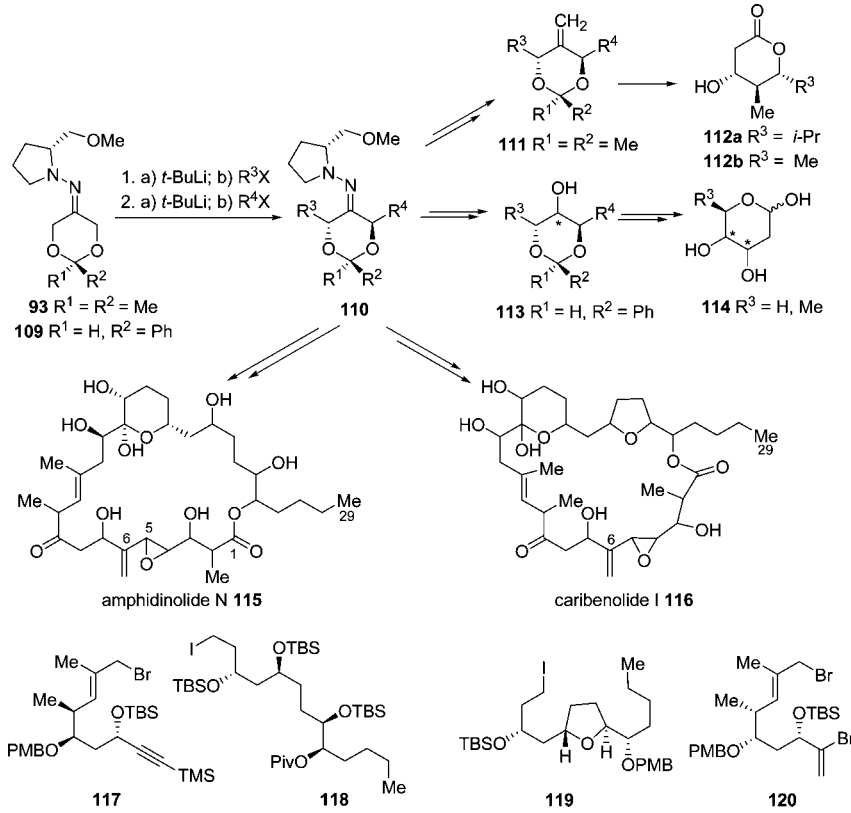
The third stereogenic center was built in a domino deprotection/cyclization/reduction sequence.[137]

The α-alkylation of the RAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one, acting as a 1,3-dihydroxyacetone equivalent, was also the key step in the asymmetric total synthesis of (+)-altholactone (**97**; Scheme 14).[138] The hydrazone alkylation with 3-(benzyloxy)-1-bromopropane and cleavage with oxalic acid gave product **96** in 82% yield (two steps) and with ee > 98%. The other reactions used in the synthesis included a boron-mediated aldol reaction, a six- to five-membered ring acetonide transacetalization, an oxidation of 1,5-diol to δ-lactone, and an Amberlist 15-catalyzed acetonide removal, concomitant with stereoselective ring closure to generate the annulated tetrahydrofuran structure of (+)-altholactone. Overall, the natural product target **97** was synthesized enantioselectively in 18 steps and 13.7% overall yield.

An elegant diastereo- and enantioselective approach to 4′-quaternary 2′-deoxy-3′-*epi*-β-*C*-nucleosides **99** (Scheme 14) through construction of the first stereocenter by the RAMP-hydrazone method is another example of a total synthesis built upon hydrazone alkylation. After alkylation of dioxanone RAMP-hydrazone with *tert*-butyl bromoacetate, and ozonolysis of the hydrazone, the resulting dioxanones were subjected to diastereoselective nucleophilic 1,2-additions of Grignard reagents (addition to the ketone group of the dioxanone). The adducts **98** were further transformed via deprotection, cyclization, organocerium addition, and reduction/cyclization to nucleosides **99** (R^2 = Naph, Ph).[139] Recently, the approach has been extended to the preparation of both enantiomers of 4′-quaternary 2′-deoxy-3′- and 4′-*epi*-β-*C*- and -*N*-nucleosides **101**.[140] The extended syntheses also involved the SAMP/RAMP-hydrazone α-alkylation and the same transformations to get the intermediate **98**.[140] Further transformations of the lactone **100**, including manipulation of the substituents in the anomeric position, allowed access to the thermodynamically more stable β-anomers of nucleosides (*N*-nucleoside **101**) with both diastereo- and enantiomeric purity of >99%.

α,α′-Alkylation of Dioxanone Hydrazones. The asymmetric α,α′-bisalkylation of dioxanone SAMP-hydrazones is another valuable synthetic approach. The method was used as a key asymmetric transformation in the diastereo- and enantioselective synthesis of pseudo-C_2-symmetric, 2-methyl-substituted, acetonide-protected diols **104** (Scheme 15). Hydrazone **102** was made by iterative diastereoselective α,α′-bisalkylation. Ozonolytic cleavage, followed by an epimerization-free Wittig olefination of the resulting ketone, and subsequent hydrogenation of the exocyclic methylene group in **103** using either the Adams ($PtO_2 \cdot H_2O$) or Wilkinson catalyst afforded the acetonide-protected 1,3-diols **104** in very good overall yields and with virtually complete stereoisomeric purity (de ≥ 96%, ee ≥ 98−99%). Quantitative

Scheme 16



removal of the acetonide protection with trifluoroacetic acid in THF/water led to the free pseudo-C_2-symmetric diols **105**.[141]

A diastereoselective SAMP-hydrazone α,α′-bisalkylation/deoxygenation protocol was effective for making the *anti*-1,3-diol moiety (intermediate **106a**, R^3 = Ph, X = $CH_2SO_2(CN_4)Ph$) which was used in the asymmetric synthesis and also in a formal asymmetric synthesis of (+)-strictifolione (**107**; Scheme 15). A Julia−Kocienski olefination was used as the key step to create the *E*-configured alkene.[131]

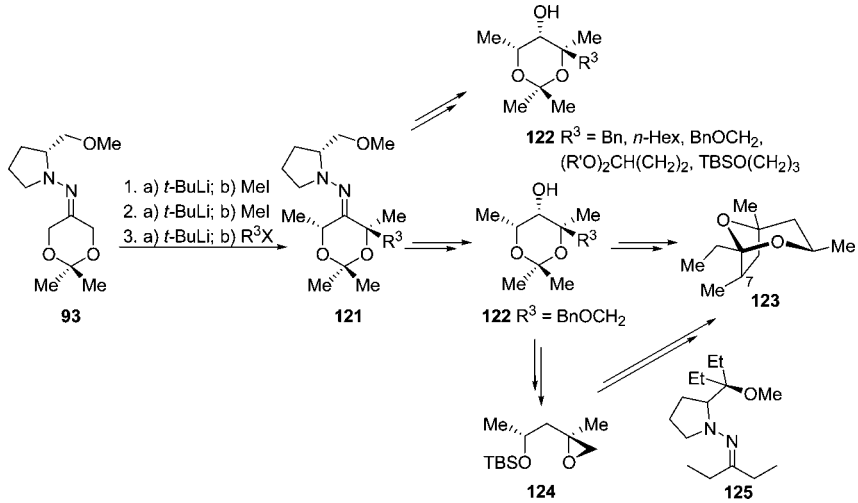
The α,α′-bisalkylation of SAMP-hydrazones, combined with Sharpless asymmetric dihydroxylation, was applied as a key stereoselective step in the convergent, asymmetric total synthesis of attenol A (**108**; from intermediate **106b**, R^3 = $CH_2CH{=}CH_2$, X = CH_2I; Scheme 15) and attenol B. The attenols, which possess challenging structures and interesting biological activities, were prepared, as a 6.3:1 mixture, in 15 steps, with good overall yield (19%) and high stereoselectivity (de, ee ≥ 96%).[142]

The above-described methodology for the synthesis of 2-methylenated 1,3-diols, and a homogeneous hydrogenation, was used for the asymmetric synthesis of δ-lactones such as prelactone B (**112a**, R^3 = *i*-Pr) and V (**112b**, R^3 = Me; Scheme 16). This time the synthesis was based on consecutive α,α′-bisalkylation of RAMP-hydrazones of dioxanones using alkyl iodides and *tert*-butyl bromoacetate as the key steps. The ketone group resulting from the hydrazone cleavage with oxalic acid (under two-phase conditions) was converted via Wittig reaction into a methylene group, giving a bisalkylation product, **111** (R^4 = CH_2COO-*t*-Bu), analogous to **103**. Acidic acetonide hydrolysis concomitant with lactonization (TFA/DCM/water) provided, after diastereoselective iridium-catalyzed hydrogenation (Crabtree's catalyst [$Ir(cod)(PCy_3)(py)PF_6$]), the lactones **112** in moderate yields and excellent diastereo- and enantiomeric purities (>98%).[143]

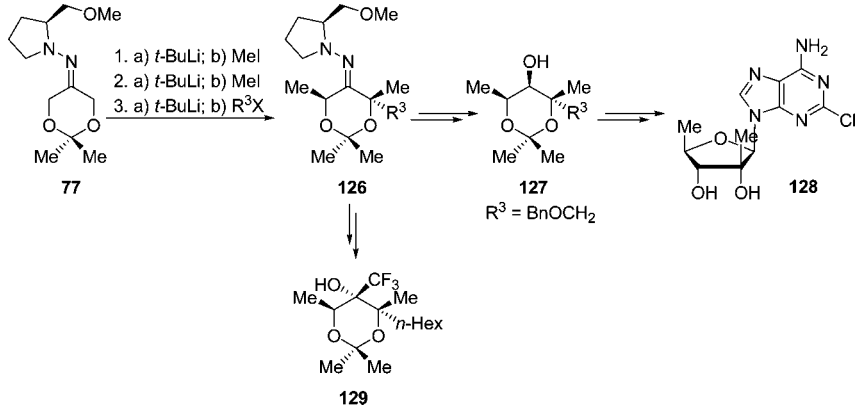
All stereoisomers of the 2-deoxypentoses and the 2,6-dideoxyhexoses can be synthesized from 2-phenyl-1,3-dioxan-5-one RAMP-hydrazone by α-alkylation with allyl bromide or α,α′-bisalkylation with allyl bromide and methyl iodide, respectively (Scheme 16).[144] Interestingly, the RAMP-hydrazone of the C_s-symmetric ketone formed one diastereomer, **109**, on equilibration by prolonged storage. The diastereomer **109** was monoalkylated, giving the product with the new α-alkyl group in the equatorial position with high selectivity. The second alkylation introduced the α′-alkyl group in the axial position, giving **110** (R^3 = Me, allyl; R^4 = allyl, Me). Aqueous ammonium dihydrogen phosphate hydrolysis of the hydrazone, followed by stereoselective carbonyl reduction, and ozonolysis of the allyl C=C, gave benzylidene-protected aldose or furanose **114**.[144] The deoxysugar diastereomers **114** were synthesized in the racemic form via the corresponding *N,N*-dimethylhydrazones.

The α,α′-bisalkylations of the RAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one **93** with elaborate alkyl halides (Scheme 16) were used also as strategic transformations in synthetic approaches to the total synthesis of the potent antitumor macrolides amphidinolide N (**115**) and caribenolide I (**116**).[145,146] The coupling of the dioxanone with alkyl iodide **118** and allylic bromide **117** through hydrazone alkylation processes (LDA, THF, −78 °C, alkylation time <1 h) generated the complete C6−C29 carbon framework of the target amphidinolide N. Subsequent hydrazone cleavage (saturated aqueous oxalic acid/Et_2O) produced the ketone intermediate in high stereoisomeric purity (dr >95:5 by ^1H NMR). Nonetheless, the intended fusion of the remaining C1−C5 part of the target onto the carbon framework of the obtained intermediate by metathesis-based methods was

Scheme 17



Scheme 18



fruitless. The C6−C29 skeleton of caribenolide I was prepared similarly through the sequential alkylation of hydrazone **93** with allylic bromide **120** (91% yield) and iodide **119**, giving, after hydrolysis (saturated aqueous oxalic acid/Et_2O), the highly functionalized ketone intermediate in 70% overall yield. Unfortunately, the transformed intermediate failed, at a later stage in the synthesis, to engage in the designed, cross-coupling reaction with other building blocks.

α,α′-Alkylation and α-Quaternization (α,α′,α-Alkylation and α,α′,α,α′-Alkylation). The triple alkylation of hydrazones is a further extension of the described bisalkylation, furnishing a challenging quaternary carbon unit. The trisalkylation sequence of 2,2-dimethyl-1,3-dioxan-5-one RAMP-hydrazone (**93**) was successful for the asymmetric synthesis of the acetonide-protected 2-keto-1,3-diols and 1,2,3-triols **122** (Scheme 17) bearing a quaternary stereogenic center. The three stereogenic centers were generated by sequential α-alkylation, ozonolytic hydrazone cleavage, and stereoselective reduction of the resulting ketones with L-Selectride. The products were obtained in good yields and high diastereomeric and enantiomeric excesses (de, ee ≥ 96%).[147]

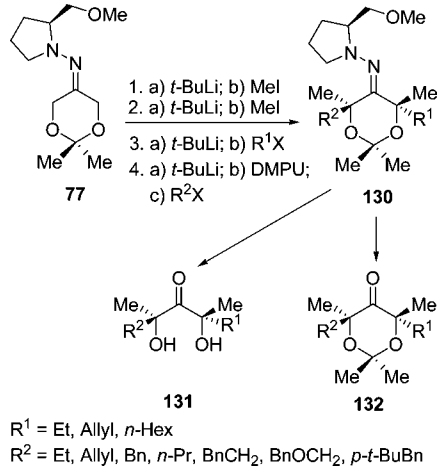
Another triple α-alkylation of the 2,2-dimethyl-1,3-dioxan-5-one RAMP-hydrazone allowed for the construction of the two stereogenic centers of (1*S*,3*R*,5*R*,7*S*)-(+)-sordidin (**123**; Scheme 17) and 7-*epi*-(1*S*,3*R*,5*R*,7*R*)-(−)-sordidin, both components of the natural male-produced aggregation pheromone of the banana weevil (*Cosmopolites sordidus* (Germar)). Another key step of the synthesis, diastereoselective alkylation via epoxide ring-opening of **124,** employed the azaenolate of 3-pentanone SAEP-hydrazone (**125**) as the nucleophile. Subsequent acidic intramolecular acetalization provided the sordidin *C*7-epimers (separable by preparative GC) in good overall yield (39%) as a 1.5:1 diastereomeric mixture. Each of the epimers could be obtained in high diastereomeric and enantiomeric purity (de ≥ 97%, ee ≥ 98% by preparative GC).[148]

The trisalkylation methodology was extended to the reaction of hydrazone **77** with methyl iodide and hexyl bromide, leading to **126** (R^3 = Hex). This was transformed to the trifluoromethylated alcohol **129**, with two neighboring quaternary stereocenters, in good yield (77%) and very good diastereo- and enantiomeric excesses (de 96%, ee 98%, Scheme 18).[132]

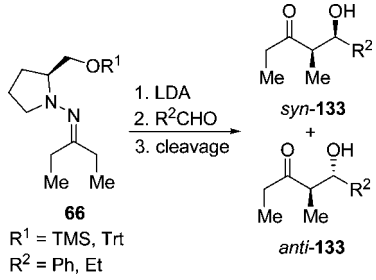
Starting from 2,2-dimethyl-1,3-dioxan-5-one, two nucleosides (potential adenosine receptor agonists), 4′-*epi*-trachycladines A (**128**) and B, were synthesized in 14 steps employing the triple α,α′,α-alkylation (α,α′-alkylation and α-quaternization) of SAMP-hydrazones (Scheme 18). Removal of the chiral auxiliary from the trisubstituted dioxanone SAMP-hydrazone, and subsequent reduction, gave the corresponding alcohol, which could be transformed over four steps into TBS-protected 2′-*C*-methyl-5′-deoxy-L-lyxose. The trachycladines were then obtained in an overall yield of 18−21%.[149]

The ultimate extension of the alkylation methodology toward the assembly of two quaternary α-carbon atoms of a hydrazone has been demonstrated in the asymmetric synthesis

Scheme 19



Scheme 20

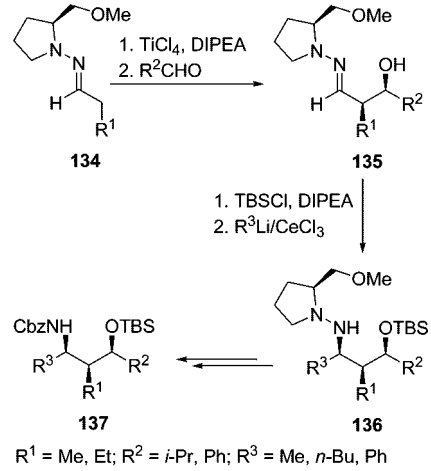


of 1,3-dihydroxy-2-ketones **131** (Scheme 19).[150] The ketones, bearing two quaternary stereocenters in the α- and α′-positions, were made starting from 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazone (**77**) by four consecutive α- and α′-lithiation/alkylation procedures. The last lithiation was carried out in the presence of DMPU additive. Ozonolysis of **130** gave the acetonide-protected 1,3-dihydroxy-2-ketones **132**, albeit in low yields (25−31%) with high diastereoselectivity (de ≥ 96% by ^{13}C NMR). The low yields were attributed to the high steric hindrance caused by the two quaternary carbon atoms. Acidic cleavage of **130** with 6 M aqueous HCl/pentane in a two-phase system (typically requiring a few days) removed both the chiral auxiliary and the acetal function (acetonide protection), providing 1,3-dihydroxy-2-ketones **131** in moderate to very good overall yields (14−61%) and with high stereomeric purity (de ≥ 91−97%, ee ≥ 96%).[150]

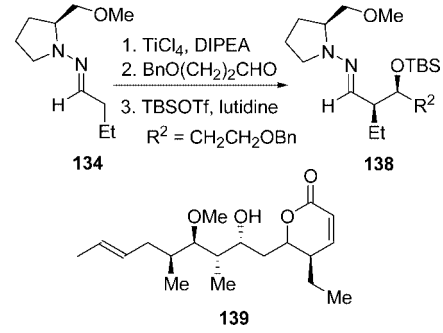
6.3. Aldol Reactions

The conditions optimized for the generation and alkylation of azaenolates of **66** (see the section on alkylation),[33] which gave rise to the highest level of stereoselection (LDA, toluene, −78 °C, 86% ee), were also applied for the aldol addition reactions of azaenolates with benzaldehyde and propionaldehyde. The diastereoselectivities of the processes were determined by proton NMR of the *syn*/*anti*-**133** (R^2 = Ph, Et, Scheme 20) mixtures, after in situ hydrazone hydrolysis (Amberlyst, acetone/water). The optimized hydrazone (R^1 = TMS) for the aldol reaction between diethyl ketone and propionaldehyde gave an *anti*-isomer (de 37%). Both isomers had an ee of 83−84%.[33] The same reaction with benzaldehyde gave predominantly the *anti*-product **133** (de 24%). In this case the *anti*-isomer had an ee of 77% and the *syn*-isomer an ee of 69%. Overall the reaction results

Scheme 21



Scheme 22

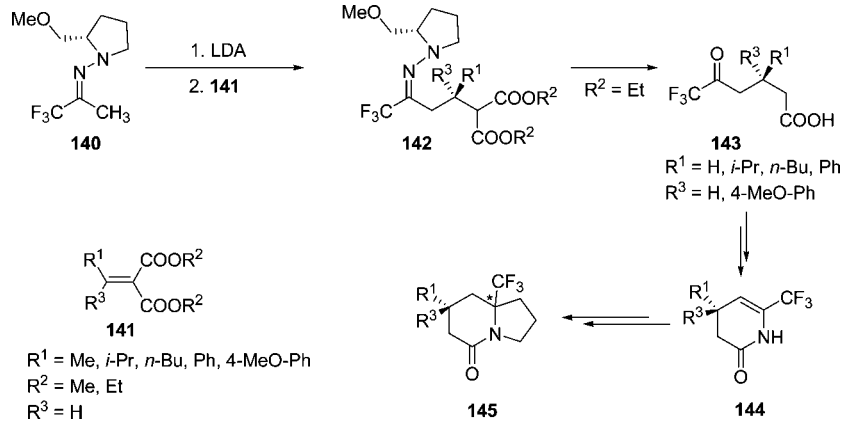


(yields 37% for propionaldehyde and 77% for benzaldehyde) were moderate but should be treated as a starting point for further investigations.

A titanium tetrachloride-mediated azaenolate aldol reaction, combined with subsequent 1,2-addition of organocerium to aldehyde hydrazone, was effective for a diastereo- and enantioselective synthesis of all-*syn*-configured, *N*,*O*-protected 1,3-amino alcohols **137** (Scheme 21).[151] The titanated SAMP-hydrazone was obtained as a deeply red DCM solution by reaction with titanium tetrachloride and diisopropylethylamine (DIPEA, Hünig's base) at −78 °C. Subsequent reaction with aldehydes afforded preferentially the *syn*-aldol-like products (β-hydroxyhydrazones) in good yields and with good diastereoselectivities (de 72−77% by ^{13}C NMR). The protection of hydroxyl with TBS allowed for enrichment of the major diastereomer (de 83% to ≥96%). Overall, the four-step synthesis gave the protected amino alcohols **137** with moderate to good overall yields (18−58%) and high diastereomeric (de 78% to ≥96%) and enantiomeric (ee ≥96%) excesses.[151]

The *syn*-selective asymmetric aldol reaction of titanium azaenolates of SAMP/RAMP-hydrazones **134** with benzyl-protected 3-hydroxypropanal was also used in an approach to the convergent, asymmetric, total synthesis of pironetin (**139**), a polyketide with immunosuppressive, antitumor, and plant-growth-regulating activities.[152] The TBS-protected product **138** (Scheme 22) was obtained in good yield (80% over two steps). The diastereoselectivity was moderate (de 55%) but could be boosted to de ≥ 96% through HPLC enrichment. The synthesis of the natural product (*ent*-**138** was used) required, in addition to the azaenolate aldol reaction, a Mukaiyama aldol reaction, an asymmetric α-alkylation (diethyl ketone SAMP-hydrazone with (*E*)-crotyl bromide,

Scheme 23



LiTMP, −110 °C, THF), and a ring-closing metathesis as other key steps.

6.4. Michael Reactions

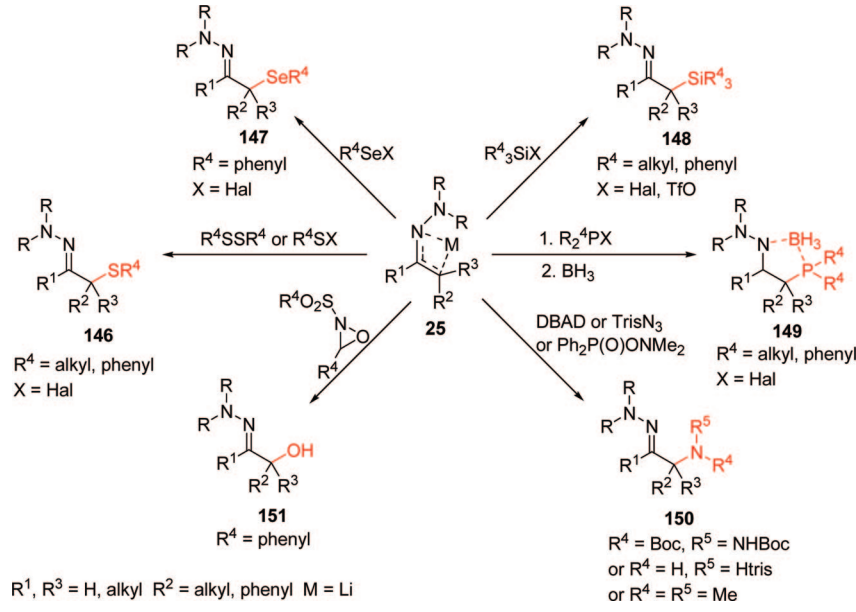
The asymmetric Michael addition of lithiated trifluoroacetone SAMP-hydrazone (**140**) to alkylidenemalonates **141** allowed the synthesis of indolizidinones **145** (Scheme 23).[153a] The addition gave products **142** in good yields (64−84%) and with variable diastereoselectivity (dr from 56:44 to 92:8). Acidolytic cleavage of the hydrazone (H_2SO_4 in formic acid), concomitant with ester hydrolysis and decarboxylation, gave enantiomerically pure keto acids **143**, which were cyclized to dihydropyridinones. Further *N*-iodopropylation, followed by radical cyclization, gave optically active trifluoromethylated indolizidinones.[153a] Some α,*β*-unsaturated hydrazones reacted unexpectedly (likely via Michael-type addition) with dimethyl oxoglutaconate (MeOOC−CH═CH−CO-COOMe) giving functionalized dihydropyrans.[153b]

7. Reactions of Azaenolates with Electrophiles: Carbon−Heteroatom Bond Formation

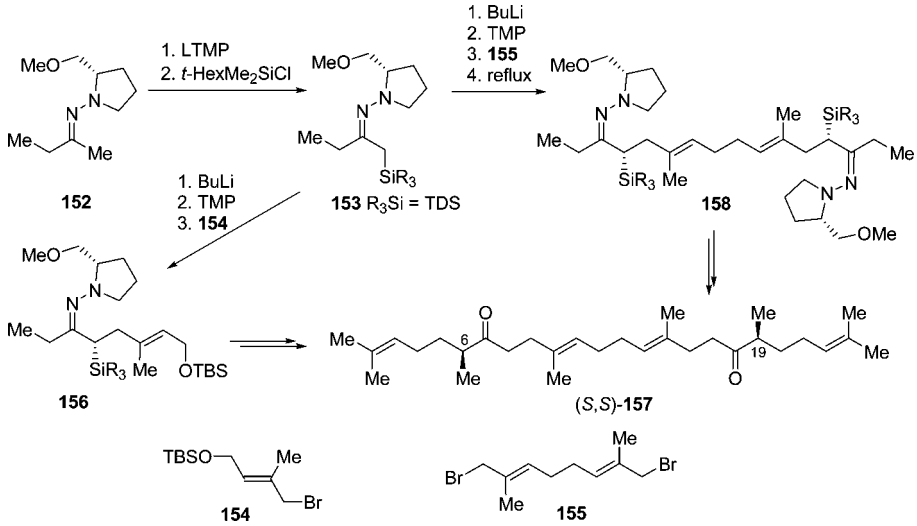
Known, synthetically useful, C−heteroatom bond forming reactions of α-metalated hydrazones **25** (Scheme 24) include α-sulfenylation with disulfides[154] or benzenesulfenyl chloride (product **146**), selenylation with benzeneselenenyl bromide (product **147**),[155] α-phosphinylation[156] with borane-protected chloro-disubstituted phosphane (product **149**), α-amination with $TrisN_3$,[157] di-*tert*-butyl azodicarboxylate (DBAD),[157] or (diphenylphosphinyl)(*N*,*N*-dimethylamino)hydroxylamine (product **150**), α-hydroxylation with oxaziridines (product **151**),[158] and α-silylation with silyl triflates or chlorosilanes to form **148**.[159] α′-Silyl enol ethers of α-silyl ketones obtained from **148** are useful reagents for regio- and enantioselective Mannich reactions (electrophile $Bn_2NCH_2OCH_3$ with $BF_3 \cdot Et_2O$).[160]

In recent years, hydrazones have been used, among other things, for the introduction of heteroatoms in the α-position of ketones and aldehydes. The α-silyl hydrazones, and the corresponding carbonyl compounds, were synthesized in ways analogous to α-alkylation (lithiation with lithium amides or alkyllithiums with subsequent addition of 2,2,6,6-teramethylpiperidine) and reaction with silyl electrophiles such as chlorides or triflates. The introduction of a removable silicon substituent, which expresses stereodirecting or activating properties ("traceless directing group"), is often advantagous from a synthetic strategy point of view (so-called "silyl trick"). Earlier applications (before the year 2000) of silyl ketones made by the SAMP/RAMP-hydrazone methodology to stereocontrolled synthesis have been sum-

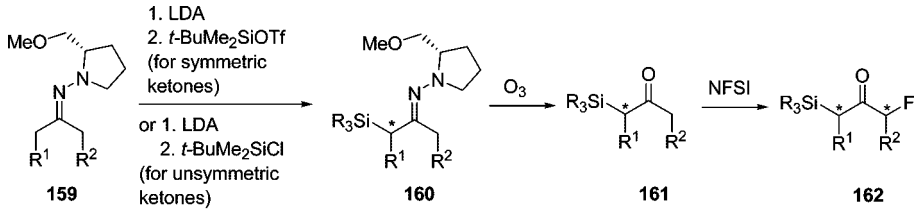
Scheme 24



Scheme 25



Scheme 26



unsymetric ketones: R^1 = Me, Et, Bn; R^2 = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, Bn
symmetric ketones: $R^1 = R^2$ = Me, Et, *n*-Pr, $(CH_2)_3$, $(CH_2)_4$, $CH_2N(Bn)CH_2$

marized in a paper.[161] The α-heterosubstituted aldehydes made by the SAMP/RAMP-hydrazone methodology could be used in further asymmetric reactions, e.g., in the Mukaiyama aldol addition, giving excellent *anti*-selectivities.[162]

The temporary introduction of a thexyldimethylsilyl blocking group was used in an elegant asymmetric synthesis of the diketotriterpenoid **157** (Scheme 25),[163] which was isolated from the Indonesian marine sponge (*Hyrtios erectus*). Starting with silylation and alkylation of butanone SAMP-hydrazone (**152**) with the appropriate allylic bromide **154**, the enantiomer of the natural product (*S*,*S*)-**157** was obtained in low overall yield (4%) due to inefficiency of one of the last steps (reductive coupling of allylic alcohols by $TiCl_3/LiAlH_4$). Alternatively, generation of both stereogenic centers at the C6 and C19 positions of the C_2-symmetrical molecule **157** and dimerization with dibromide **155** were effected via α-alkylation of SAMP/RAMP-hydrazones. Finally, the racemization-free, hydrazone cleavage, combined with desilylation ($CuCl_2$ or oxalic acid), allowed for the synthesis of both enantiomers in good overall yields (56%) and with high asymmetric inductions (de, ee ≥ 96%). The absolute configuration of the natural material was determined as *R*,*R* owing to the known absolute stereocontrol by the SAMP/RAMP-hydrazone alkylation.[163]

The α-silylation (Me_2(Thex)SiCl), followed by α-alkylation (MeI) of SAMP-, RAMP-, and DMH-hydrazones of acetaldehyde or acetone, allowed for the synthesis of both enantiomers and the racemic form of organosilicon odorants.[164]

Analogous, temporary α-silylation of SAMP-hydrazones of simple cyclic and acyclic ketones **159** was used to obtain enantiopure α-silyl ketones **161** (ee > 98%, Scheme 26). Subsequent regio- and diastereoselective electrophilic fluorination of the α-silylketones **161,** using *N*-fluorobenzosulfonimide as the fluorinating agent, gave α′-fluorinated products **162** (de 37% to ≥98%). An almost quantitative, racemization-free cleavage of the silyl directing group with a buffered mixture of fluorides (HF, Bu_4NF, NH_4F, KH_2PO_4 in THF/water) gave α-fluoroketones in good yields (88−99%) and high enantiomeric excesses (ee 87−96%).[165]

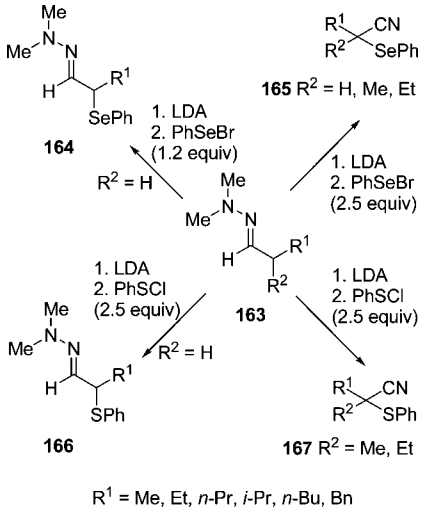
Some enantiomerically pure α-silyl ketones **161**, prepared via the above-described SAMP/RAMP-hydrazone methodology, were used in regio- and enantioselective Mannich reactions for the preparation of α-substituted *β*-amino ketones.[166]

α-Silyl dioxanones, made by silylation of dioxanone RAMP-hydrazones, have found similar synthetic applications.[167,168]

Interestingly, α-phenylselenenylation of lithium *N*,*N*-dimethylhydrazone azaenolates, formed in the reaction of LDA with linear aliphatic aldehyde hydrazones **163**, led to α-phenylselenenyl hydrazones **164** (R^2 = H) when 1.2 equiv of phenylselenenyl bromide was used (Scheme 27). However, when excesses (2.5 equiv) of the base and of PhSeX (X = Cl, Br) were used, phenylselenenyl nitriles **165** were formed. Hydrazones of α-branched aldehydes ($R^2 \neq$ H) also gave nitriles **165**. SAMP-hydrazones reacted analogously, albeit providing the corresponding nitriles in racemic form. The reactions of linear aldehyde hydrazones with PhSCl in place of PhSeBr led to α-phenylsulfanyl hydrazones **166,** but α-branched aldehyde hydrazones again gave nitriles **167**.[155]

The asymmetric formation of the carbon−heteroatom (Si, P, S) bonds was also possible via *ortho*-lithiation in the enantioselective synthesis of planarly chiral 1,1′-bisbenzoylferrocene and diferrocenyl ketone derivatives (Schemes 10 and 11).[125−127]

Scheme 27



8. Reactions at the Azomethine Carbon with Electrophiles

8.1. Typical Reactions of Formaldehyde and Higher Aldehyde Hydrazones (Prior to 2000)

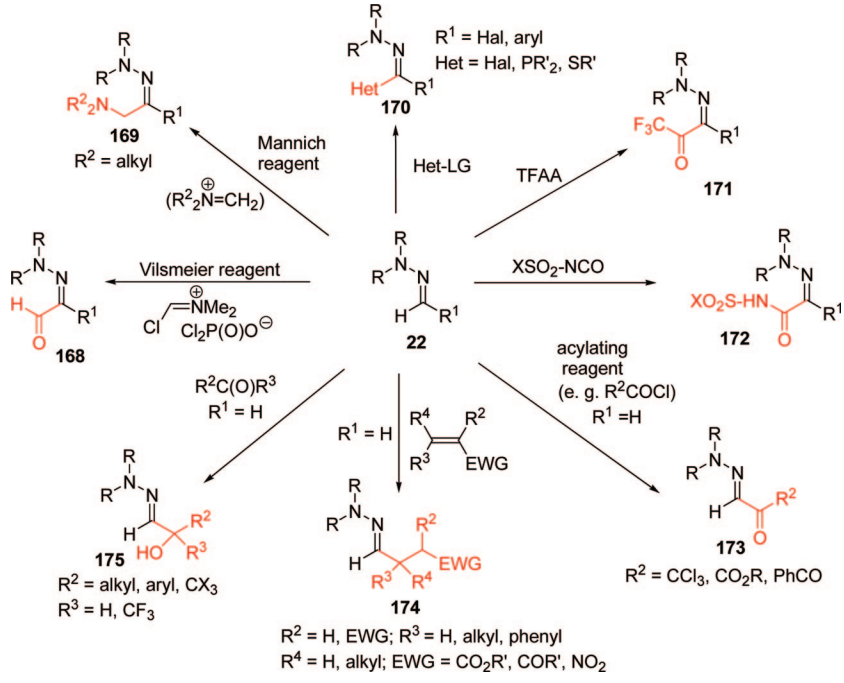
Direct reactions on the second nucleophilic site of hydrazones **22** (the azomethine carbon) with active electrophiles (Scheme 28) can be combined with further hydrazone transformations. The overall process, in which hydrazones (especially formaldehyde hydrazones) act as nucleophilic acyl (and nitrile) equivalents, can be used for the preparation of aldehydes, nitriles, and 1,2-dicarbonyl compounds. The applications of this useful synthetic methodology have been recently reviewed.[9,169]

Hydrazones (derived from DMH, diisopropylhydrazine, *N*-aminopyrrolidine, SAMP, or SAMP analogues) of formaldehyde and some higher aldehydes (saturated, unsaturated, or aromatic aldehydes) react with a multitude of reagents including Vilsmeier-type formylating reagent (product **168**), Mannich aminomethylating reagent ($CH_2{=}NR_2^+X^-$) or Böhme reagent ($(CH_2)_5N{=}CH_2^+Cl^-$) (product **169**), bromine (giving geminal dibromo hydrazones), Ph_2PCl/Py (phosphorylation), *p*-nitrophenylsulfenyl chloride (sulfenylation) to form corresponding products **170**, TFAA (in the presence of 2,6-lutidine or pyridine, trifluoroacetylation, product **171**), and sulfonyl isocyanates (e.g., $TsSO_2N{=}C{=}O$, product **172**).[9,169] Reactions known for formaldehyde hydrazone *only* include acylation with milder reagents (to form **173**), e.g., acetyl chloride, ethyl chloroglyoxylate, and trichloroacetyl chloride, and reactions with other electrophilic reagents, e.g., chloral and trifluoromethyl substituted phthalazine. Other known reactions of formaldehyde hydrazones are additions to Michael acceptors (to form **174**), alkylidenemalonates, α,β-unsaturated ketones, α,β-unsaturated lactones, nitroalkenes, or activated cyclic alkenes with two electron-withdrawing groups. The reactions on the nucleophilic azomethine carbon of formaldehyde hydrazones with aldehydes (e.g., *n*-BuCHO, CyCHO, and PhCHO) are also possible but require the Lewis acid promoters (product **175**). The same reactions with more active aldehydes, Cl_3CCHO, $(TBS)OCH_2CHO$, may be run without the promoters. Other reactions with α-amino aldehydes, with carbohydrate-derived aldehydes (to give α-hydroxy hydrazones); with trifluoromethyl ketones (to give α-hydroxy-α-(trifluoromethyl) hydrazones) are also known. In some of the additions, the electrophiles also required activation by Brønsted acid or Lewis acid catalysts.[169]

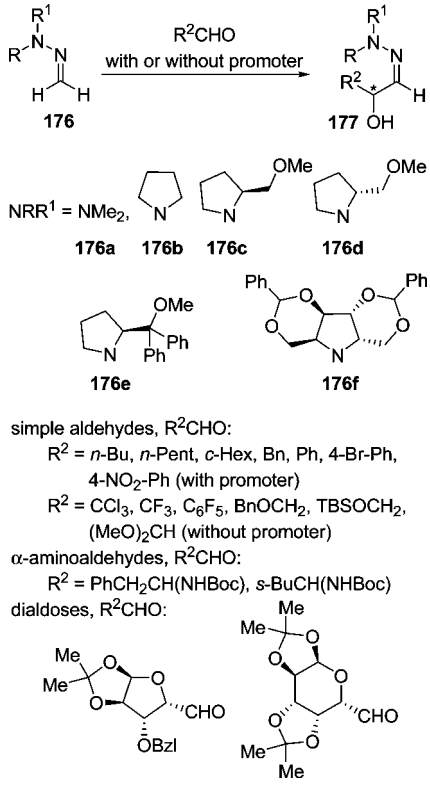
8.2. 1,2-Addition of *N,N*-Dialkylhydrazones to Aldehydes

The known reactions on the azomethine carbon of aldehyde hydrazones **176b**,**c** and **176e**,**f** have been extended to aldehydic electrophiles. The $ZnCl_2$- or Et_2AlCl-promoted 1,2-addition of achiral and chiral formaldehyde *N*,*N*-dialkylhydrazones to simple aldehydes afforded the corresponding α-hydroxy hydrazones **177** (Scheme 29).[170] More reactive aldehydes reacted without the addition of promoters. Reac-

Scheme 28



Scheme 29



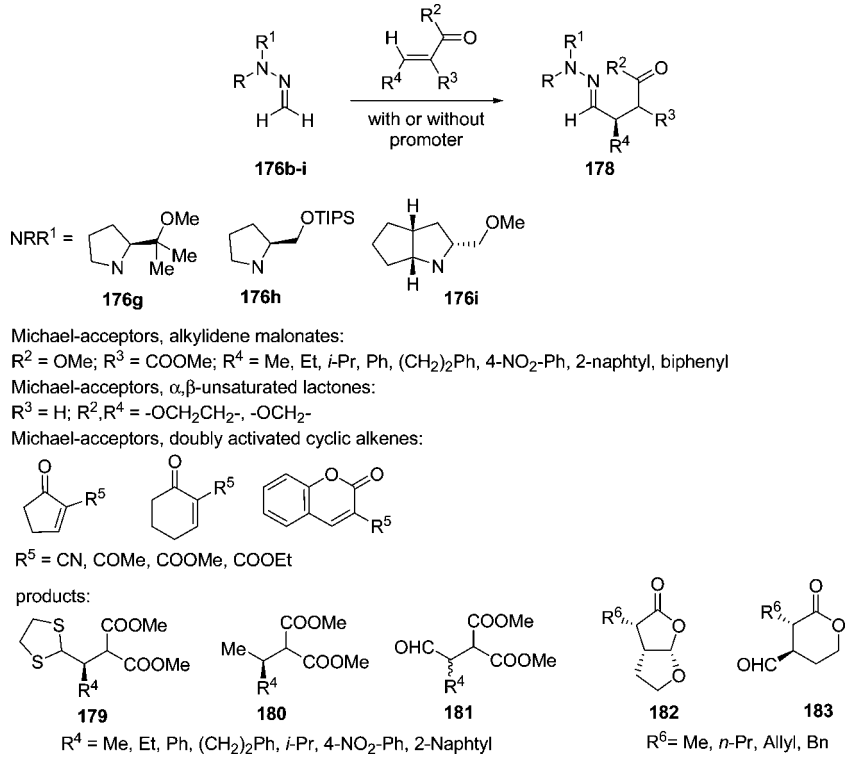
tions of SAMP-hydrazone (**176c**) and the D-mannitol-derived hydrazone afforded the corresponding adducts with low stereoselectivity and as inseparable mixtures of diastereomers, albeit in high yields. Application of the formaldehyde hydrazone of (*S*)-1-amino-2-(methoxydiphenylmethyl)pyrrolidine (SAPP, **176e**) gave chromatographically separable mixtures of diastereoisomers, also in good yields. Thus, the chiral hydrazone acted in this process as a resolving agent allowing for the preparation of enantiomerically pure adducts.

Similarly, 1,2-addition of formaldehyde *N,N*-dialkylhydrazones such as DMH-hydrazone (**176a**), *N*-aminopyrrolidine hydrazone (**176b**), and SAMP/RAMP-hydrazone (**176c**,**d**) to carbohydrate-derived α-alkoxy aldehydes took place under neutral conditions and in the absence of promoters (Scheme 29).[171] The corresponding α-hydroxy hydrazone products were obtained in fair to good yields (38−80%) and with high *anti*-diastereoselectivities (dr from 79:21 to >98:2). The same addition reaction of formaldehyde *N*-aminopyrrolidine hydrazone (**176b**) to *N*-Boc-protected α-amino aldehydes (Boc-leucinal and Boc-phenylalaninal) provided the corresponding adducts in good yields and diastereoselectivity (75% and 82%, dr 78:22 and 85:15, respectively). A variety of interesting molecules including α-homologated carbohydrates, cyanohydrins, or hydroxy-β-(aminocarbonyl) compounds could be accessed upon subsequent manipulation of the hydrazone functionality following known procedures.

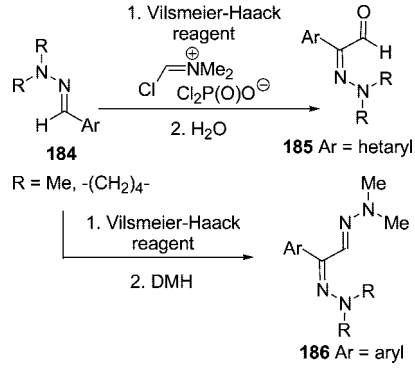
8.3. Michael Reactions

The Michael addition of formaldehyde hydrazones **176c**−**i** (Schemes 29 and 30) to aliphatic and aromatic alkylidene malonates was investigated.[172] The addition of SAMP- and SAPP-hydrazones (**176c** and **176e**) in the presence of MgI_2 (mild Lewis acid) afforded Michael adducts **178** corresponding to **179**−**181** (Scheme 30) in excellent yields (70−98%) and good diastereoselectivities (68−79%). Subsequent ozonolysis, or direct $BF_3 \cdot OEt_2$-catalyzed thiolysis of the hydrazone C=N bond, gave the corresponding aldehyde **181** or dithioketals **179** in enantiomerically enriched form (ee 68% to >98%).[173] Additional dithioketal desulfurization (Raney Ni, ultrasound) to give **180** or decarboxylation was also possible. In the series of aromatic aldehyde hydrazones, diastereomerically pure (de > 98%) major Michael addition products (*S*,*S*)-**178** were obtained in good yields (77−93%) after chromatographic purifications.[172]

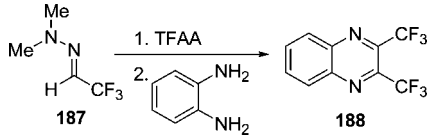
Scheme 30



Scheme 31



Scheme 32



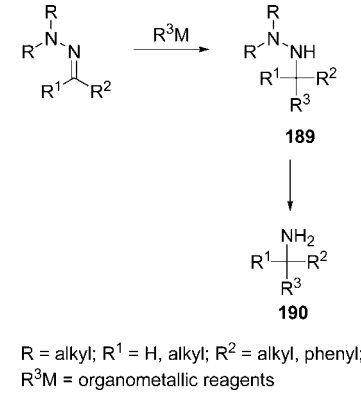
The Michael addition of formaldehyde SAMP-hydrazone (**176c**) to 5,6-dihydro-2*H*-pyran-2-one (α,β-unsaturated lactone) under neutral conditions, followed by *trans*-selective α-alkylation, was used in the asymmetric synthesis of α-substituted β-formyl δ-lactones **183** (de ≥ 98%, ee 80−95%) and 4-substituted furofuran lactones **182** (de ≥ 98%, ee 80% to >98%). The final products were obtained in acceptable overall yields by cleavage of the auxiliary, using ozonolysis or a hydrolytic domino reaction.[174]

The same nucleophilic conjugate addition of chiral SAMP- and SAPP-hydrazones of formaldehyde (**176c** and **176e**) to doubly activated cyclic alkenes was reported to afford the corresponding Michael adducts **178** (Scheme 30) in variable yields (71−97%) and selectivities (dr from 1.3:1 to 5:1). The reactions of achiral hydrazone **176b** were also tested. Major isomers could be chromatographically purified. The reactions took place either with or without the presence of MgI_2 (mild Lewis acid) depending on the type of substrate.[175] Further reactions, i.e., hydrazone cleavage and carbonyl transformations, provided access to ketones, acetals, thioacetals, and nitriles.

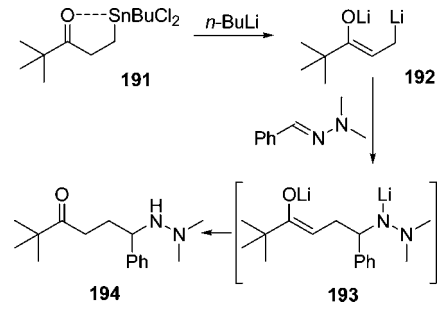
Related reactions of 1,3-disubstituted 1*H*-pyrazole-4-carbaldehyde *N*,*N*-dimethylhydrazones with the Vilsmeier−Haack reagent have been investigated.[176] The electrophilic substitution reactions of the hydrazone azaenamine at the azomethine C-atom yielded the 1,4,5-triazapentadienium salts, hydrolysis of which gave 2-hydrazono-2-(1*H*-pyrazol-4-yl)ethanals **185** (Scheme 31). The same reactions of substituted benzaldehyde *N*,*N*-dialkylhydrazones (DMH-hydrazones and *N*-aminopyrrolidine hydrazones) gave 1,4,5-triazapentadienium salts that reacted with *N*,*N*-dimethylhydrazine to give (1*E*,2*Z*)-2-(*N*,*N*-dialkylhydrazono)-2-phenylethanal *N*,*N*-dimethylhydrazones **186**.[177]

Reaction on the azomethine carbon was also used for the synthesis of a heterocyclic nucleus. A key reaction in a sequence leading to 2,3-bis(trifluoromethyl)quinoxaline (**188**; Scheme 32) was the reaction of trifluoroacetaldehyde *N*,*N*-dimethylhydrazone (**187**) with TFAA followed by reaction with *o*-phenylenediamine and cyclization.[178]

Scheme 33



Scheme 34



9. Nucleophilic Additions to N,N-Dialkylhydrazones

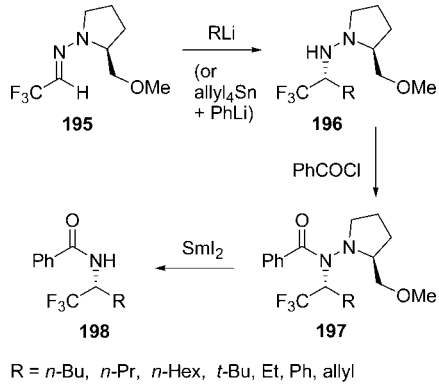
9.1. Reactions of Hydrazones with Organometallics

The nucleophilic 1,2-addition of various organometallics, including organocerium, organomagnesium, organolithium, organoytterbium (e.g., $RLi/YbCl_3$), and organobarium compounds, and (TMS)CN to the C═N group[1,179,180] can be used for the preparation of many hydrazines **189** and amines **190** (Scheme 33). This methodology, combined with other reactions of hydrazones, mostly chiral SAMP-hydrazones, is successful for the preparation of chiral amine natural products.[1] The diastereoselectivity of the 1,2-addition to SAMP analogue hydrazones have been studied by Denmark (see reactivity characteristics).[32] Syntheses of indolizidine, pyrrolidine, and piperidine alkaloids based on stereoselective 1,2-addition of organometallics to the C═N bond of SAMP/RAMP-hydrazones have been described by Enders.[181] The nucleophilic addition of organometallics to C═N double bonds combined with Raney Ni or samarium iodide cleavage of the hydrazine bond is widely used in the synthesis of amines, including bioactive chiral amines.

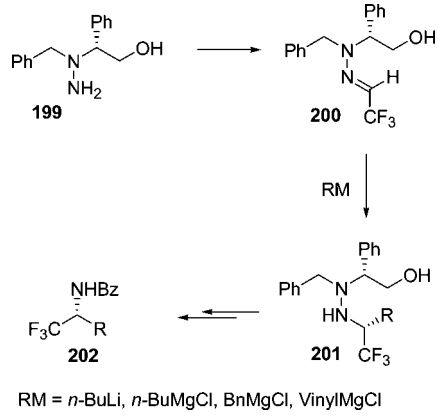
The addition reaction of dilithiated ketones **192** (ketone dilithio α,β-dianions prepared from β-(dichlorobutyl)stannyl ketone **191** with *n*-BuLi) to the DMH-hydrazone of benzaldehyde to give lithium (*Z*)-enolates containing a lithium hydrazone amide, **193** (Scheme 34), was recently reported.[182] The addition to the C═N bond took place selectively at the β-position of the dianion. Quenching (water) or trapping ((TMS)Cl) of the enolate resulted in racemic γ-hydrazino ketone **194** or the silyl enol ether of **194**, respectively (74% yield for both reactions).

The asymmetric version of the 1,2-addition was almost exclusively realized with the SAMP-hydrazones. For example, efficient asymmetric synthesis of α-trifluoromethyl-

Scheme 35



Scheme 36

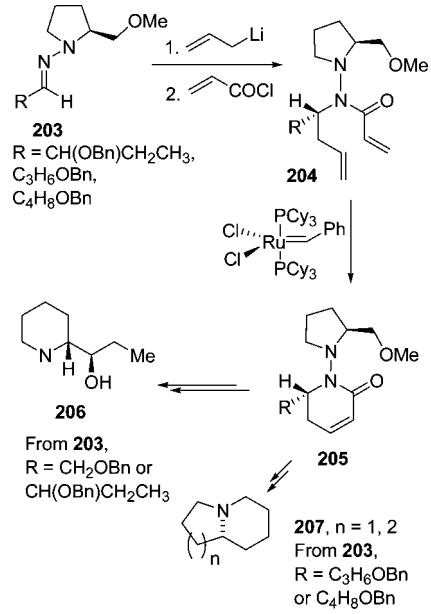


substituted primary amines (usually isolated as amides) was possible via 1,2-addition of alkyllithium reagents (including allyllithium) to trifluoroacetaldehyde SAMP- or RAMP-hydrazones **195**.[183,184] The addition gave hydrazines **196**, which in turn were benzoylated and transformed into chiral amines via SmI_2-promoted N−N bond cleavage (Scheme 35). Reaction of trifluoroacetaldehyde SAMP- or RAMP-hydrazone **195** with alkyllithiums resulted in the hydrazines in good yields (48−79%) and good to excellent diastereoselectivities (72−98%). However, the reaction with phenyllithium gave low yield (15%) but good de (86%, after chromatography 88%). The subsequent benzoylation (PhCOCl, DMAP, Et_3N or *n*-BuLi, PhCOCl) and cleavage (SmI_2, THF/DMPU) produced the *N*-benzoyl α-trifluoromethylated amides (R = alkyl) usually in good yields (71−95%) and enantioselectivities (97−99%).[183] The allylation reaction with an achiral morpholine-derived hydrazone was also investigated; yields varied from 0% to 62%.[184] The approach via the oxidation of chiral α-trifluoromethylated homoallylamines was also effective for the synthesis of *β*-amino aldehydes, carboxylic acids, and esters.[185]

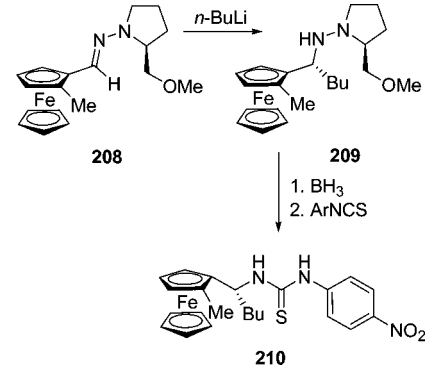
Very high diastereoselectivity (>98% de) was also reported in an analogous addition reaction of organolithium and Grignard reagents to trifluoroacetaldehyde hydrazone **200** derived from (*R*)-*N*-benzylphenylglycinol (Scheme 36). The addition proceeded on the *Re* face of the chelated hydroxyhydrazone, providing, after hydrogenolysis, the (*R*)-α-trifluoromethylated amines **202**.[186]

An ingenious approach to the construction of chiral benzazepine derivatives[187] and cyclic alkaloid skeletons[188] was realized by the combination of a diastereoselective 1,2-addition and the ring-closing metathesis reaction. For example, the highly stereoselective 1,2-addition to benzyl-

Scheme 37



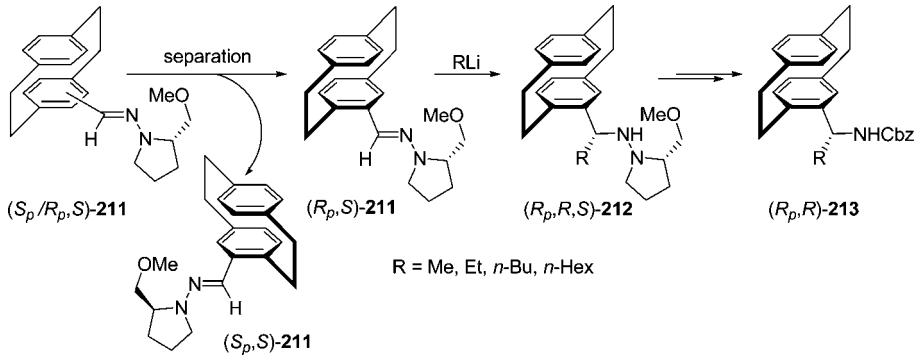
Scheme 38



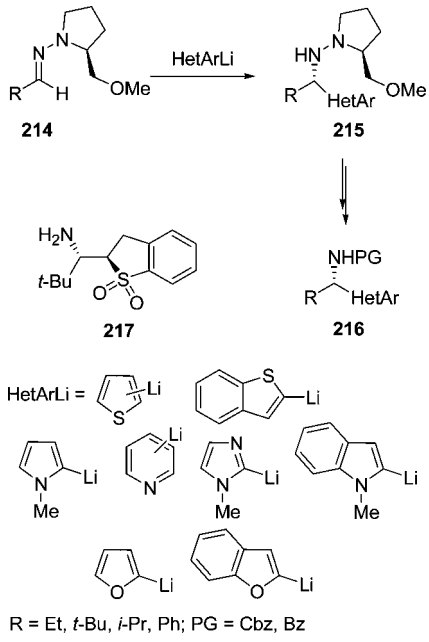
protected 4-hydroxybutyraldehyde or 5-hydroxypentanal SAMP-hydrazones (Scheme 37), combined in a one-pot reaction of the directly resulting lithium hydrazide with acryloyl chloride, gave hydrazine derivatives **204**. A ring closure metathesis of **204** with the first-generation Grubbs catalyst, $Cl_2Ru(=CHPh)(PCy_3)_2$ (or the second-generation catalysts[189]) gave lactams **205**. The intermediates **205** could be transformed to chiral bicyclic lactams and further to (−)-coniceine[188b] (**207**, $n = 1$) in high enantiomeric purity. The analogous 1,2-addition, acryoylation, and metathesis on benzyl-protected 2-hydroxybutyraldehyde SAMP-hydrazone as the starting material provided intermediate **205**, which was used for synthesis of the enantiomerically pure piperidine alkaloid (+)-*β*-conhydrine[188a] (**206**). In these syntheses the N−N bonds were cleaved either reductively (BH_3/THF) with simultaneous lactam reduction[188a] or oxidatively (MMPP).[188b]

The planar chirality of ferrocenes bearing hydrazone groups (SAMP-hydrazone **208** or analogous RAMP-hydrazones and *N*-aminopyrrolidine-derived hydrazones, Scheme 38) competes with the typically excellent stereocontrol of diastereoselectivity afforded by the chiral auxiliaries (SAMP, RAMP) in the nucleophilic addition to the C=N hydrazone bond (dr 24.3:1 for matched pair, 2.1:1 for mismatched pair, and 19.3:1 for the achiral *N*-aminopyrrolidine-derived hydrazone),[190] despite the fact that the chiral hydrazone auxiliary remained the dominant stereocontrolling element.

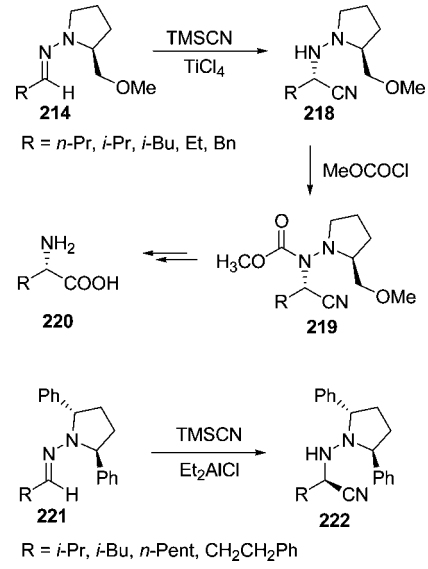
Scheme 39



Scheme 40



Scheme 41



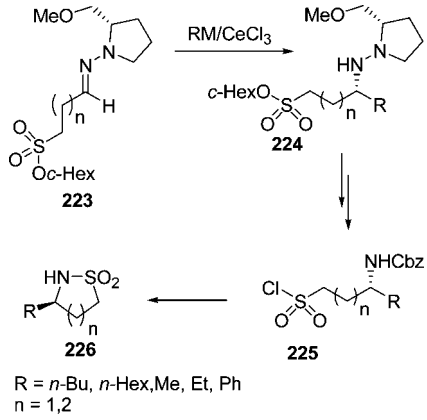
The nucleophilic 1,2-addition of alkyllithium reagents to SAMP/RAMP- or RAMBO/SAMBO-hydrazones of 4-formyl-[2.2]paracyclophane was a key reaction in the synthesis of all four possible stereoisomers of enantiopure and diastereomerically highly enriched, α-branched [2.2]paracyclophanylalkylamines (Scheme 39). The chiral SAMP/RAMP or RAMBO/SAMBO auxiliaries allowed chromatographic separation of the epimers **211**. Addition of alkyllithiums gave hydrazines **212**. Reductive N−N hydrazine bond cleavage, followed by treatment with benzyloxycarbonyl chloride afforded the *N*-Cbz-protected, virtually diastereo- and enantiopure (de, ee 99%), or diastereomerically enriched (de 89−96%), amines **213**.[191] A series of analogous reactions, but with DMH-hydrazones, which were prepared in enantiomerically pure form via chiral phase HPLC separation, was also reported.[192]

Similarly, an efficient enantioselective synthesis of α-(heteroaryl)alkylamines **216** by nucleophilic 1,2-addition of lithiated heteroarenes to aldehyde SAMP-hydrazones **214** was also described (Scheme 40).[193] As before, the hydrazine N−N single bonds were cleaved by SmI_2 or BH_3/THF, giving amines which were isolated in the form of the corresponding amide or urethane (Cbz or benzoyl) derivatives in good overall yields (40−78%) and again excellent enantiomeric excesses (ee 88−99%). Analogous addition reactions of 2-lithiobenzo[*b*]thiophene, followed by oxone oxidation and L-Selectride reduction, were used for the asymmetric five-step synthesis of heterocyclic β-aminosulfones—the α-(1,1-dioxo-2,3-dihydro-1*H*-1λ6-benzo[*b*]thiophen-2-yl)-substituted amines **217** (overall yields 23−49%, de > 96%, ee 88−99%).[194]

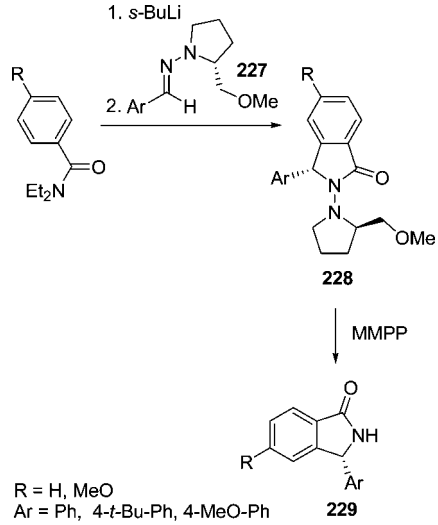
A related reaction, the asymmetric 1,2-addition of trimethylsilyl cyanide to aldehyde SAMP-hydrazones **214**, provided access to amino acids **220** (Scheme 41). The addition reaction required 2 equiv of titanium tetrachloride for activation of the imine bond. Methoxycarbonylation of the resulting hydrazine, and removal of the chiral auxiliary by action of MMPP (1 week at room temperature) followed by acid hydrolysis (6 M aqueous HCl), afforded the amino acids in high enantiomeric excesses (yields 60−98%, ee 94−97%).[195] The analogous cyanosilylation reaction of (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine-derived aliphatic hydrazones **221**, promoted by Et_2AlCl, afforded the corresponding hydrazinonitriles **222** with high diastereoselectivity (dr 91:9 to >99:1). The resolving properties of the auxiliary allowed chromatographic isolation of the adduct products in diastereomerically pure form (dr >99:1) and in good yields (80−84%).[196]

The classical, diastereoselective, nucleophilic 1,2-addition of various organocerium compounds to the C=N double bond of ω-SAMP-hydrazonosulfonates **223** was used as the key step in a flexible asymmetric synthesis of various 3-substituted γ- and δ-sultams **226** (Scheme 42).[197] The resulting hydrazines were obtained in good to excellent diastereomeric excesses (de 78−96%). Removal of the chiral auxiliary by reductive (BH_3/THF) N−N bond cleavage and

Scheme 42



Scheme 43

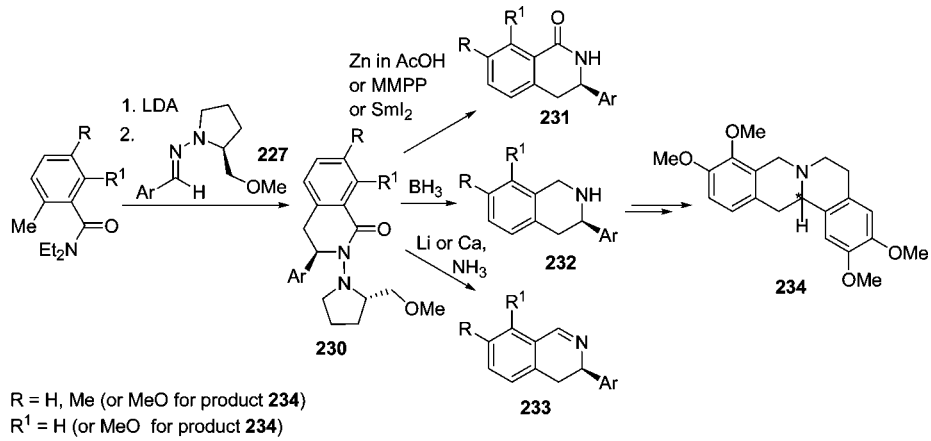


reaction with chloroformate afforded the corresponding *N*-protected aminosulfonates **225** without racemization. Hydrolysis of the sulfonic acid ester, and subsequent treatment of the free sulfonic acids with phosgene in toluene, led to the aminosulfonyl chlorides, which were cyclized to 3-substituted γ- and δ-sultams **226** in good to excellent overall yields (39−51%) and high enantiomeric excesses (ee 78−99%).

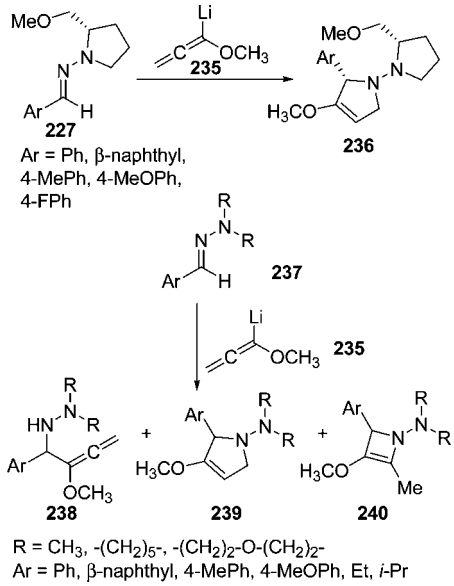
The 1,2-addition to C═N was combined with other reactions in a spontaneous reaction sequence. A tandem nucleophilic 1,2-addition and ring closure of SAMP- or RAMP-hydrazones, followed by oxidative cleavage of the auxiliary, was used for the asymmetric synthesis of 3-aryl-substituted 2,3-dihydro-1*H*-isoindol-1-ones **228** and **229** (overall yields 31−69%, ee ≥ 97%, Scheme 43)[198] and 3-substituted 3,4-dihydro-2*H*-isoquinolin-1-one **233** (Scheme 44). Addition of the ring-lithiated or methyl-lithiated diethylbenzamides (prepared by directed *ortho*-metalation) produced the lithiated hydrazines, which in turn reacted, in situ, in a substitution reaction with the amide group closing the five-membered (**228**) or six-membered (**230**) rings (yield 36−70%, de up to ≥96%). The hydrazine cleavage (oxidative with MMPP) gave the corresponding five-membered isoindolinones **229** (yield 83−97%, ee up to ≥99%), the six-membered dihydroisoquinolines **233** (Scheme 44, yield 23−67%, ee 0% to ≥96%), the dihydro-2*H*-isoquinolin-1-ones **231** (yield 14−93%, ee 0% to ≥96%), or the tetrahydroisoquinolines **232** (yield 35−85%, ee ≥ 97%). Depending on the specific hydrazine product, three different cleavage methods (Zn/AcOH, MMPP, or SmI_2) were used to give racemization-free N−N bond cleavage to amides **231** with varied degrees of success.[199] Other methods used were: BH_3/THF to give amine **232** and Li or Ca in liquid NH_3 to give imine **233**. The method based on borane cleavage was applied to the enantioselective synthesis of both enantiomers of a natural alkaloid belonging to the tetrahydroprotoberberine family—tetrahydropalmatine (**234**; ee 98%). The natural product (*R*)-(+)-**234** was obtained in seven steps in 9% overall yield, while the (*S*)-(−)-**234** isomer was prepared in 17% overall yield.[200]

An interesting addition of α-lithiomethoxyallene (**235**; prepared in situ by reaction of *n*-BuLi with methoxyallene in THF at −40 °C) to aromatic hydrazones **227** and **237** in THF, leading to *N*-(dialkylamino)-3-pyrrolines **236**, was also described (Scheme 45).[201] In the case of SAMP-hydrazones **227**, this reaction occurred with excellent stereoselectivity (de > 99%) and good yields (69−88%). The reaction with other hydrazones (**237**, dimethyl, piperidinyl, morpholinyl) gave, besides 3-pyrrolines **239**, azetidine byproducts **240** and the uncyclized intermediates α-allenyl hydrazines **238**. It was shown that formation of azetidines could, however, be reversible: at higher temperatures and longer reaction times, the azetidines transformed to 3-pyrrolines. The reaction in diethyl ether, instead of THF, stopped at the stage of addition and provided α-allenic hydrazines **238**.[202] In this case, cleavage of the N−N hydrazine bond could be effected under

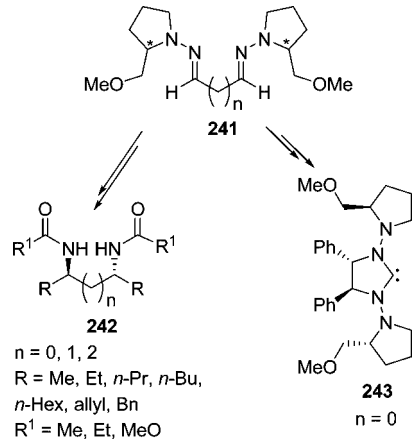
Scheme 44



Scheme 45



Scheme 46



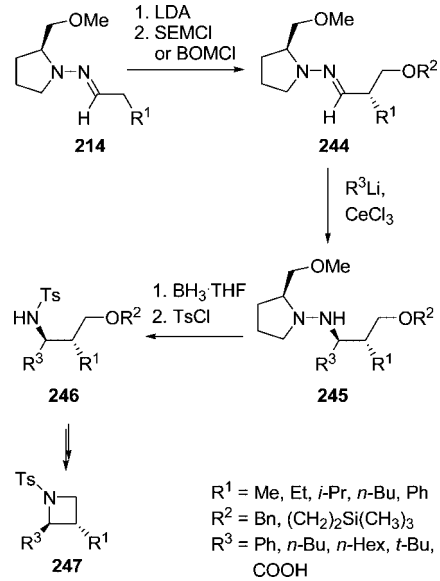
a variety of conditions, giving various products: chloroformate followed by Ni/H_2 gave a mixture of pyrrolines and pyrrolidines, *m*-CPBA gave pyrroles, and aqueous HCl gave aminopyrroles.

A double addition of organometallics to bishydrazones derived from SAMP/RAMP-hydrazines and dialdehydes is an interesting expansion of the methodology. Bis(SAMP-hydrazone)s (C_2-symmetric) of dialdehydes **241** also underwent nucleophilic 1,2-addition of organocerium reagents to the C═N double bond and, according to previously described typical procedures, gave amide-protected C_2-symmetric 1,*n*-diamines **242** in high diastereo- and enantiomeric purity (de 72−98%, ee 96−98%).[203] The addition of PhMgCl to the glyoxal bis(RAMP-hydrazone) **241** (Scheme 46) was used for the synthesis of stable *N*-heterocyclic carbenes **243**.[204]

9.2. α-Alkylation Combined with 1,2-Addition to the Hydrazone

The combination of α-alkylation of chiral aldehyde hydrazones (usually SAMP/RAMP-hydrazones) with subsequent diastereoselective 1,2-addition is an effective method for assembling two adjacent stereocenters. The procedure, which is typically followed by cleavage of the N−N bond of the resulting hydrazine, offers access to chiral

Scheme 47



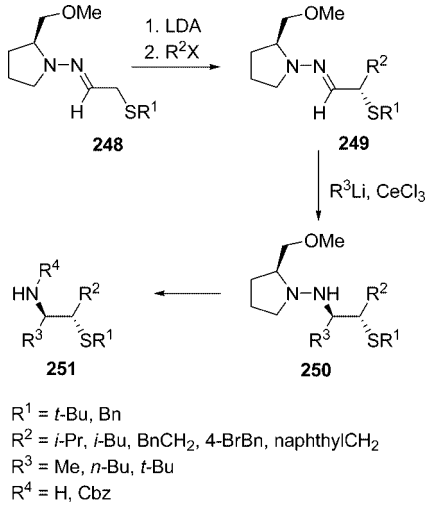
amines including tetrahydrobenzazepines,[205] disubstituted azetidines,[206] and piperidines.

The combination of α-alkylation with 1,2-addition allowed for the synthesis of 2,3-*trans*-disubstituted azetidines (Scheme 47)[206a] including 3-substituted azetidine-2-carboxylic acids (Scheme 47, R^3 = COOH).[206b] Alkylation of aldehyde SAMP-hydrazones **214** with SEM- or BOM-Cl was followed by nucleophilic 1,2-addition of various organocerium reagents to the hydrazone C═N double bond to give 1,3-hydrazino alcohols **245**. Epimerization-free reductive cleavage of the auxiliary with borane/THF, *N*-tosylation of the resulting amine, and cyclization under Mitsunobu conditions provided the corresponding *N*-tosylazetidines **247** in good yields (77−97%). Detosylation of the azetidine could be accomplished with sodium/naphthalene. The products were obtained with excellent diastereomeric (de 93−96%) and enantiomeric (ee 96%) excesses. The 2-phenylhydrazino alcohols **245** (R^2 = SEM, R^3 = Ph), obtained by addition of $PhLi/CeCl_3$, gave an azetidine that could be oxidatively transformed (oxidation of the phenyl group to the carboxyl group with $RuCl_3$, H_5IO_6, and $MeCN/CCl_4$/water at room temperature) into α-amino acid-type azetidine **247** (R^3 = COOH) with excellent stereochemical purity (de, ee 96%).[206b] In this case the phenyl moiety served as a synthetic equivalent of the carboxylic acid function.

The diastereoselective α-alkylation of α-*tert*-butyl- or α-benzylsulfanylated acetaldehyde SAMP-hydrazones with various electrophiles, and subsequent nucleophilic 1,2-addition of organocerium reagents to the hydrazone C═N double bond, was also used for the asymmetric synthesis of various protected *anti*-1,2-sulfanyl amines **251** bearing two adjacent stereogenic centers (Scheme 48). The resulting hydrazines **250** were again converted, by reductive N−N bond cleavage, to amines which were protected with the Cbz group before isolation or isolated directly. The products, again, had excellent diastereomeric and enantiomeric excesses (de, ee 96%).[207,208]

The unnatural enantiomer of the alkaloid α-conhydrine (**256**) was synthesized starting from a protected glycol aldehyde SAMP-hydrazone, **252**, via α-alkylation and 1,2-addition of alkyllithium reagent **254** (Scheme 49). After borane cleavage of the auxiliary and simultaneous acidic

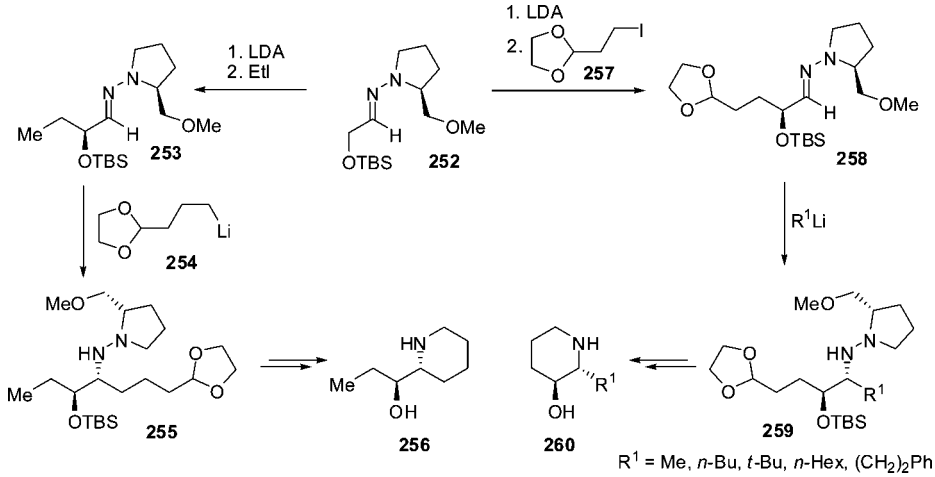
Scheme 48



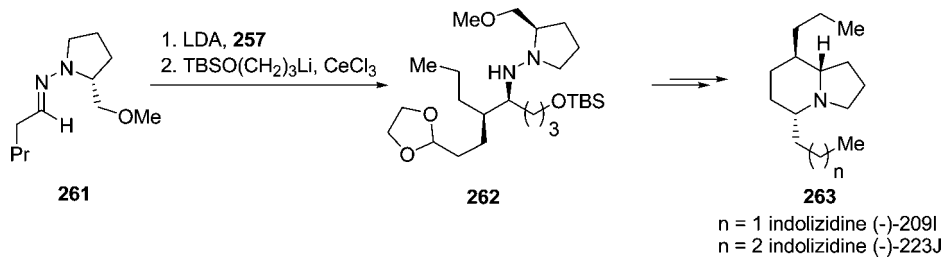
hydrolysis of the acetal, hydrolysis of the *tert*-butyldimethylsilyl ether and imine formation took place during acidic workup. The final alkaloid product **256** was obtained by imine reduction in moderate overall yield (21%) and with excellent diastereo- and enantiomeric excesses (de, ee > 96%).[209] Analogously, starting from the same protected glycol aldehyde hydrazone, the 2-substituted piperidin-3-ols **260** were also obtained in good overall yields (51−76%) and excellent diastereomeric and enantiomeric excesses (de, ee > 96%, Scheme 49).[210]

Similarly, the 1,2-addition of an organocerium reagent (made from [3-(*tert*-butyldimethylsiloxy)propyl]lithium) to an α-alkylated (alkylating reagent **257**, Scheme 49) *n*-pentanal RAMP-hydrazone, **261**, was used successfully for the synthesis of indolizidine alkaloids (−)-209I and (−)-223J and their *C*5-epimers with high stereoselectivity (de 96−99%, ee > 99%, Scheme 50).[211]

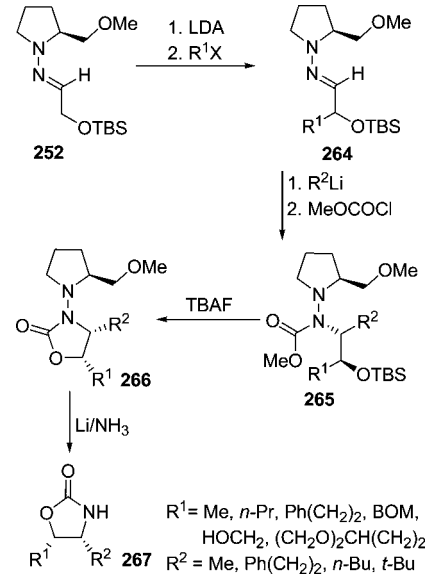
Scheme 49



Scheme 50



Scheme 51

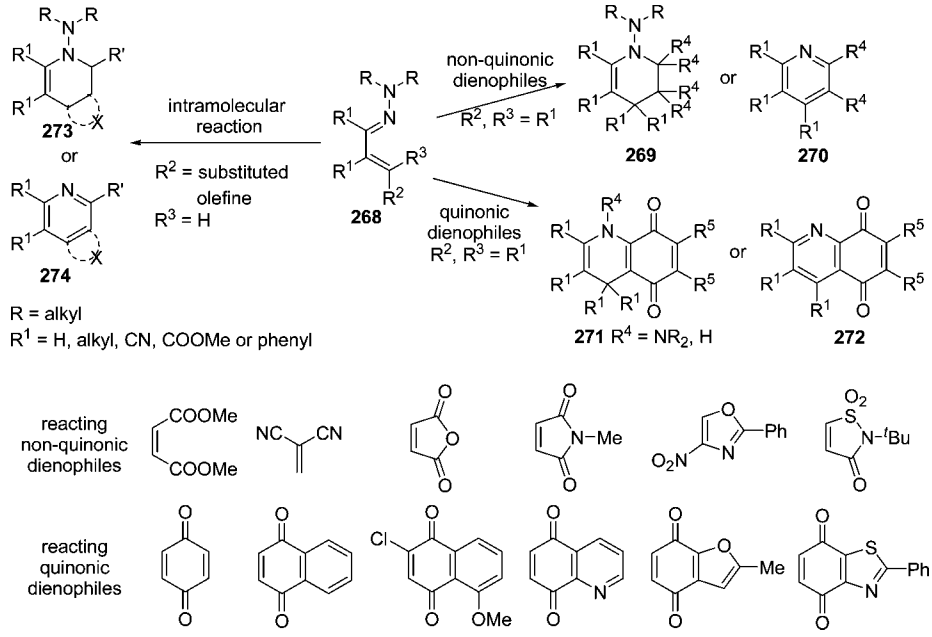


Following a four-step reaction sequence of α-alkylation, organolithium 1,2-addition (with later carbamate protection of the formed hydrazine), TBS-deprotective cyclization, and cleavage of the auxiliary, several *cis*-4,5-disubstituted oxazolidin-2-ones **267** (Scheme 51) were obtained in fair to good yields (27−78%) and in high diastereo- and enantiomeric purities (de 88% to >96%, ee > 96%).[212]

10. Formation of Heterocycles

The application of electrophilic and nucleophilic reactions toward the synthesis of heterocyclic structures is covered in the relevant sections of the review. Cycloaddition reactions, and carbene insertion reactions giving heterocycles, will be covered in this section.

Scheme 52



10.1. Hetero-Diels−Alder Cycloaddition

α,β-Unsaturated *N*,*N*-dimethylhydrazones (azadienes) react with electron-deficient dienophiles in [4 + 2] cycloadditions, building six-membered *N*-heterocyclic products (Scheme 52).[74,213] The reactions provide, depending on the reactants and reaction conditions, access to substituted pyridines and tetrahydropyridines, important azaheterocyclic frameworks useful for the synthesis of polycyclic alkaloids.[214,215] Depending on the reaction conditions, the cycloaddition (to give **269**, **271**, and **273**) may, or may not, be accompanied by spontaneous dimethylamine elimination (to form dihydropyridine structure), usually followed by aromatization, to form the pyridine nucleus (**270**, **272**, **274**). In the intermolecular version of the Diels−Alder reaction, active dienophiles, e.g., acrylate, isothiazole, maleimide, oxazoles, and quinone derivatives, were used with varying degrees of success (yields varied from <10% to >90%). The intramolecular version of the Diels−Alder cycloaddition reaction usually gives low to moderate yields (12−87%) of the cyclized products (**273**, **274**). The Diels−Alder reaction of a boronate-functionalized diene (4-boronato-1-azadiene), e.g., DMH-hydrazone or chiral hydrazone (SAMP analogues), can be combined with allylboration to form tandem aza [4 + 2]/allylboration reactions.[216]

More recently, the well-known [4 + 2] cycloadditions of *N*,*N*-dimethylhydrazones of α,β-unsaturated aldehydes acting as azadienes to dienophiles, described in the literature as aza-Diels−Alder (ADA reaction) or hetero-Diels−Alder (HDA reaction), were used as key steps in the syntheses of many marine alkaloids and other products with piperidine and pyridine skeletons. Figure 6 shows the main heterocyclic products synthesized by this approach, 9-(methoxycarbonyl)-7*H*-[1]benzothieno[4,5,6-*ij*][2,7]naphthyridin-7-one (**275**), an analogue of kuanoniamine A (marine alkaloid),[217] a regioisomer of the marine alkaloid meridine 9-hydroxybenzo[*b*]-pyrido[4,3,2-*de*](1,10)-phenanthrolin-8-one (**276**),[218] diazaquinomycin A (**277**),[219] dihydrofuroquinolinedione derivative **278**,[220] substituted 1,8-diaza-9,10-anthraquinone **279**,[221] 1,5-diazaanthraquinone derivatives **280**,[222,223] and tetracyclic compound **281**.[224]

The Diels−Alder reaction of **282** (Scheme 53) was the key transformation in the synthesis of analogues of the marine pyridoacridines meridine and ascididemin. Mixtures of diazaanthraquinones **284** and **285** (R^3 = Me, Scheme 53; the major isomer was **284**) were obtained by the reaction of different quinoline-5,8-diones and substituted *N*,*N*-dimethylhydrazones.[225] A series of tetracyclic compounds **286** and **287** were subsequently made by the action of dimethylfor-

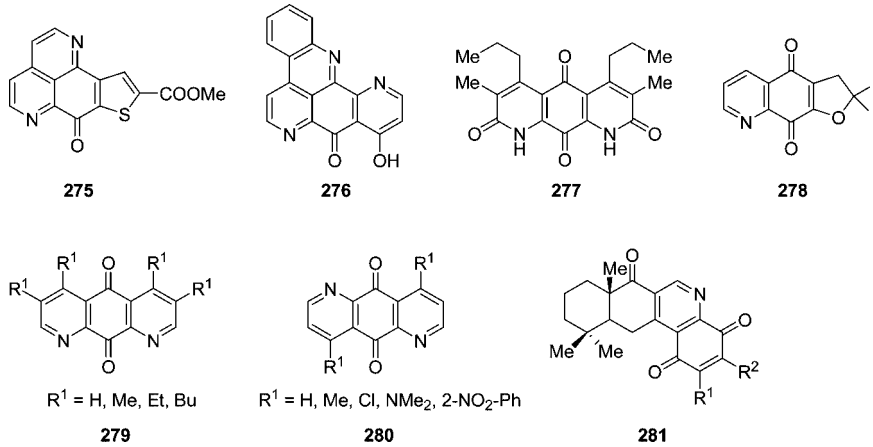
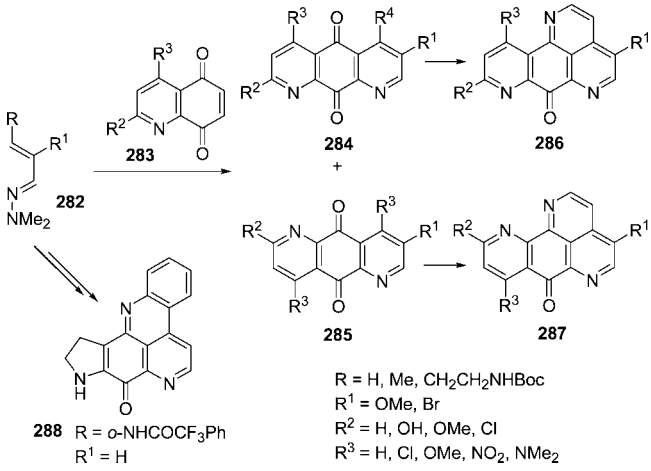


Figure 6. Selected heterocyclic products synthesized by aza-Diels−Alder reaction.

Scheme 53



mamide diethylacetate and cyclization. The alkaloid sebastianine A (**288**) and its regioisomer were prepared in analogous reactions of *N*-protected indole-4,7-diones with (trifluoroacetamido)cinnamaldehyde *N*,*N*-dimethylhydrazone[226] followed by cyclization. The β-unsubstituted α,β-unsaturated *N*,*N*-dimethylhydrazone (acroleine DMH-hydrazone) was also tested and typically gave a mixture of products **284** and **285** ($R^3 = H$).[227]

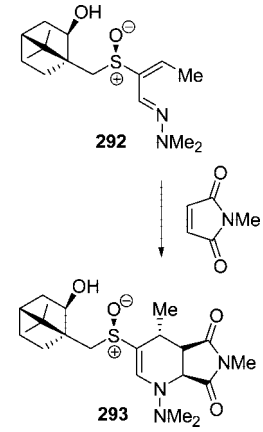
Notable examples of these new applications are the reactions of phosphorus, sulfur, and silicon substrates as azadienes. The hetero-Diels−Alder cycloaddition of the azadiene **289** with *N*-phenylmaleimide or an excess of diethyl acetylenedicarboxylate (Scheme 54) gave the phosphorylated pyridine derivatives **290** (yield 37%) and **291** (yield 63%), respectively. The substituted pyridine **291** resulted from two subsequent [4 + 2] additions of two substituted acetylene molecules to **289**.[228] The substrate for the reaction, 3-phosphinyl-1-aza-1,3-butadiene **289**, was obtained in the reaction of *N*,*N*-dimethylformamide dimethyl acetal with (hydrazonoalkyl)phosphine oxide.

The Wittig-type reactions of saturated β-phosphorylated hydrazones can provide azadiene substrates for the hetero-Diels−Alder reactions.[229]

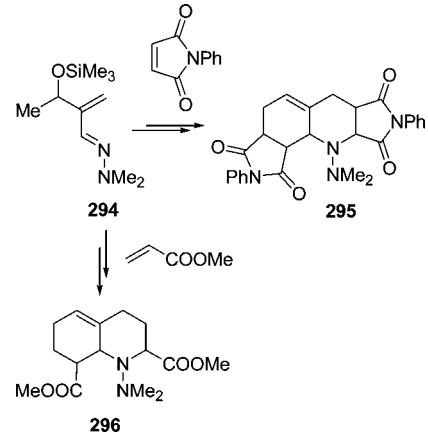
Despite constraints of unfavorable diene configuration, (R_S,*E*,*E*)-2-[(1*S*)-isoborneol-10-sulfinyl]-2-butenal *N*,*N*-dimethylhydrazone (**292**; Scheme 55) acted as 1-azabuta-1,3-diene in a reaction with *N*-methylmaleimide, giving a cycloadduct (**293**) in 20% yield and with total *endo*-selectivity and facial selectivity.[230] Enantiopure, sulfinyl α,β-unsaturated hydrazones were prepared by addition of isoborneolsulfenic acid—the chiral auxiliary—to the corresponding alkynyl hydrazones, or by reaction of the chiral sulfenic acid with an alkynyl aldehyde or ketone, and subsequent hydrazone formation with H_2NNMe_2.

A cascade of two subsequent Diels−Alder cycloaddition reactions of the *N*,*N*-dimethylhydrazone of α-[(trimethylsilyl)oxy]alkylacrolein (**294**) with an excess of *N*-phenylmaleimide or methyl acrylate as the dienophile was reported to

Scheme 55



Scheme 56



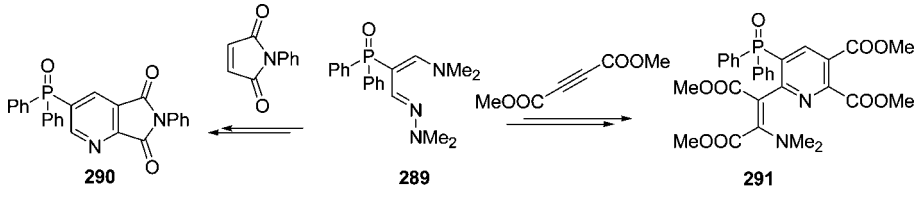
give heterocyclic compound **295** or **296** with good yields (75−80%, Scheme 56).[231,232]

An implementation of the HDA reaction that demonstrates its powerful synthetic utility is the intramolecular formation of multiple cyclic structures. For example, a double intramolecular hetero-Diels−Alder reaction of α,β-unsaturated hydrazones **297** was applied to the synthesis of 2,2-bipyridines **298** (Scheme 57).[233]

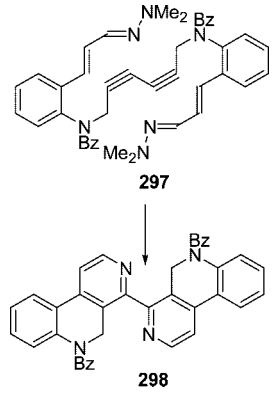
10.2. Staudinger-like [2 + 2] Cycloaddition

The [2 + 2] Staudinger-like addition of ketenes to formaldehyde,[234] alkyl aldehyde,[235] or benzaldehyde[236] *N*,*N*-dialkylhydrazones (regarded as *N*-amino-substituted imines) can be used to synthesize β-lactam rings (azetidin-2-one rings). The ketene substrates (benzyloxy)ketenes **299**[236] and α-aminoketenes (glycine derivative **300**[237] or oxazolidinone derivative **301**[238]) were made in situ through the reaction of acid chlorides with tertiary amines or via the corresponding acids, with 2-chloro-*N*-methylpyridinium iodide as the activating agent in the presence of Et_3N or DIPEA (Scheme 58). Simple achiral hydrazones, DMH- and *N*-aminopyrrolidine-derived, typically gave good yields (57−84%). Chiral

Scheme 54



Scheme 57



hydrazones such as SAMP-hydrazones, their analogues SAEP (**302d**) and **302e**, chiral hydrazones from C_2-symmetrical hydrazines, e.g., (2*S*,5*S*)-2,5-dimethylpyrrolidine (**302f**), (2*S*,5*S*)-2,5-diphenylpyrrolidine (**302g**), and **302h** were all used to produce stereoselectively β-lactam hydrazides **303**−**305**. There was no diastereoselectivity for the addition of the chiral SAMP-hydrazone of formaldehyde; however, the diastereoselectivity was good to excellent for more sterically demanding auxiliaries (e.g., for SAEP de 64−98% and for C_2-symmetrical hydrazone **302h** de 98%).[234] Yields of the additions ranged from 57% to 96%. The addition of formaldehyde hydrazones to ketenes formed only *C*3-substituted β-lactams (4-unsubstituted azetidin-2-ones). Higher aldehyde hydrazones gave disubstituted (substituted in positions C3 and C4) β-lactam rings. In general, the best stereoselectivities were observed for C_2-symmetric auxiliaries, in particular for the (2*S*,5*S*)-*N*-amino-2,5-dimethylpyrrolidine hydrazone of different aldehydes (Scheme 58, R^3 = *i*-Pr, *i*-Bu, $PhCH_2CH_2$, Ph) and (benzyloxy)ketene in the presence of Et_3N in toluene at 60−100 °C, where *cis*-3*R*,4*S*-products **303** were obtained with excellent diastereoselectivity (typically *cis*:*trans* = 99:1, yield 67−97%).[236] Interestingly, the use of the same aldehyde hydrazones and glycine derivative **300** with DIPEA base in toluene at 80 °C resulted in the *trans*-(3*R*,4*R*)-product in good yield (59−74%) and diastereoselectivity (*cis*:*trans* = 99:1).[235] The use of (benzyloxy)acetaldehyde hydrazone under the same conditions produced a 54:46 mixture of *trans* and *cis* products. It was found that the *cis*-product dominated (99:1) at both room temperature and 40 °C. The *trans*-product predominated at higher temperatures (at 120 °C, *cis*:*trans* = 3:97).[237] An extension of this method, using a subsequent oxidative N−N bond cleavage reaction by MMPP[239] for selected cycloadducts (hydrazides), gave access to β-lactams.[234,235,238]

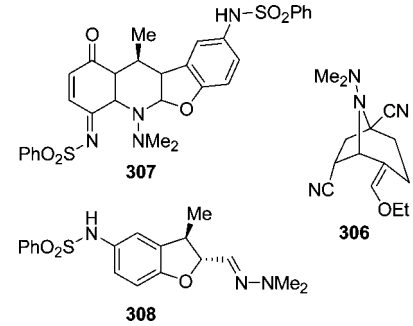
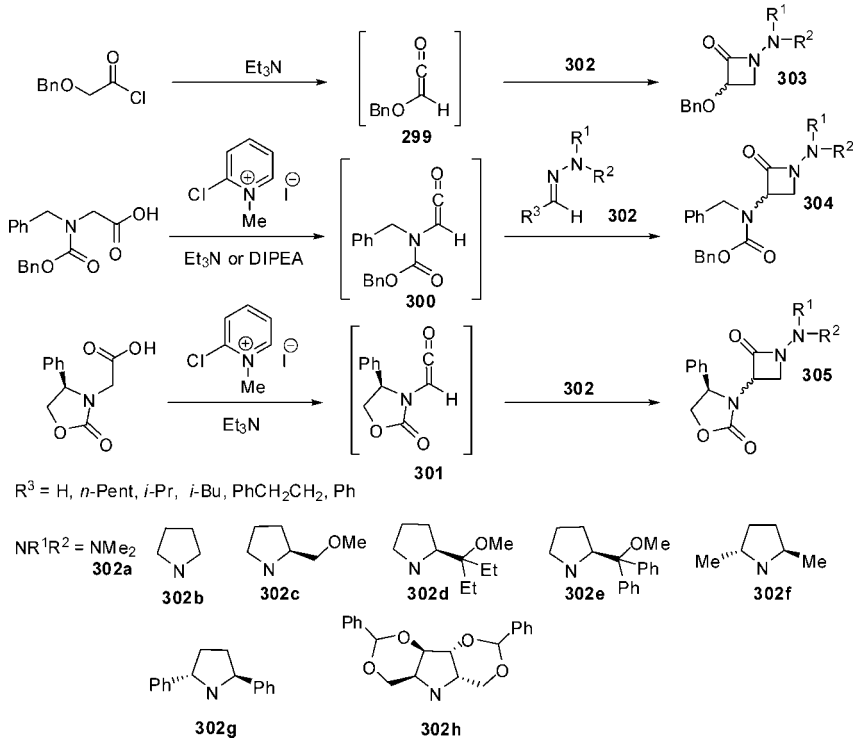


Figure 7. Adducts prepared in cascade cycloadditions.

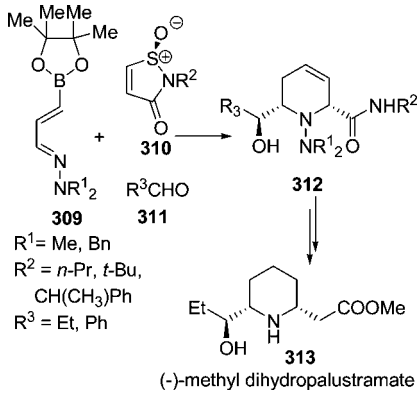
10.3. Miscellaneous Cyclization Reactions

Some cycloaddition reactions could be successfully combined in cascades, resulting in even more powerful synthetic transformations. For example, a [4 + 2]/[3 + 2] cascade cycloaddition of α-(diethoxymethyl)acrolein *N*,*N*-dimethylhydrazone to acrylonitrile gave bicyclic adduct **306** (Figure 7).[231,232] In this case, the product of the first [4 + 2] cycloaddition subsequently reacted with a second molecule of acrylonitrile, affording the [3 + 2] cycloaddition adduct **306** with good yield (80%).

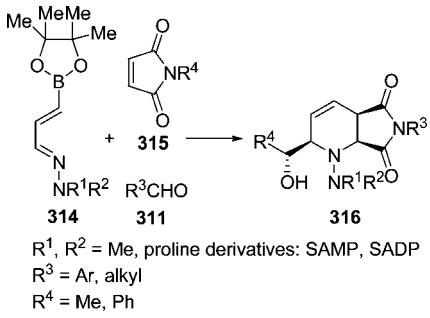
Scheme 58



Scheme 59



Scheme 60



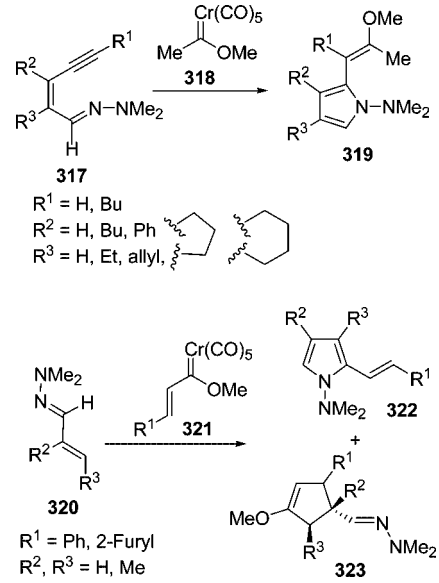
The analogous [4 + 2]/[3 + 2] cascade reaction of crotonaldehyde *N,N*-dimethylhydrazone and *p*-quinone monoimide gave the bicyclic adduct **307**.[240] Alongside cycloadduct **307** (yield 24%) the reaction produced 5-sulfonamido-2,3-dihydrobenzofuran **308** according to [3 + 2] cycloaddition only (yield of the major product 32%).

A three-component cascade of reactions, [4 + 2] cycloaddition, allylboration, and retro-sulfinyl-ene reaction of boronate-substituted unsaturated *N,N*-dialkylhydrazones with chiral sulfinimide **310** and an aldehyde, was reported to give 2,6-disubstituted *N*-(alkylamino)piperidines **312** (Scheme 59). This transformation was used in the total synthesis of dihydropalustramate **313**.[241−243]

Boronate-substituted, achiral or chiral, unsaturated *N,N*-dialkylhydrazones **314** (Scheme 60) were also used as dienes in tandem, multicomponent [4 + 2] cycloaddition/allylboration reaction with maleimides **315** and aldehydes **311**.[244] Polysubstituted α-(hydroxyalkyl)piperidines **316** were prepared in this way with good yields (39−80%) and good to excellent diastereoselectivities (80% to >95%). SAMP and its dimethyl analogue SADP were used for the enantioselective approach. The hydrazone substrates for the reaction were prepared from the pinacol ester of 3-acroleinboronic acid and achiral or chiral hydrazines.

Related syntheses use hydrazone azadienes and carbene complexes: the coupling reaction of enyne *N,N*-dimethylhydrazones **317** with Fischer carbene complexes **318** provided alkenylpyrrole derivatives **319** (Scheme 61). An alkyne insertion, followed by nucleophilic attack of the azomethine nitrogen at the intermediate alkenylcarbene complex, was suggested as a mechanism for the reaction.[245] An analogous reaction of Fischer alkenylcarbene complexes **321** with alkenyl *N,N*-dimethylhydrazones (1-amino-1-azadienes) **320** furnished substituted cyclopentenes **323** (45−55%) in a regio- and diastereoselective way, along with minor amounts of pyrroles **322** (25−28%). The diastereoselective modification of the reaction using enantiopure carbene complexes derived from (−)-8-phenylmenthol and (−)-8-(2-naphthyl)-menthol was investigated and showed preference for products of type **323** with face selectivity up to dr 96:4 (yields 25% and 43%).[246]

Scheme 61

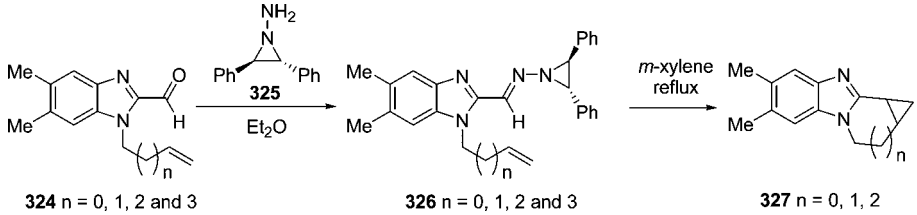


The carbene-generating thermolysis of the Eschenmoser hydrazones **326** (prepared in the reaction of aldehydes with 1-amino-*trans*-2,3-diphenylaziridine **325**, Scheme 62) was used for the preparation of cyclopropane rings fused to benzimidazole derivatives (**327**) and benzimidazolquinones, albeit in varied yields (11−85%).[247−249] The effectiveness of the process could be affected adversely by the formation of a carbene insertion byproduct.[249]

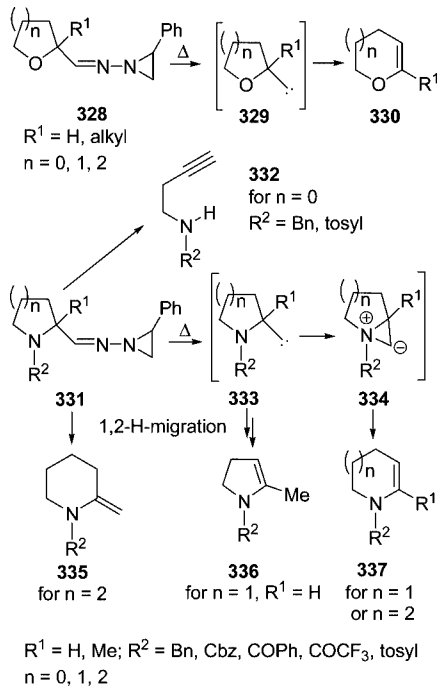
Similarly, carbenes generated thermolytically in refluxing toluene, from Eschenmoser hydrazones such as α-oxacyclo-*N*-aziridinylimines **328** and α-azacyclo-*N*-aziridinylimines **331** underwent ring expansions via the insertion of alkyl carbenes into carbon−carbon bonds and intramolecular ammonium ylide formation, respectively (Scheme 63). Competition with 1,2-hydrogen shift was observed and investigated. The ring expansion reaction of α-oxetanyl-*N*-aziridinylimines **328** ($n = 0$) involved alkylidenecarbene intermediates, whereas the reaction of α-azetidinyl-*N*-aziridinylimines **331** ($n = 0$) gave α-aminoacetylenes **332** (81% and 78% yield) via 1,2-migration of the hydrogen atom in alkylidenecarbene intermediates.[250] The thermal ring expansion reaction applied to five-membered rings **331** ($n = 1$) gave the six-membered ring structures **337** ($n = 1$, $R^1 = H$, 0−71% yield, Scheme 63) along with 1,2-H migration products **336** (0−60%). On the contrary, the thermal reaction of the six-membered substrates **331** ($n = 2$) afforded preferentially the migration products **335** (54−72% yield) with small amounts (0−19% yield) of the seven-membered ring expansion product **337** ($n = 2$, $R^1 = H$). The product distribution depended on the ring size and the nitrogen substituent R^2.

In addition, *N,N*-dialkylhydrazones may react to form cyclic products such as **338** and **339** (Figure 8). A β-keto ester *N,N*-dimethylhydrazone reacted in the presence of NaH with a cyclic, sugar-derived, epoxy triflate (*C*-alkylation) to form, after intramolecular in situ cyclization (*N*-alkylation) of a sodium azaenolate, the polyfunctionalized dihydropy-

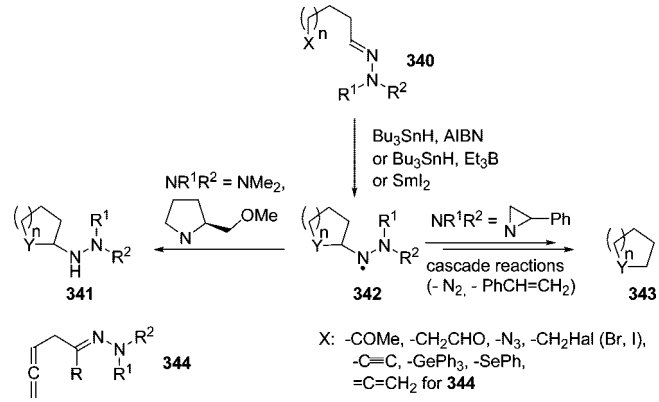
Scheme 62



Scheme 63



Scheme 64



rrolidine **338**.[251] The slow reaction (storage over 6 months) of benzaldehyde *N*,*N*-dimethylhydrazone with 4-oxo-2-(pentafluorophenoxy)-5,6-benzo-1,3,2-dioxaphosphorinane in DCM solution yielded a product of the phosphorus heterocycle expansion. In this way, the hydrolytically labile product 4-(dimethylamino)-2,5-dioxo-2-(pentafluorophenoxy)-3-phenyldihydro-6,7-benzo-1,4,2-oxazaphosphepine (**339**) was formed with high stereoselectivity, in the form of large yellow crystals.[252]

11. Free Radical Reactions

Radical reactions of *N*,*N*-dialkylhydrazones reported before year 2000 embraced mostly additions to *N*-aziridinylimines and consecutive transformations of so-formed radicals. The consecutive cascade reactions typically involved diazo compounds that decomposed to nitrogen and styrene, giving products of type **343** (Scheme 64). The early synthetic applications of free radical chemistry of *N*-aziridinylimines came from the research group of Sunggak Kim.[85,253,254] The radical reactions of *N*,*N*-dimethylhydrazones[255−257] and SAMP-hydrazones[257−259] of suitably functionalized radical precursors, including β-allenic hydrazones **344**, were limited to intramolecular cyclizations, leading typically to hydrazines **341** (Scheme 64). This type of hydrazone reaction has been covered in several reviews.[20,21,24,25,260] Radical reaction of *N*,*N*-diphenylhydrazones and acyl hydrazones, which are outside the scope of the present review, have also been reviewed.[20,21]

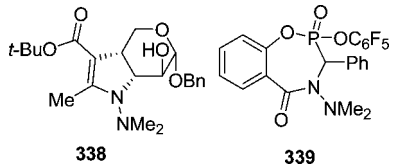


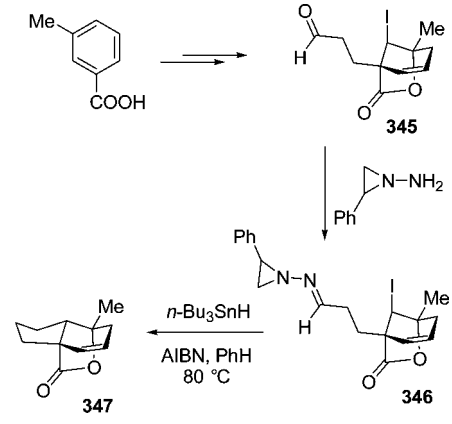
Figure 8. Cyclic products accessible from *N*,*N*-dimethylhydrazones.

11.1. Radical Cyclization Reactions

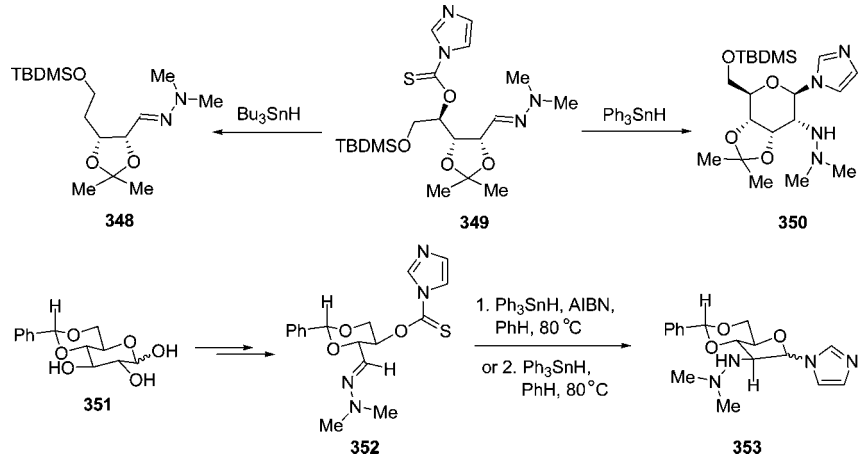
More recently, the free radical cyclization reaction of *N*-aziridynylimine (hydrazone **346**) was used as a key transformation in the synthesis of a hispidospermidin analogue starting from *m*-toluic acid (Scheme 65).[261] The radical cyclization, followed by consecutive cascade reactions, gave the *trans*-fused perhydroindan **347** in 80% yield.

An appropriately placed *N*,*N*-dimethylhydrazone acted as a suitable radical acceptor in an *exo*-hept-6-enyl- or *exo*-hex-5-enyl-type cyclization (Scheme 66). The addition of the first radical intermediate of the thiourethane-mediated alcohol deoxygenation (the Barton−McCombie reaction) to the hydrazone group in **349** was moderately efficient (yield of 56%) with triphenyltin hydride as the radical source

Scheme 65



Scheme 66



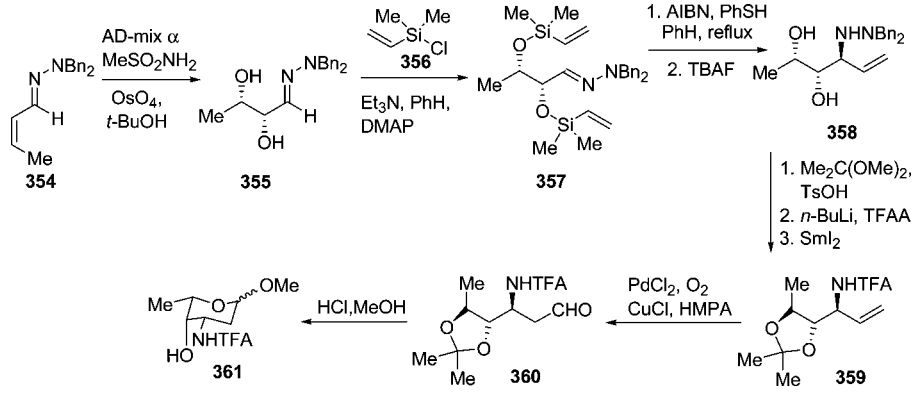
(product **350**, isomer ratio *altro*-α:*altro*-*β*:*allo*-α:*allo*-*β* = 4:9:0:100). On the other hand, use of tributyltin hydride in this reaction resulted in no cyclization but deoxygenation, giving product **348** in 41% yield. When **352** was used as a substrate in the cyclization, a 10:3 mixture of anomers of the cyclized *N*-furanosides **353** was formed with preference for the α-anomer.[262,263]

11.2. Radical Addition of Silicon-Tethered Vinyl and Acetylene Groups

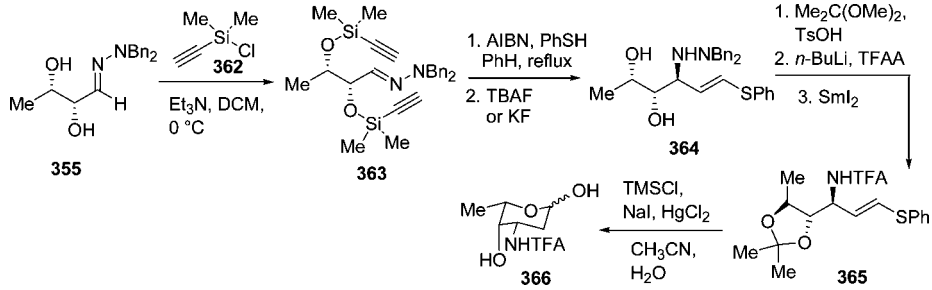
Silicon-tethered vinyl or acetylene (ethynyl) groups are advantageous for C−C bond construction via radical addition to hydrazones. The temporary incorporation of the silicone group avoids unfavorable intermolecular reactions and may provide control of diastereoselectivity of the addition via a chairlike Beckwith−Houk transition state.[264,265] The thiyl radical-mediated transfer of a vinylsilane group to *N*,*N*-dibenzylhydrazone (or related *N*,*N*-diphenylhydrazone) (Scheme 67) was skillfully used as one of the synthetic steps in an asymmetric synthesis of an aminosugar, L-daunosamine, derivative.[266] Addition of thiyl radical (generated from PhSH and AIBN) to the vinyl group in **357** generated an intermediate alkyl radical which underwent cyclization with the C=N bond of the hydrazone group. The one-pot treatment of the resulting intermediate with fluoride removed silicon and regenerated the vinyl group via elimination of benzenethiolate. The resulting allylic hydrazine **358** was obtained in 77% yield and high diastereomeric purity (dr 91:9). The yield and diastereoselectivity of this transformation were higher compared to those of the analogous method based on *N*,*N*-diphenylhydrazone. Compared to dibenzyl, the diphenyl analogue was less stable during storage and handling. Diol protection and trifluoroacetylation of the hydrazine **358** followed by SmI_2 N−N bond cleavage provided a suitable substrate for the Wacker oxidation reaction. The unusually regioselective Wacker oxidation transformed the vinyl group in the aldehyde function of the protected form of L-daunosamine trifluoroacetamide **360**. Acidolitic deprotection of the acetal in methanolic solution provided the methyl pyranoside of the (trifluoroacetyl)-L-daunosamine **361** in quantitative yield (3:1 mixture of anomers, Scheme 67).[266]

A similar approach, based on the radical addition to a silicon-tethered ethynyl group, obviated the need for the Wacker oxidation (Scheme 68).[267] However, contrary to the vinylsilane case, the desilylation of the cyclized intermediates gave no analogous thiolate elimination and consequently resulted in (phenylthio)vinyl adduct **364**, which may be considered a masked *β*-aminoaldehyde. Accordingly, the daunosamine derivative **366** was prepared via diol protection, hydrazine bond cleavage, and conversion of the vinyl sulfide to aldehyde under Grieco's conditions ((TMS)Cl, NaI, $HgCl_2$, and moist MeCN). One of the anomers of **366**, separated by crystallization, was found to be *N*-(trifluoroacetyl)-L-daunosamine, ultimately confirming the stereochemical course of the thiyl radical-initiated cyclization of the *N*,*N*-dialkylhydrazone with the silicon-tethered ethynyl group. Overall, the one-pot, tin-free method for radical addition−cyclization with thiophenol and treatment with fluoride leads to diastereoselective group transfer from a silicon-tethered ethynyl group to the C=N bond of *N*,*N*-dibenzylhydrazones, affording *anti*-hydrazino alcohols with a *trans*-2-(phenylthio)vinyl substituent. Combined with methods for the conversion of vinyl

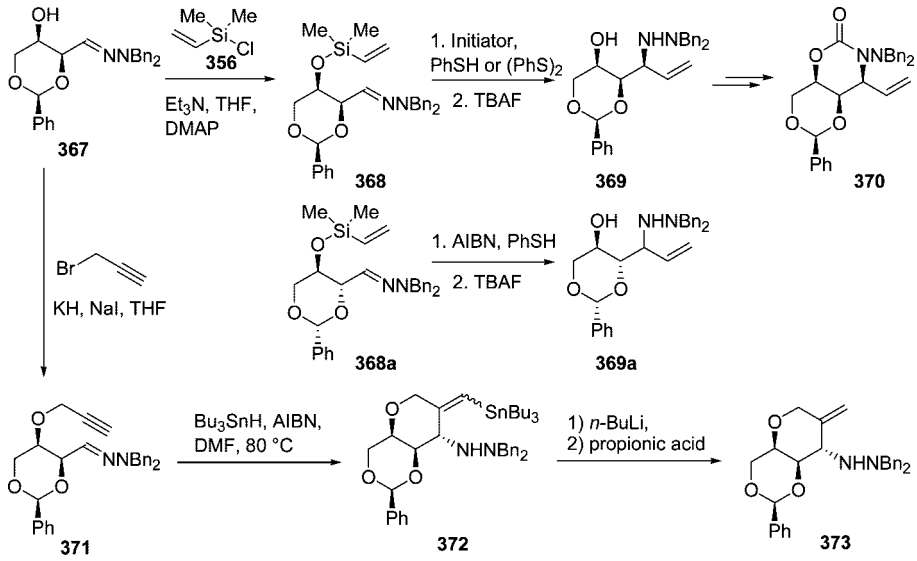
Scheme 67



Scheme 68



Scheme 69



sulfides to carbonyls, the described method for radical cyclization of silicon-tethered ethynyl may constitute a free radical equivalent of the Mannich reaction of acetaldehyde.[267]

Synthetic applications of radical reactions of *N*,*N*-diphenylhydrazones, which are not the subject of the present review, are similar to their *N*,*N*-dibenzyl counterparts.[267] It was noted, however, that the electron-rich *N*,*N*-dibenzylhydrazones are rather susceptible to elimination of β-hydroxy and β-silyloxy groups.[268]

The thiyl radical-initiated addition−cyclization under previously described conditions provided a product of vinyl transfer from silicon to the hydrazone azomethine carbon in **368** (6-*exo*-cyclization) with almost complete diastereoselectivity (98:2, Scheme 69). The yield was dependent upon the choice of initiator and reaction conditions (10−55%). The resulting hydrazine **369** was transformed further to the dihydroxylation substrate **370**, a key intermediate for aminosugar synthesis. The stereochemical outcome of the reaction was in disagreement with the usual prediction of the Beckwith−Houk model. This observation was explained on the grounds of a hypothetic dipole repulsion modification to the Beckwith−Houk model. It was assumed that minimizing the dipole repulsion between neighboring C═N and C−O bonds favored a C_α−C(═N) dihedral angle, placing the C═N bond axial within a chairlike transition state. The hypothesis was substantiated by experimentally observed lowering of diastereoselectivity for diastereomeric substrate **368a** (from dr 98:2 for product **368** to dr 70:30 for product **369a**).[269] Two key structural features in the substrates were proposed to play a crucial role in successful, silicone-tethered 6-*exo*-cyclizations: (i) the presence of α-alkoxy substituents and (ii) conformational constraints such as the benzylidene acetal ring. In analogy to silanes, a carbon-tethered acetylene (propargyl ether) 6-*exo*-cyclization, induced by tributyltin radicals under conventional heating or microwave irradiation, produced **372**. It is noteworthy that a protodestannylation of crude **372** (filtration through silica, *n*-BuLi followed by propionic acid) provided the functionalized product **373** with complete diastereoselectivity and in 48% yield from D-galactose.[269]

12. Catalytic Reactions

In general, catalytic reactions of *N*,*N*-dialkylhydrazones can be divided into organometallic reactions catalyzed with hydrazones acting as ligands or metal−hydrazone complexes and reactions of hydrazone substrates catalyzed with organic Brønsted acid (BA) catalysts (organocatalysts) or metal-containing Lewis acids (LAs).

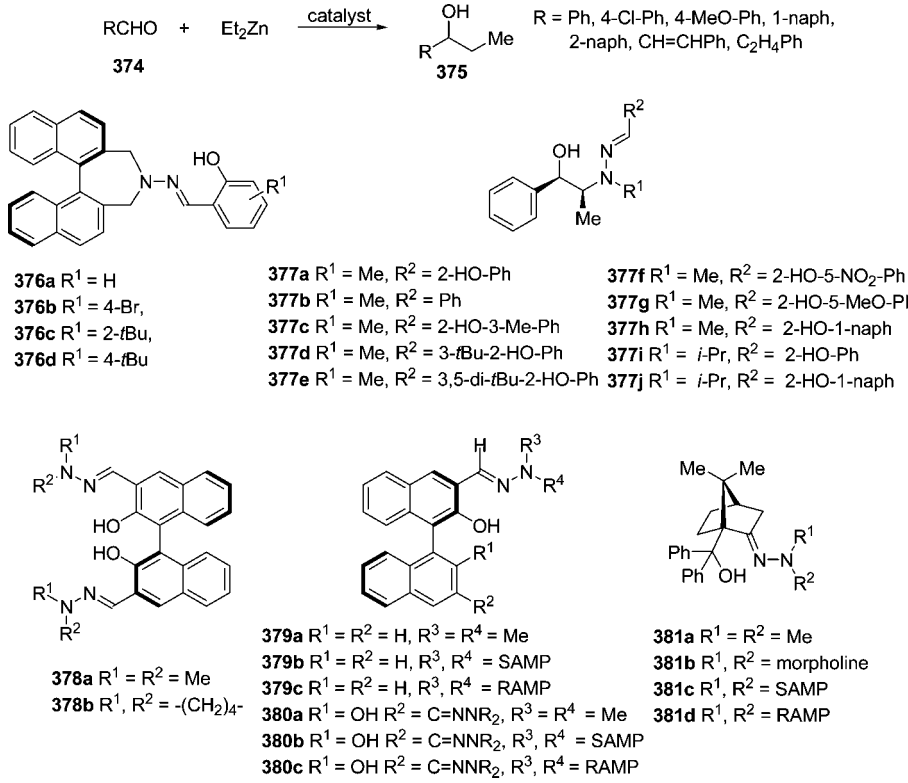
12.1. Catalytic Reactions of Hydrazone Catalysts in Organometallic Chemistry

12.1.1. *N*,*N*-Dialkylhydrazone Catalysts for Addition of Organometallics to Aldehydes

The enantioselective addition of diethylzinc to aromatic (e.g., benzaldehyde) and aliphatic (e.g., 3-phenylpropionaldehyde) aldehydes **374** can be catalyzed with chiral *N*,*N*-dialkylhydrazones (Scheme 70) such as binaphthyl-derived salicylhydrazones of type **376**.[270]

The best of the hydrazone catalysts, in terms of achievable yield (48%) and enantioselectivity (58%) of the addition, was

Scheme 70

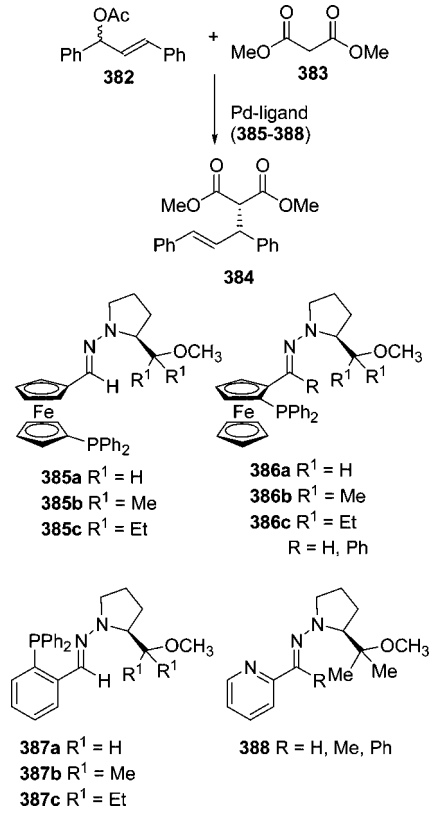


the hydrazone **376a** (R^1 = H). Catalysis of the same reaction with binaphthyl hydroxy hydrazones **379**[271] gave better yields (75−94%) but low selectivity (20−29% ee). The use of the bis(RAMP-hydrazone) of type **378**[271] resulted in the best ee (60% at −35 °C at 5 mol % catalyst loading) of the entire series (16−60%); unfortunately, this was usually at the expense of the yield (36−58%). The terpene-related ketopinic acid-derived hydrazones **381**,[271] used with an equimolar amount of *n*-BuLi, were also moderately stereoselective (34−58% ee) but effective catalysts (74−98% yield at 4 mol % loading). The best yield of 98% was achieved with the SAMP-hydrazone **381c** and the best ee with its DMH analogue **381a** (58%). The β-binaphthol-derived DMH-hydrazone **378a**[270] (R = Me) gave a quantitative yield of the diethylzinc addition to 4-methoxybenzaldehyde with a disappointing ee of 31%. On the other hand, the best ee of 80% was obtained in the addition to benzaldehyde. The *N*-aminopyrrolidine analogue hydrazone **378b** (R = $N(CH_2)_4$) gave yields of 51−80% with 72−76% ee. The most effective catalyst from another group of hydrazones, the (1*R*,2*S*)-ephedrine- and (1*R*,2*S*)-*N*-isopropylnorephedrine-derived β-hydroxysalicyl hydrazones,[272] **377** was the ephedrine-based hydrazone **377h** (R^1 = Me, R^2 = 2-hydroxy-1-naphthyl). This gave the (*S*)-product of addition with ee from 78% for 3-phenylpropenal to 92% for chlorobenzaldehyde. The yields ranged from 50% to 84% depending on the aldehyde used. No clear winner emerges from the gathered data. It seems necessary to optimize the structure of the hydrazone catalysts for each specific reaction.

12.1.2. N,N-Dialkylhydrazones as Ligands for Pd-Catalyzed Allylation

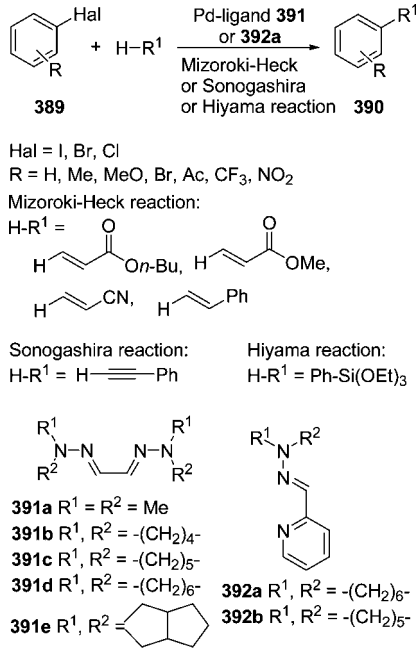
Several SAMP- and SAMP analogue-derived chiral phosphino hydrazones, **385**,[273] **386**,[274] **387**,[275−277] and **388**,[278] have been developed as ligands for asymmetric palladium-catalyzed allylation of dimethyl malonate with racemic 1,3-diphenyl-2-propenyl acetate (Scheme 71).

Scheme 71



From all the investigated hydrazones, i.e., derivatives of SAMP/RAMP (R^1 = H), SADP (R^1 = Me), or SAEP (R^1 = Et), the best performance was reported for the SAMP-hydrazones regardless of the aldehyde part of the hydrazones.

Scheme 72



In general, the allylation products were obtained with moderate to good enantiomeric excesses (48−98%) and with yields of 26−99%. Typical conditions (2 mol % [Pd(η^3-C_3H_5)Cl]$_2$ and 6 mol % **387a**,[276] *N*,*O*-bis(trimethylsilyl)acetamide, LiOAc, room temperature, 24 h, and THF as a solvent) gave a product with 98% ee. Substitution of LiOAc base with KOAc lowered the ee to 87% and that with NaOAc lowered the ee to 72%. A change of the solvent from THF to DCM, or a change from SAMP to another hydrazine, also lowered the enantioselectivity.

Asymmetric allylic amination (*N*-allylation of benzylamine with racemic allylic acetate) was also described under similar conditions with SAMP-hydrazone **386a** as the palladium complex ligand.[274]

12.1.3. N,N-Dialkylhydrazones as Ligands for Pd-Catalyzed Mizoroki−Heck, Sonogashira, and Hiyama Reactions

Some *N*,*N*-dialkylhydrazones have been developed as air-stable ligands for phosphine-free palladium catalysts for C−C bond forming reactions such as Mizoroki−Heck, Sonogashira, and Hiyama reactions (Scheme 72). Two types of hydrazones **392**, prepared from 2-pyridinecarboxaldehyde, and bishydrazone **391**, prepared from glyoxal and various dialkyl hydrazines (DMH and differently sized cyclic hydrazines), were tested for the Heck palladium-catalyzed cross-coupling reaction of alkenes with aryl halides.[279a] During optimization of the reaction conditions (different ligands, **392** or **391**; palladium sources, $PdCl_2(MeCN)_2$, $PdCl_2$, $Pd(OAc)_2$; solvents, DMF, DMAc, DMSO; bases, K_3PO_4, NaOAc, Cs_2CO_3 with or without tetrabutylammonium bromide) the best conditions were found to be $PdCl_2(MeCN)_2$, K_3PO_4, DMF, and **391d** as the best hydrazone ligand. Reactions of conjugated olefins gave conjugated vinyl aromatic products in good yields for aryl iodides (73−99%) and aryl bromides (30−93%) as substrates. Significantly worse performance was observed for aryl chlorides (yields from trace to 69%). Hydrazones of type **391** (in particular, **391d**) were also used as effective ligands for coupling of allyl aryl ethers with aryl iodides.[279b]

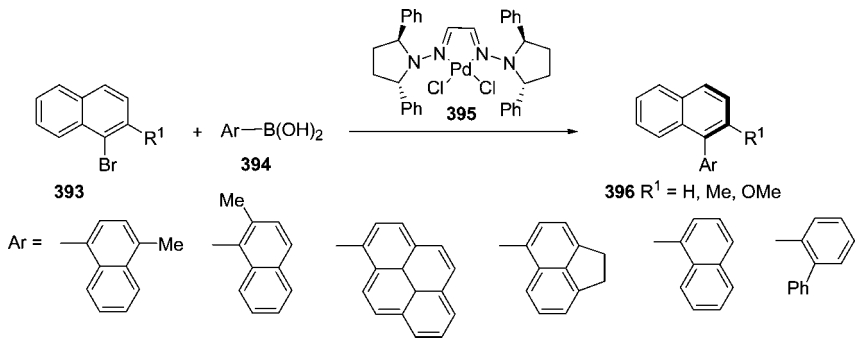
The optimized conditions (DMF, K_3PO_4, 80 °C, 5 h) using $PdCl_2(MeCN)_2$ with added CuI as a cocatalyst and the best hydrazone ligand for the Heck reaction, i.e., **391d**, were applied for the Sonogashira cross-coupling reaction of terminal alkynes with aryl halides. In the case of the Sonogashira reaction, however, the bishydrazone ligand with a seven-membered ring (**391d**) gave the arylated alkyne[280] in low yield (37%). A very good yield (93%) was obtained with the aryl alkyl hydrazone ligand derived from *N*-phenyl-*N*-methylhydrazine and 2-pyridinecarboxaldehyde.

Analogous results were reported for the Hiyama cross-coupling reaction of aryltrialkoxysilanes with aryl bromides. Use of the bishydrazone ligand **391d** (dioxane, $Pd(OAc)_2$, TBAF, 80 °C, 20 h) gave the biphenyl[280] with a moderate yield of 49%. Again, application of an aryl alkyl hydrazone ligand improved the yield to 83%.

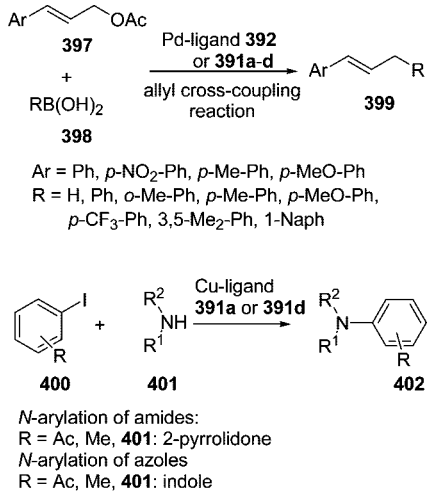
12.1.4. N,N-Dialkylhydrazones as Ligands for Pd-Catalyzed Asymmetric Suzuki−Miyaura Cross-Coupling

Very recently, the C_2-symmetric bishydrazone of glyoxal and chiral (*S*,*S*)-*N*-amino-2,5-diphenylpyrrolidine **395** (Scheme 73) was very successfully used as a ligand for phosphine-free, asymmetric Suzuki−Miyaura cross-couplings. The catalyzed reactions afforded a variety of enantiomerically enriched biaryls with different substitution patterns. The catalytically active complex [$PdCl_2$(bishydrazone)] allowed for room temperature reactions (typical catalyst loading 5 mol %, Cs_2CO_3, toluene, at 20 °C, 7 days, 36−98% yield) and showed excellent enantioselectivities (ee 77% to >98%) in all tested cases.[281] At higher temperature (80 °C), the reactions required shorter times (from 3.5 to 16 h) and the yields were slightly higher (66−99%); however, this was at the expense of the enantioselectivity (70−90% ee).

Scheme 73



Scheme 74



12.1.5. N,N-Dialkylhydrazones as Ligands for Pd-Catalyzed Allyl Cross-Coupling Reactions and Cu-Catalyzed N-Arylation of Amides and Azoles

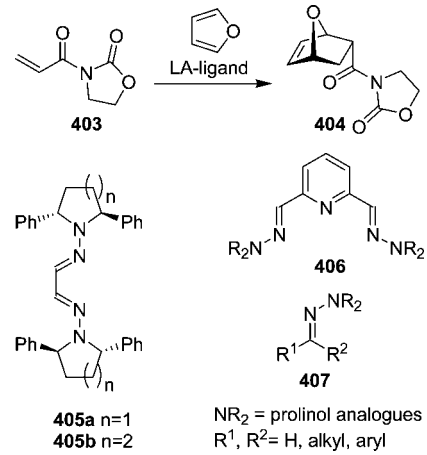
N,N-Dialkylhydrazones were also used as phosphine-free ligands in the palladium-catalyzed cross-coupling reaction of allylic acetates with a range of boronic acids. The room temperature reaction required $Pd(OAc)_2$ as a palladium source (2 mol % $Pd(OAc)_2$, 2 mol % of the optimal ligand **391c**, K_2CO_3, DMF/H_2O) and gave the allylbenzene derivatives **399** in good yields of 52−96% (Scheme 74).[282]

Hydrazones **391a** and **391d** were also used in related, copper-catalyzed transformations, the C−N bond forming Ullmann-type *N*-arylation of azoles and Goldberg-type *N*-arylation of amides with aryl iodides **400** (Scheme 74).[283] In both cases, the best yields of *N*-arylated products **402** were observed for hydrazone ligand **391d**. Optimal conditions for *N*-arylation of azoles (5 mol % CuI, 10 mol % **391d**, Cs_2CO_3, DMF, 110 °C, 24 h) resulted in yields of up to 98%, and those for *N*-arylation of amides (5 mol % CuI, 10 mol % **391d**, K_3PO_4, DMSO, 110 °C, 5 h) resulted in yields of 25−92%.

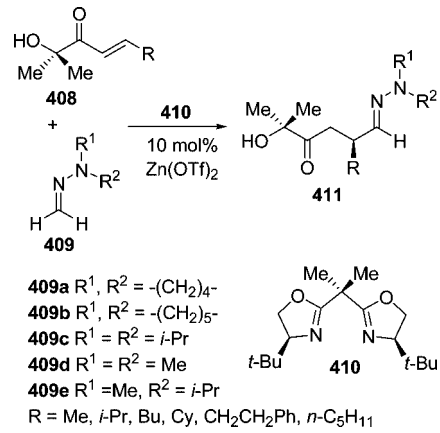
12.1.6. N,N-Dialkylhydrazones as Ligands in Lewis Acid-Catalyzed Diels−Alder Reaction

A new class of effective Lewis acid metal catalysts with monohydrazone and bishydrazone ligands was developed for enantioselective, metal-catalyzed, Diels−Alder reactions (Scheme 75).[284] The C_2-symmetrical hydrazone ligands **405a** and **405b** have been synthesized. Use of the Lewis acid $Cu(OTf)_2$ on the model reaction of *N*-acryloyloxazolidinone with cyclopentadiene revealed the best bis(2,5-diphenyl hydrazone) ligand **405a** (90% yield of the (*R,R*)-*endo*-product with 96% de and 95% ee). The cycloaddition of *N*-acryloyloxazolidinone to different dienes (80−91% yield), in the presence of a 1:1 complex of $Cu(OTf)_2$ with **405a**, gave the (*R,R*)-*endo*-adduct of furan with the best ee of 96% and diastereoselectivity of 74% de (88% yield). The least enantioselective reaction (ee 84%) was observed for cyclohexadiene, albeit with high (*R,R*)-*endo*-selectivity (>99% de). The other mono- and bishydrazone ligands **406** and **407** gave low ee's (0−18%) with the following Lewis acids: MgI_2, EtMgBr, $Sc(OTf)_3$, and $Cu(OTf)_2$.

Scheme 75



Scheme 76



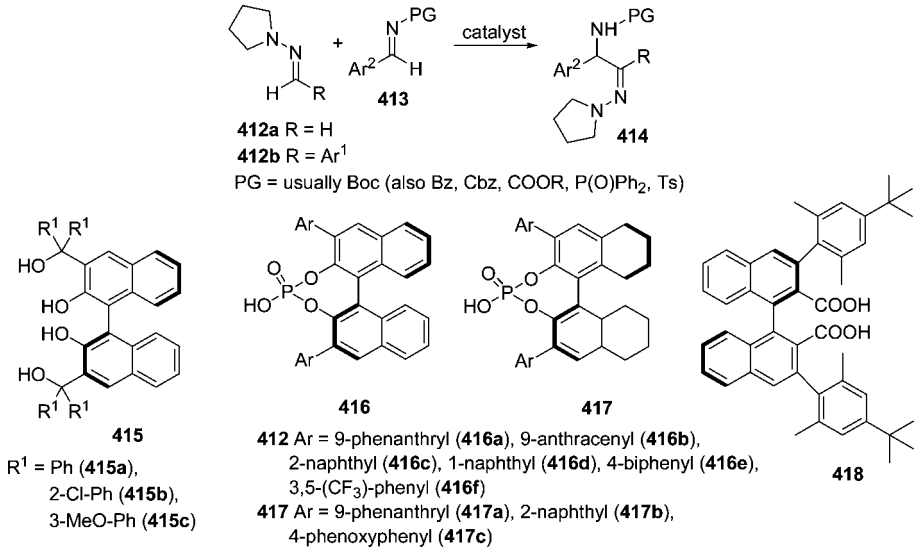
12.1.7. Lewis Acid-Catalyzed Addition of Formaldehyde N,N-Dialkylhydrazones to Hydroxy Enones

Two classes of ligands for metal-containing Lewis acid catalysts, BINOL-derived ligands and bis(oxazoline)s such as PhBOX, PyBOX, *t*-BuBOX, were tested in formaldehyde hydrazone additions to hydroxy enones **408** and related compounds (Scheme 76).[285] From several tested acyclic and cyclic *N,N*-dialkylhydrazone substrates, the best was the *N*-aminopyrrolidine-derived cyclic hydrazone of formaldehyde (**409a**). The other hydrazones, acyclic (**409c−e**) and piperidine-derived (**409b**), were poor substrates in these addition reactions. From the tested Lewis acids (triflates, halides, hexafluoroantimonates, and tetrafluoroboranes of Mg, Zn, and Cu), the zinc triflate showed the most promising activity. The optimal catalyst was found to be the complex of bis(oxazoline) *t*-BuBOX (**410**) with $Zn(OTf)_2$. Optimal conditions for *N*-aminohydrazone addition to aliphatic α-hydroxy enones were as follows: 10 mol % $Zn(OTf)_2$, 11 mol % **410**, toluene, 5 or 10 °C, 17−168 h. Depending on the hydroxy enone **408** used, the yields ranged from 50% to 95% and enantioselectivities from 66% to 84% (er 83:17 to 92:8). Cleavage of the resulting hydrazones with MMPP could provide a route to the corresponding nitriles.

12.2. Organocatalytic Reactions (Brønsted Acid Catalysis) of *N,N*-Dialkylhydrazones

Recent dynamic developments in the field of organocatalysis are also relevant to the chemistry of *N,N*-dialkylhydrazones. One of the approaches to catalysis with small

Scheme 77



organic molecules uses activation of reactants by organic Brønsted acids and hydrogen bonding. This approach found implementation in aldehyde hydrazone addition to imines[286] and Michael acceptors such as β,γ-unsaturated α-keto esters[287] and nitroalkenes.[288]

12.2.1. Addition of Aldehyde Hydrazone to Imines

The first organo-catalyzed addition of formaldehyde hydrazone to *N*-protected (*N*-SO_2R or *N*-CO_2R) imines[286] in the presence of BINOL and binaphthol-derived bisalcohol BIMBOL **415** (Scheme 77) was reported in 2005. Although the uncatalyzed reaction of benzaldehyde *N*-protected imines with formaldehyde *N*-aminopyrrolidine hydrazone **412a** took place with 0−15% conversion in 22 h, the addition of chiral BINOL increased the conversions to 30% for the *N*-Boc derivative, to 66% for the *N*-CO_2Et derivative, and to 71% for the *N*-tosylimine derivative. The reactions, however, showed no enantioselectivity whatsoever. The application of a novel class of (*S*)-BINOL-derived, 3,3′-bismethanol-2,2′-bisnaphthol catalysts resulted in a moderately enantioselective (3−67% ee, 4−48% conversion) addition reaction for benzaldehyde *N*-Boc-imine. The optimal catalyst structure for this reaction was **415**[286] (specifically **415a**, R^1 = Ph). Other aromatic *N*-Boc aldehyde imines gave, with the optimized catalyst, products in 44−87% yields and with ee's from 17% to 75% (best ee 75% for 2-methylbenzaldehyde in $CDCl_3$). Subsequent MMPP hydrazone cleavage was shown to proceed without racemization to give the corresponding *N*-Boc amino nitriles.

Other Brønsted acids, synthesized and tried as catalysts in the same formaldehyde addition to *N*-protected imines, were chiral phosphoric acid derivatives of BINOL[289] (**416** and **417**, Scheme 77). The *N*-aminopyrrolidine-derived hydrazone and *N*-Boc-imine were again found to be the best substrates in terms of achievable enantioselectivity. The best enantioselectivities of 74−90% ee (48−82% yields) were observed for the catalyst **417a** (90% ee in the case of piperonal aldimine). The best yield was obtained for the benzaldehyde aldimine reaction catalyzed by **416a** (92% yield and 61% ee).

Recently, the application of axially chiral, dicarboxylic acid derivatives of BINOL (**418**)[290] as effective catalysts in addition reactions of both formaldehyde and aromatic aldehyde hydrazones was reported (Scheme 77). The *N*-aminopyrrolidine-derived *N*,*N*-dialkylhydrazones of formaldehyde (**412a**) reacted with aromatic *N*-Boc-aldimines **413** in chloroform with good to excellent enantioselectivities (89−96% ee, 70−89% yields). The highest enantiomeric excess of 96% was obtained in the reaction of benzaldehyde imine. The work showed the first successful application of arylaldehyde hydrazones in the addition to imines. The dicarboxylic acid-catalyzed (5 mol % (*R*)-**418**, −20 °C, 96 h, MS 4A, $CHCl_3$) reactions of arylaldehyde tetramethylenehydrazones (*N*-aminopyrrolidine-derived **412b**) with aromatic *N*-Boc-aldimines provided α-aminohydrazones in 35−77% yields and with 84−95% ee. Ozonolysis of the products gave the corresponding α-amino ketones in good yields.

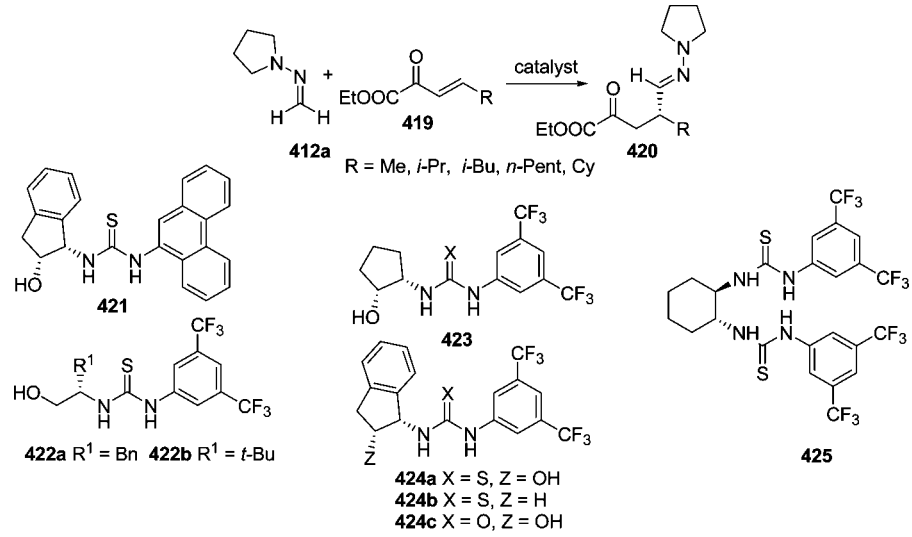
12.2.2. Addition of Formaldehyde Hydrazone to β,γ-Unsaturated Keto Esters

In analogy to the above-discussed addition of formaldehyde hydrazone nucleophiles to electrophilic acceptors catalyzed with metal complexes,[285] addition to Michael acceptors can be catalyzed with thiourea-derived organocatalysts **421**−**425** (Scheme 78).[287] Catalysis of the addition of the formaldehyde hydrazone **412a** to β,γ-unsaturated α-keto esters with potential catalysts such as BINOL, BINOL phosphate, mandelic acid, and ureas **421**−**425** was recently tested. The only catalysts showing enantioselectivity were thioureas **421** and **424a** and urea **424c** (28−32% ee) with **424a** selected as the best performer. The optimal conditions for this catalyst (10 mol % catalyst loading, DCM, low temperature of −60 °C) gave the addition product for the keto ester (R = Me) with 80% ee. In the reactions with other unsaturated keto esters the catalyst **424a** gave yields from 60% to 80% and ee's of 58−80%. As before oxidative cleavage (MMPP or ozonolysis) of the hydrazones could be used to gain access to nitriles and esters.[287]

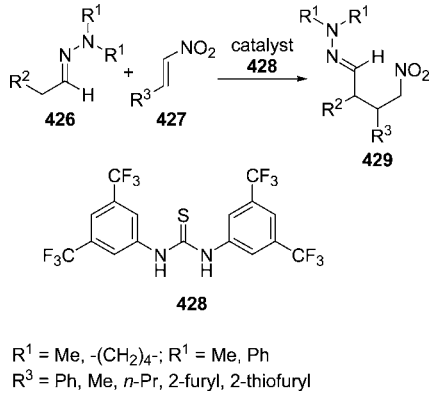
12.2.3. Addition of Aldehyde Hydrazone to α,β-Unsaturated Nitroalkenes

Strictly related to the aforementioned applications of organocatalysts is the addition of different aldehyde hydrazones to electrophilic nitroalkenes.[291] The conjugate addition of formaldehyde or aliphatic aldehyde hydrazones to β-ni-

Scheme 78



Scheme 79



trostyrene or other nitroalkenes catalyzed by thiourea **428**[288] (catalyst loading 20 mol %, DCM, 24 h) gave γ-nitro hydrazones (Scheme 79), as a mixture of diastereoisomers, in good yields (58−90%). The uncatalyzed reaction was also observed, albeit with lower conversion at the same reaction time (yield 61% in 18 h vs catalyzed yield 90%). Interestingly, the use of ionic liquids ($BMImBF_4$ or $BMImPF_6$) as the solvent for the uncatalyzed reaction accelerated the completion of the conversion, but gave products in low isolated yields, and was not feasible with the use of the thiourea catalyst **428**.

12.3. Lewis Acid Catalysis

The indium trichloride-catalyzed (10 mol %) reaction between aromatic imines and the *N,N*-dimethylhydrazone of methacrolein afforded 1,2,3,4-tetrahydroquinolines bearing a hydrazone function at C4. The one-pot process involving diastereoselective formation of two stereocenters, one of them quaternary, gave the products **430** (Figure 9) in good to excellent yields (70−93%). According to the authors, the process illustrated the first example of an α,β-unsaturated *N,N*-dimethylhydrazone behaving not as a diene, but as a dienophile in a hetero-Diels−Alder reaction.[292]

The *N*-amino-2,6-diphenylpiperidine moiety was used as a chiral hydrazone auxiliary in a scandium triflate-catalyzed Mannich-type addition of aldehyde hydrazones **431** to ketene silyl acetal (ester silyl enol ether, **432**) or thioacetals (thioester silyl enol ether, Scheme 80). The reaction proceeded in aqueous THF (THF/water, 9:1), giving the expected adducts in high yields (88−98%) and with good to high diastereoselectivities (dr from 4:1 to 99:1). The N−N bond cleavage in **433** removed the chiral auxiliary, affording enantiomerically pure β-amino esters.[293]

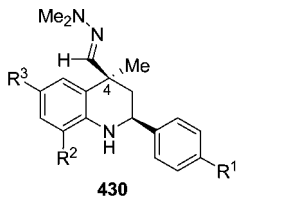
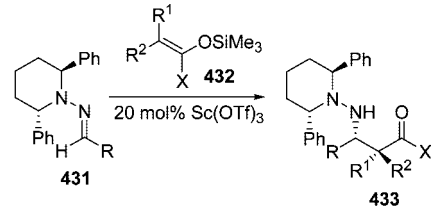


Figure 9. 1,2,3,4-Tetrahydroquinoline products of the reaction of imines with *N,N*-dimethylhydrazones.

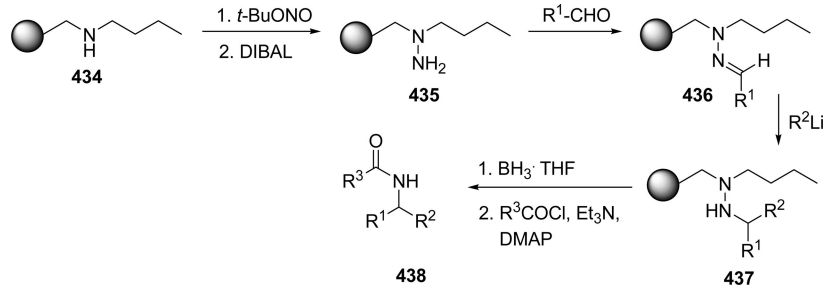
13. N,N-Dialkylhydrazones in Solid-Phase Organic Synthesis

Solid-phase synthesis of small molecules has been developing rapidly for over a decade. It is one of the workhorses used in automated synthesis and combinatorial chemistry.[294,295] The reversibility of hydrazone formation and the known reactivity[3] of *N,N*-dialkylhydrazones make the hydrazones attractive reagents for multifunctional linkers[296,297] and for construction of varied carbon frameworks of small molecules. Methodologies which allow for construction of C−C bonds on the solid phase are especially important from the synthetic point of view.[298]

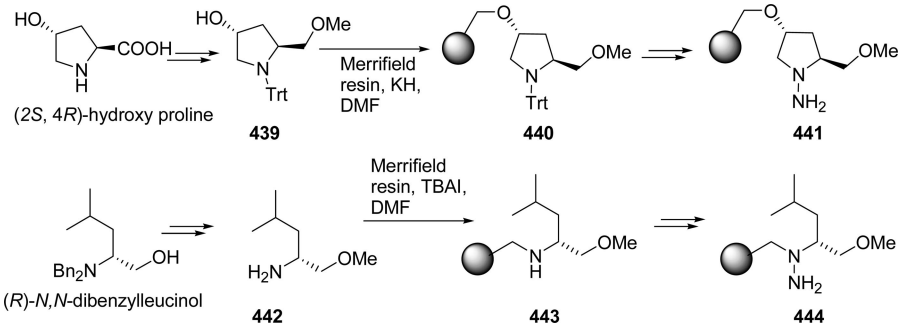
Scheme 80



Scheme 81



Scheme 82



Hydrazones serving as linkers can in principle be used either for reversible binding of carbonyl compounds to solid supports functionalized with hydrazine groups or for binding of hydrazines to supports exhibiting ketone or aldehyde carbonyls. It is noteworthy that all hydrazones used to date on a solid support functioned as linkers for carbonyl compounds but also took part in the supported reactions.[296] The polymers with *N*,*N*-dialkylhydrazine functional groups that could be used for binding carbonyl compounds as hydrazones are not available commercially, and therefore, synthesis of polymer-supported hydrazines is a precondition. The supported *N*,*N*-dialkylhydrazines have been prepared on Merrifield-type polymers by typical reduction of previously produced *N*-nitrosoamines,[299−304] anchoring protected *N*,*N*-dialkylhydrazines,[62,305−307] or the direct functionalization of the polymer with *N*-alkylhydrazine.[46] The last method is the simplest but may be limited by poor regioselectivity of monalkyl hydrazine alkylation. Nonetheless, the direct functionalization of Merrifield polymer with *N*-methylhydrazine was used to prepare a polymer-supported reagent for the synthesis of nitriles from aldehydes.[46] Despite many synthetic applications in solution chemistry, *N*,*N*-dialkylhydrazones were applied so far only in four groups of C−C bond forming reactions on a solid support, 1,2-addition, α-alkylation, cycloaddition combined with allylboration, and in a very limited way (one example) reaction on the azomethine carbon with an aldehyde.

13.1. 1,2-Addition of Organolithiums to Polymer-Supported Hydrazones

Polymer-supported hydrazones could be used in the same way as hydrazones in solution for the synthesis of amines by 1,2-addition of organometallic reagents. For the implementation of the idea a synthesis of polymer-supported hydrazines was crucial.

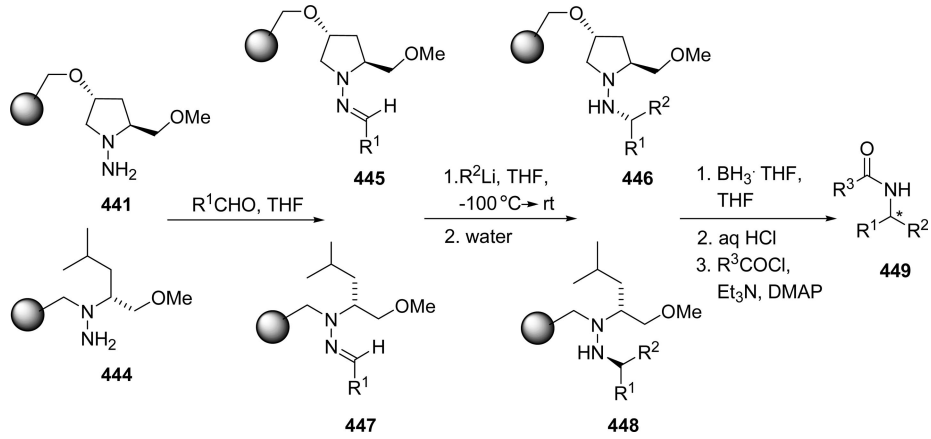
Polymer-supported hydrazine **435** was synthesized on Merrifield polymer through reaction of *n*-butylamine with (chloromethyl)polystyrene, nitrosation of the resulting secondary amine **434** with *tert*-butyl nitrite, and reduction with diisobutylaluminum hydride solution (Scheme 81).[299] The hydrazine **435** was subsequently reacted with several aldehydes. The resulting hydrazones **436** (i.e., aldehydes immobilized via the hydrazone linker) underwent the known-from-solution synthesis, 1,2-nucleophilic addition of organolithium reagents to give the corresponding supported hydrazines **437** (Scheme 81). The reductive cleavage of the hydrazine N−N bonds with borane/THF complex released secondary amines. To facilitate isolation, the amines were transformed to the amides **438**.

Solid-phase asymmetric synthesis (SPAS) is a recently introduced concept.[308] The chiral analogue of the described supported hydrazine and the analogous, diastereoselective 1,2-addition was used for the synthesis of enantiomerically enriched chiral secondary amines.[300] Two polymer-supported chiral hydrazines, a SAMP-hydrazine analogue (**441**) and a, so-called, RAML analogue (**444**), were synthesized from readily available chiral building blocks, *trans*-4-hydroxy-L-proline and *N*,*N*-dibenzyl-L-leucinol, respectively (Scheme 82). The supported chiral hydrazines **441** and **444** reacted with 3-phenylpropionaldehyde or *p*-methylbenzaldehyde, and the resulting hydrazones **445** and **447** acted as acceptors in the nucleophilic 1,2-addition of *n*-BuLi, *t*-BuLi, *n*-HexLi, and PhLi (Scheme 83). Subsequent application of the previously described cleavage provided primary amines protected as amides **449** in yields from 24% to 53% and moderate to high ee's (50−86%).

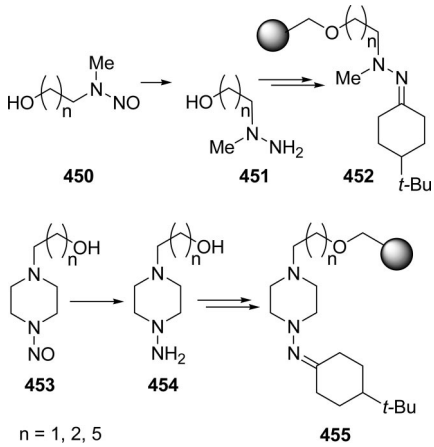
13.2. α-Alkylation of Polymer-Supported Hydrazones

As in the case of the above-presented 1,2-addition, the α-alkylation of solid-phase-supported achiral and chiral hydrazones derived from immobilized hydrazines was investigated. Two approaches to the synthesis of polymer-supported hydrazines, which bind both aldehydes and ketones via hydrazones and allow for their alkylation, were used. One strategy that allowed for the first hydrazone alkylation on a solid phase[303] was based on the preparation of supported *N*-nitrosoamines and their reduction to *N*,*N*-dialkylhydra-

Scheme 83



Scheme 84

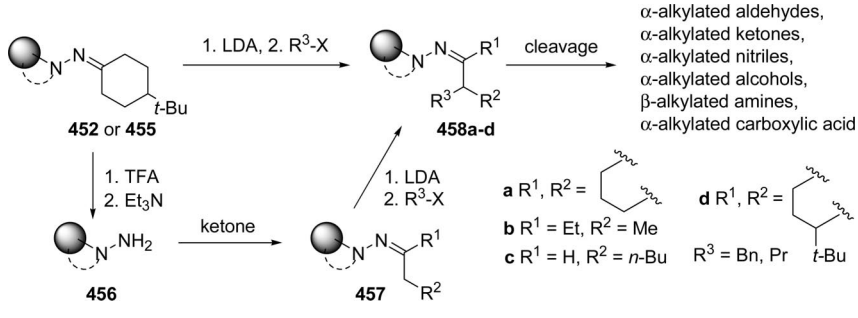


zines,[304] while the other way was based on the use of hydrazones as masking groups for *N,N*-dialkylhydrazine during anchoring on Merrifield-type polymers (Scheme 84).[62]

Thus, supported *N,N*-dialkylhydrazines **456** were prepared on Merrifield-type polymers either by loading of nitrosoamines and reduction of the *N*-nitrosoamines on the polymer or by loading of 4-*tert*-butylcyclohexanone hydrazones (Scheme 84)[62] acting as protected hydrazines and giving **452** or **455**. The latter method furnished typically cleaner polymeric materials. The hydrazone-protected hydrazines could be stored for prolonged periods of time. The protected, polymeric hydrazines needed activation by washing with 10% TFA solution in wet THF prior to loading of a new ketone or aldehyde. The hydrazones of the immobilized ketones and aldehydes could be lithiated with LDA and alkylated with alkyl halides.[62,303,304,309] The alkylated products were isolated in good yields (47−94%) and typically in acceptable purity (59−91%).[62] This alkylation method allowed for the expansion of the carbon skeleton of carbonyl compounds. The availability of various methods for the cleavage of *N,N*-dialkylhydrazones provided the opportunity for multifunctional cleavage of the hydrazone linkers. Depending on the cleavage method, different final products could be isolated: (i) aldehydes and ketones under acidic conditions (TFA/THF/water), (ii) acids or nitriles (from aldehyde hydrazones) with oxidative workup (peroxide) or oxidative cleavage (*m*-CPBA), (iii) alcohols or amines with reductive workup ($NaBH_4$) or reductive cleavage with a borane/THF complex (Scheme 85).[62] It has also been shown that aldehydes (and presumably ketones) immobilized via *N*-monoalkylhydrazone could be released from the polymeric support in the form of *N,N*-dialkylhydrazone via a hydrazone exchange reaction, i.e., treatment with a solution of *N,N*-dialkylhydrazine in the presence of concentrated hydrochloric acid (1-amino-4-methylpiperazine, 37% aqueous HCl/THF, 1:100).[310]

Asymmetric alkylation of ketones or aldehydes is waiting to be widely implemented in SPAS. Proof of concept studies on the asymmetric (enantioselective) alkylation of ketones via supported chiral hydrazone auxiliaries have already been conducted independently by some research groups (Figure 10). The polymer-supported SAMP analogue derived from *trans*-4-hydroxy-L-proline **441,** previously described as an auxiliary for 1,2-addition[301] when used for hydrazone alkylation, gave alkylated ketones and aldehydes with enantiomeric excesses in the range of 55−79% at −78 °C (Scheme 86). Improvement of the stereoselectivity was observed by lowering the reaction temperature to −100 °C (alkylation of cyclohexanone with *n*-HexI and 3-pentanone with *n*-PrI, giving **464c**, R^3 = *n*-Hex, 86% ee, and **464a**, R^3 = *n*-Pr, 85% ee). This was still lower than that achievable for the same alkylations with SAMP-hydrazone in solution (91% and 99% ee, respectively). Using a different anchoring site

Scheme 85



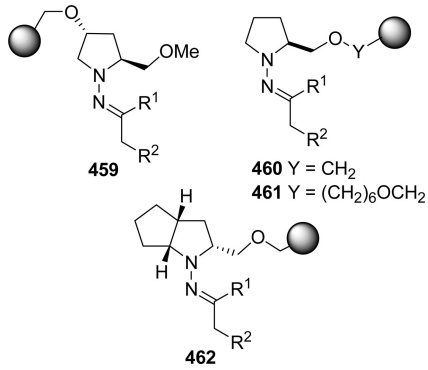


Figure 10. Polymer-supported chiral hydrazones utilized in alkylation reactions.

for the SAMP auxiliary, i.e., SAMP analogue anchored to a solid support via an oxymethylene group (**460** and **461**),[306,307] resulted in enantioselectivities ranging from 10% to 73%. The best performance was shown by alkylation of 3-pentanone with *n*-propyl iodide (at −78 °C, product **464a**, R^3 = *n*-Pr, 73% ee) and the chiral auxiliary connected to the polymer matrix through a six-carbon atom spacer (Scheme 87). Interestingly, somewhat increased enantiomeric excesses of alkylation products (by 25−47%) were obtained for the alkylation of a C_s-symmetrical ketone, anchored via the chiral SAMP analogue hydrazone, when a chiral bidentate lithium amide was used for lithiation of the polymeric hydrazone.[307]

In an independent study, the polymer-supported hydrazones **460** and **462**, analogues of known-in-solution SAMP- and RAMBO-hydrazones (Figure 10), immobilized via the oxymethylene bridge, were also used for immobilization of aldehydes ($PhCH_2CH_2CHO$, *p*-methoxybenzaldehyde) and ketones (3-pentanone, cyclohexanone).[302] The ketone hydrazones were alkylated with MeI or PrI and cleaved with ozonolysis or acidolytically with TFA. Generally, overall enantioselectivities of the process ranged from 58% to 66% for ozonolysis and from 54% to 73% for TFA cleavage. The best enantioselectivity (73%) was obtained for the alkylation of 3-pentanone with PrI and the TFA cleavage.[302]

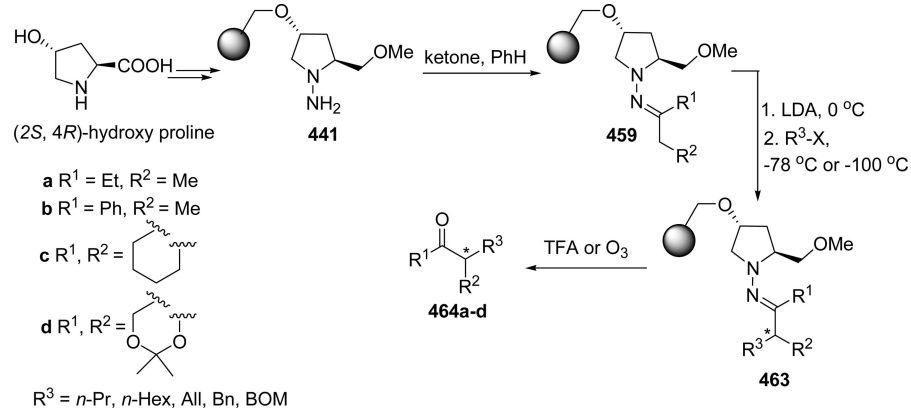
The investigations on hydrazone alkylation by three different groups, and with hydrazone auxiliaries anchored via an oxymethylene group or oxygen atom on C4, reached similar levels of stereoselection. Overall, the performance of the asymmetric alkylation on the studied solid supports in terms of enantioselectivities was moderate. The low to moderate enantioselectivities could be a result of a detrimental effect of the polymer matrix on this type of reaction.

13.3. Other Polymer-Supported Reactions

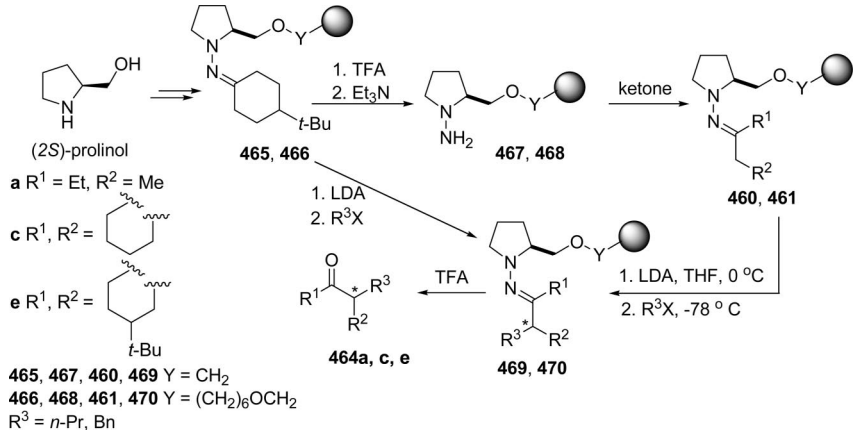
13.3.1. Polymer-Supported Reactions of Azomethine Carbon Nucleophiles

To date, there is only one example of the reaction of polymer-bound formaldehyde hydrazone at the azomethine carbon. A polymer-supported, chiral *N*-aminopyrrolidine-derived hydrazine was prepared through anchoring (KH, THF) of the hydroxy group of *N*-trityl-protected (3*R*)-1-amino-3-pyrrolidinol (synthesized in solution from commercial (3*R*)-3-pyrrolidinol by *N*-nitrosation and $LiAlH_4$ reduction of the resulting *N*-nitrosoamine) on the Merrifield polymer. The immobilized formaldehyde hydrazone **471** was obtained by the reaction of the free hydrazine polymer with

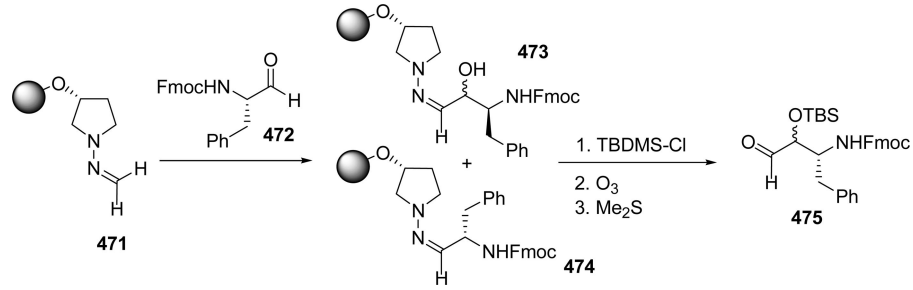
Scheme 86



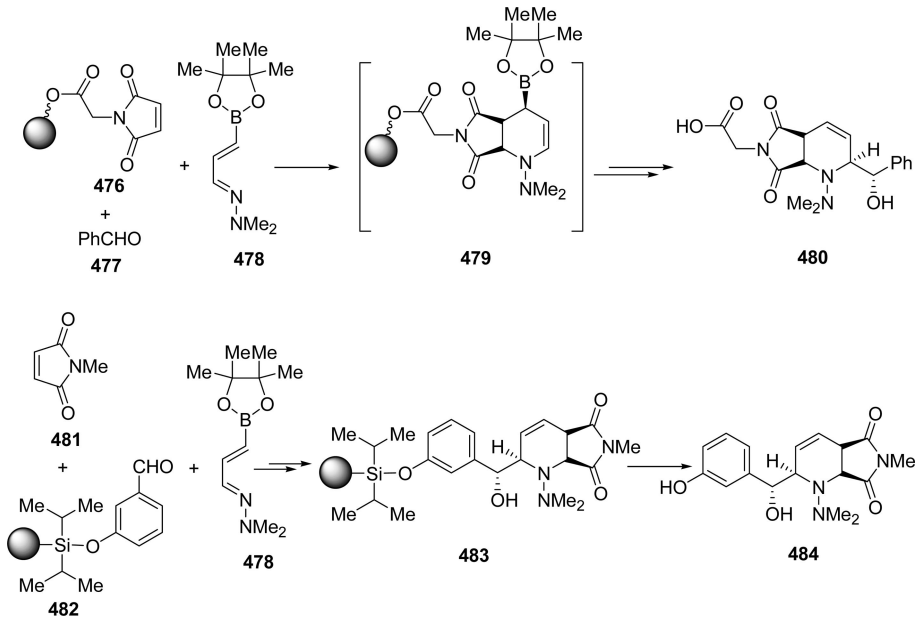
Scheme 87



Scheme 88



Scheme 89



an excess of formalin in THF or paraformaldehyde in THF/methanol. The addition of the nucleophilic azomethine carbon of the *N*-aminopyrrolidine-derived hydrazone **471** to Fmoc-phenylalaninal **472** was attempted and gave after hydroxyl protection and ozonolytic cleavage a mixture of diastereomeric products **475** (Scheme 88).[305]

13.3.2. Polymer-Supported Multicomponent Reactions

The previously discussed (vide cyclizations), multicomponent aza [4 + 2] cycloaddition/allylboration reaction between 1-aza-4-boronobutadienes, maleimides, and aldehydes was also performed on a solid support (Scheme 89). The supported tandem reaction was realized through either immobilization of maleimide on a Sasrin resin (**476**) or the anchoring of *m*-hydroxybenzaldehyde via a silyloxy linker (**482**). The loaded resins were reacted with other components, giving the immobilized products, which, in turn, were cleaved from the Sasrin supports by washing with 2% TFA in DCM or from the silyloxy resin by treatment with HF·Py in THF. The resulting products **480** and **484** were obtained in overall yields of 50% and 75%, respectively.[311]

14. Hydrazones as Protecting Groups and Miscellaneous Applications

N,N-Dimethylhydrazone was used as the protecting group for an aldehyde in phosphonate reagents. Two phosphonates **485** (Figure 11), diethyl (ethylformyl)-2-phosphonate *N,N*-dimethylhydrazone and diethyl (1-propylformyl)-2-phosphonate *N,N*-dimethylhydrazone, containing protected aldehyde groups were used as Horner−Wadsworth−Emmons reagents in a reaction with (2*E*)-2-methyl-2-butenal. The reaction was a key step in the synthesis of (2*E*,4*E*,6*E*,8*E*)-3,5-dimethyl-7-ethyl-2,4,6,8-undecatetraene, a pheromone of the beetle *Carpophilus lugubris*. Removal of the hydrazone protective group was effected with a biphasic mixture of dilute HCl and petroleum ether.[312]

N,N-Dimethylhydrazone was also used as a protecting group for aldehydes (hydrazone **486**, **487**) in the synthesis of furyl-1,4-naphthoquinones and furyl-1,4-benzoquinones.[313]

Ketone (cyclohexanone, *tert*-butylcyclohexanone) hydrazones **488** served as protection for the hydrazine group during

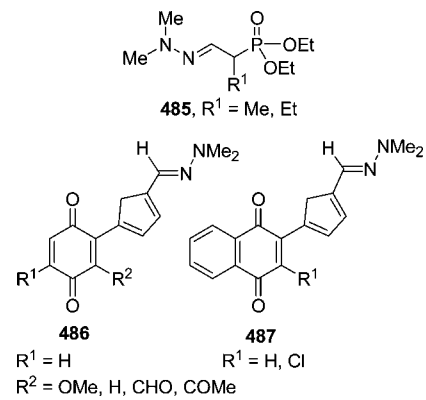
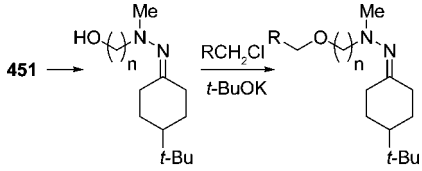
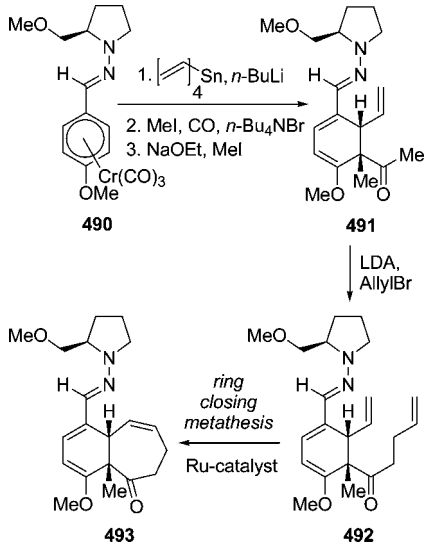


Figure 11. *N,N*-Dimethylhydrazone-protected aldehydes used in synthesis.

Scheme 90



Scheme 91



O-alkylation of hydroxy hydrazines **451** with benzyl chloride and its polymeric analogue, the Merrifield resin (Scheme 90).[62]

A highly enantiomerically enriched [6,7]-*cis*-fused system, **493**, was obtained by addition of vinyllithium to the RAMP-hydrazone of (η^6-arene)tricarbonylchromium(0) complex **490** (Scheme 91) followed by acetylation (MeI, CO), methylation with methyl iodide, and allylation.[314]

The *N*,*N*-dialkylhydrazone group served simultaneously as a heteroaryl activating group and a masked formyl and nitrile group. Hydroxyalkylation of furfural and pyrrole-2-carbaldehyde *N*,*N*-dimethylhydrazones with or without concomitant isomerization gave the heteroaryl analogues of α-benzoins **495** or **496** in 10−92% yields (Scheme 92).[315,316] Subsequent *N*-methylation followed by acidic (giving aldehyde) or aqueous (giving nitrile) hydrolysis provided **497** and **498**.

Chlorodifluoroacetylated *N*,*N*-dialkylhydrazones **499** reacted with aromatic aldehydes, ethyl pyruvate, and benzaldehyde *N*-tosylimine in a reductive coupling mediated by tetrakis(dimethylamino)ethylene (TDAE; Scheme 93). The method gave access to a series of new, α-diketone-derived, *gem*-difluorinated monohydrazone derivatives **501**.[317]

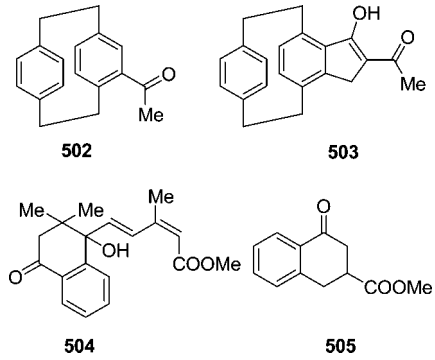
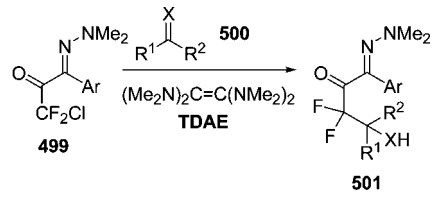


Figure 12. Racemic aldehydes and ketones resolved via diastereomeric SAMP/RAMP-hydrazones.

Scheme 93

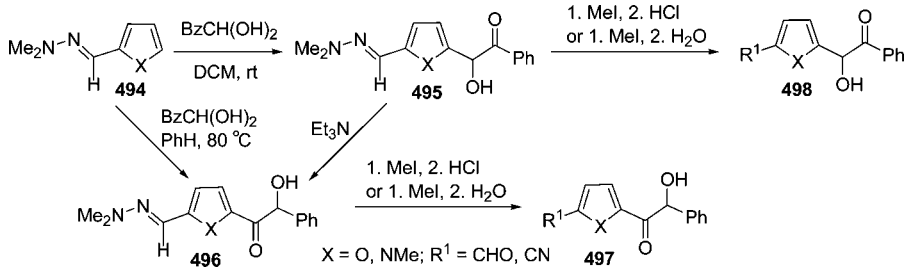


Resolution of racemic aldehydes or ketones **502**,[318] **503**,[319] **504**,[320] and **505**[321] (Figure 12), through formation of a mixture of diastereomeric hydrazones and their separation by column chromatography[320,321] or crystallization,[318,319] was another preparative application of SAMP/RAMP-hydrazones. The resolved diastereomeric hydrazones were typically hydrolyzed to optically enriched carbonyl compounds using an aqueous oxalic acid/organic solvent (ether, hexane) two-phase system.

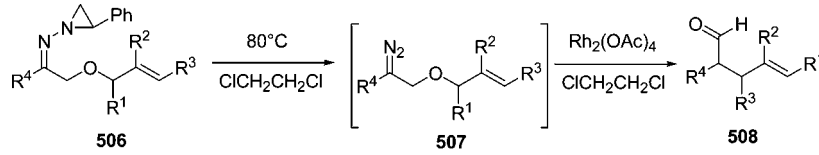
N-Aziridinylimines (Eschenmoser hydrazones **506**) are a specific type of *N*,*N*-dialkylhydrazones that were used for the generation of non-carbonyl-stabilized diazo compounds (possibly of type **507**). Thermal decomposition of the Eschenmoser hydrazones gave a mixture of decomposition products, presumably by a carbene pathway. The likely products of the same reaction in the presence of rhodium(II) catalyst were rhodium carbenoid intermediates.[322] Combination of the process with stereoselective 1,2-hydride migration and thermal Claisen rearrangement resulted in a highly stereoselective tandem Rh-catalyzed Bamford−Stevens/Claisen (or even Cope) reaction (**508**, Scheme 94, yields 62−88%, dr from 3:1 to >20:1).[322]

The reaction of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines **509** with alkyllithiums R^2Li (Scheme 95) afforded the products **510** (59−70% yield) via anionic addition followed by fragmentation with the liberation of stilbene and nitrogen gas. The reaction was also effective for the aziridines **509**

Scheme 92

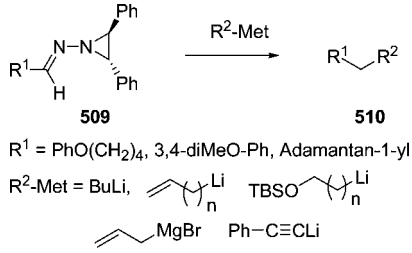


Scheme 94

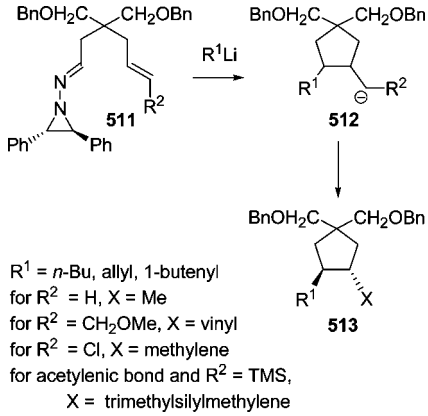


R^1, R^2, R^3 = H or various substituents: Ph, alkyl, alkenyl
R^4 = Ph, *i*-Pr, alkenyl

Scheme 95



Scheme 96



where R_1 = $PhO(CH_2)_4$ using organocuprates where R_2 = *n*-Bu (68%), Grignard reagent R_2 = *n*-Bu, allyl (59%, 84%), and organolithiums *n*-BuLi (52%) and PhCC-Li (75%).[323] The analogous reaction of monosubstituted Eschenmoser hydrazones, *N*-(2-phenylaziridin-1-yl)imines, gave an anomalous byproduct. The consecutive trapping reactions of the putative anionic intermediates with benzaldehyde and anhydrides were probed with varying degrees of success. On the other hand, anionic cyclizations of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines using unactivated alkenes and alkynes as acceptors proceeded smoothly, yielding various cyclized products **513** in good yields (60−91%, Scheme 96) and preference for the *trans*-isomers (X = Me or −CH=CH_2).[323]

15. Conclusions and Outlook

Since the 1970s, we have witnessed major developments in both the synthetic methodology and the target-oriented synthetic applications of *N,N*-dialkylhydrazones. Methods of asymmetric synthesis and C−C bond formation have especially benefited from the blossoming of hydrazone chemistry prior to 2000.[1,3] Today, C−heteroatom (Si, Se, S, O, P, N, F) bond formation and C−C bond formation using both achiral and chiral hydrazone methods are well-known synthetic transformations. In the past few years we have seen a steady growth of applications of the known reactions of *N,N*-dialkylhydrazones such as α-alkylation, 1,2-addition to C=N bonds, and hetero-Diels−Alder reactions as key steps in the syntheses of natural products and other complex molecules.

Alkylation is the most prominently used transformation of hydrazones (ca. 60 cited references report on α-alkylation in solution and 6 on a solid phase out of ca. 190 published after 2000). The second most popular *N,N*-dialkylhydrazone reaction in the years covered by the review was the nucleophilic 1,2-addition (ca. 35 cited papers) followed by the hetero-Diels−Alder reactions of unsaturated hydrazones (17 citations).

The 1,3-dihydroxyacetone equivalent 1,3-dioxanone[97] is a synthetically important building block, for which *N,N*-dialkylhydrazone transformations are well suited (over 20 cited papers). The sophisticated buildup on 1,3-dioxanone molecules by sequential α-alkylation, α,α′-alkylation, or even triple α,α′,α-alkylation (quaternization) has been used as the central process in multistep syntheses. The ultimate quaternization of both α-carbons of a 1,3-dioxanone was also possible by the SAMP-hydrazone method. Diastereoselectivities and enantioselectivities of chiral hydrazone reactions utilized in the syntheses were typically excellent (90% to >99%) or could be improved by separation of the diastereomeric hydrazone mixtures. Although several chiral hydrazines are available in both enantiomeric forms, the SAMP and RAMP auxiliaries dominate the asymmetric transformations based on chiral hydrazones. Aside from the notable case of titanated hydrazones, the aldol reaction and, similarly, the acylation and Michael reactions of metalated hydrazones have found little application in target-oriented synthesis and relatively little attention in methodological studies.

On the other hand, the dynamically growing methodological research in areas of *N,N*-dialkylhydrazones as catalysts and catalyst ligands, organocatalytic reactions of the hydrazones, and electrophilic reactions of aldehyde hydrazones (mostly formaldehyde) on the azomethine carbon (e.g., Michael reaction) have so far found little synthetic utility in actual multistep syntheses of specific complex targets. It seems that, contrary to α-alkylation and 1,2-addition, these areas of hydrazone chemistry are not yet mature. The majority of the reported reactions at the azomethine carbon involved formaldehyde hydrazone substrates. In the modern area of catalysis, *N,N*-dialkylhydrazones (ca. 25 references on catalysis) have been used as catalysts for asymmetric Et_2Zn addition, as ligands for Pd catalysts (allylation, Heck-, Sonogashira-, and Hiyama-type reactions), and in Lewis acid-catalyzed Diels−Alder reactions. Although relatively less developed, the free radical chemistry of *N,N*-dimethylhydrazones, *N,N*-dibenzylhydrazones, SAMP-hydrazones, and *N*-aziridinylimines (Eschenmoser hydrazones) have also found applications in synthesis. The radical transformations were pioneered by Sunggak Kim and more recently developed by Gregory K. Friestad. Organocatalytic reactions of *N,N*-dialkylhydrazones are confined to several notable examples (BA organocatalyzed) of hydrazone substrates react-

ing with electrophiles such as imines, α,β-unsaturated keto esters, and nitroalkenes. In addition, Lewis acid-catalyzed reactions of hydrazones have also been reported. The recyclability of hydrazone-based catalysts (especially chiral) has, so far, not been addressed.

Applications of hydrazone chemistry in supported synthesis are also limited to reports of methodological studies and to the classical reactions (α-alkylation, 1,2-addition). The hydrazone units fulfill a dual role in supported syntheses, the linker and the reacting functional group. The *N*,*N*-dialkylhydrazone linkers are well suited for, and already have been used as, multifunctional linkers. There are no reports on reactions of solid-phase-supported hydrazones not acting as linkers, i.e., reactions of hydrazone molecules anchored via other functionalities.

The majority of the hydrazone methodology and total syntheses using *N*,*N*-dialkylhydrazone chemistry comes from the research group of Dieter Enders of RWTH-Aachen (ca. 120 references in this review). Other groups leading in specific areas are the teams of José M. Lassaletta (24 references, mostly reactions on azomethine carbon and catalysis) and Takashi Mino (14 references, mostly catalysis with hydrazones).

It is rather hard to judge whether the current state of hydrazone chemistry is beginning to show the limits of synthetic hydrazone applicability or, on the contrary, whether we can expect to see a dynamic expansion of the frontiers of hydrazone chemistry, to the benefit of preparative technologies. Clearly, some issues of hydrazone methodologies may still need improvement: Chiral auxiliary recycling and hydrazone catalyst recovery may be addressed by solid-phase immobilization approaches. However, it seems that better, less stereoselectivity attenuating, polymeric supports will be needed before truly high levels of enantioselectivity with polymer-supported, recyclable chiral hydrazine auxiliaries can be achieved. So far, the SAMP analogues anchored on (chloromethyl)polystyrene (Merrifield polymer) consistently provided products with ee's up to 86%.

The accelerated progress in synthetic methodology and significant position of *N*,*N*-dialkylhydrazone methods in organic synthesis ensures that we will continue to see new hydrazone methods, reactions, and catalysts and their novel and inventive application toward the syntheses of complex molecules in the coming years.

16. List of Abbreviations

ADA	aza-Diels−Alder
BA	Brønsted acid
BIMBOL	3,3′-bismethanol-2,2′-binaphthol
BINOL	1,1′-bi-2-naphthol
BOM-Cl	benzyloxymethyl chloride
BOX	bis(oxazoline)
m-CPBA	3-chloroperoxybenzoic acid
dap	2,6-diaminopyridine
DBAD	di-*tert*-butyl azodicarboxylate
DHA	dihydroxyacetone
DHAP	dihydroxyacetone phosphate
DIPEA	diisopropylethylamine
DMAB	dimethylamine−borane complex
DMH	*N*,*N*-dimethylhydrazine
DMPU	*N*,*N*′-(dimethylpropylene)urea
EWG	electron-withdrawing group
FDMH	formaldehyde *N*,*N*-dimethylhydrazone
FSAMPH	formaldehyde SAMP-hydrazone
GABA	γ-aminobutyric acid
HAD	hetero-Diels−Alder
LA	Lewis acid
MMPP	magnesium monoperoxyphthalate
NFSI	*N*-fluorobenzenesulfonimide
PPL	porcine pancreatic lipase
RAMBO	(*R*,*R*,*R*)-2-amino-3-(methoxymethyl)-2-azabicyclo-[3.3.0]octane
RAML	(*R*)-*N*-amino-*O*-methylleucinol
RAMP	(*R*)-1-amino-2-(methoxymethyl)pyrrolidine
SADP	(*S*)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine
SAEP	(*S*)-1-amino-2-(1-methoxy-1-ethylpropyl)pyrrolidine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
SAPP	(*S*)-1-amino-2-(methoxydiphenylmethyl)pyrrolidine
SEM-Cl	[2-(trimethylsilyl)ethoxy]methyl chloride
SPAS	solid-phase asymmetric synthesis
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TDAE	tetrakis(dimethylamino)ethylene

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