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Aldehyde *N*,*N*-Dialkylhydrazones as Neutral Acyl Anion Equivalents: Umpolung of the Imine Reactivity

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Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

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The isoelectronic replacement of the α-carbon of enamines by nitrogen leads to the corresponding hydrazones, and thus, they can be termed "aza-enamines". Hence, aldehyde *N*,*N*-dialkylhydrazones enable analogous electrophilic substitutions at the imine carbon that corresponds to the β-carbon of enamines. In addition, after hydrolysis of the product hydrazones to the parent ketones or aldehydes, these reactions constitute an umpolung of the classical carbonyl reactivity and overall a nucleophilic acylation or formylation. This review covers the aza-enamine chemistry from its very beginning in the late 1960s up to this year. In the first part, reactions of aromatic, aliphatic, and heterocyclic aldehyde *N*,*N*-dialkylhydrazones with highly reactive substrates such as the Vilsmeier and Mannich reagents, sulfonyl isocyanates, perfluoroacetic anhydride, and inorganic electrophiles such as halogens and phosphorus tribromide are described. The hydrazones of α,β-unsaturated aldehydes react as vinylogous aza-enamines at the terminal carbon providing unsaturated aldehydes. As electron-rich dienes and dienophiles, they also form Diels–Alder adducts and thus interesting N-heterocycles. The second part covers carbon–carbon bond formations of the sterically less-demanding formaldehyde *N*,*N*-dialkylhydrazones with synthetically very useful electrophiles such as various Michael acceptors and carbonyl compounds. Formaldehyde SAMP-hydrazone and related derivatives generally give excellent asymmetric inductions. Finally, first organocatalytic versions of the aza-enamine chemistry are presented. In summary, the rich chemistry of aldehyde *N*,*N*-dialkylhydrazones as neutral acyl anion, formyl anion, and cyanide equivalents is demonstrated.
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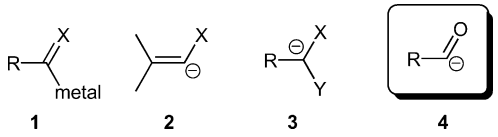
1. Introduction

The methods for the reversible umpolung of the natural reactivity of functional groups, developed over the last four decades proved to be a significant enrichment in synthetic organic chemistry.[1–3] The problem − although early recognized[4] − was investigated much later and owes the start of its vigorous research to Corey and Seebach in the mid 1960s.[5]

Seebach subdivided the methods of the nucleophilic acylation into three categories (Figure 1):[6,7] unprotected acyl or acyl-analogous derivatives **1**, vinyl ether type protected acyl anions **2**, and acetal-type protected compounds **3**. Most of the many different nucleophilic acylating reagents are derived from type **3**.



1 **2** **3** **4**

Figure 1. Basic equivalents **1**–**3** of acyl anion synthon **4**.

Aldehyde hydrazones are an additional category of compounds that undergo nucleophilic acylations. The oldest and most known of them are aldehyde monophenylhydrazones **5** (R^1 = Ph). They can attack electrophilic substrates after deprotonation to ambident anion **6** not only with the azomethine nitrogen atom, but under suitable conditions also with the azomethine carbon atom. The best known examples in this field are their reactions with diazonium ions, leading to formazanes **7** (Scheme 1).[8a] They proceed contrary to the natural polarity of the azomethine functionality and can thus be regarded as nucleophilic acylations of diazonium ions by aldehyde phenylhydrazones. Many examples of such reactions have been described forming not only carbon–heteroatom[8] but also carbon–carbon bonds.[9,10]

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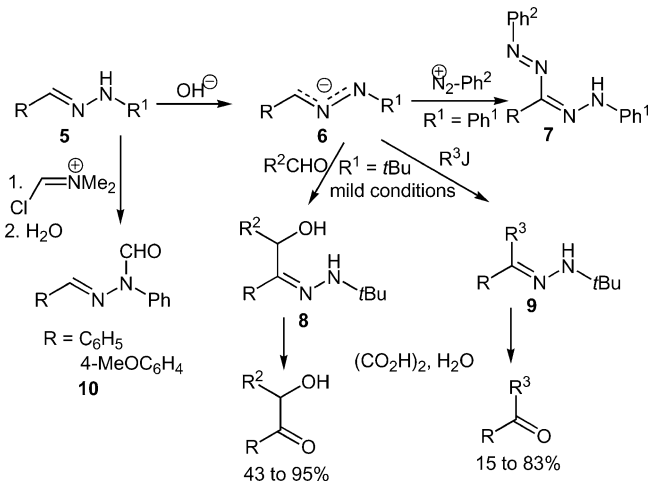
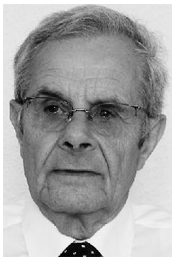


Scheme 1. Nucleophilic acylation with aldehyde phenylhydrazones to afford formazanes **7** and with Baldwin's sterically hindered aldehyde hydrazones to afford alkylated hydrazones **8** and **9** following hydrolysis. *N*-formylation of benzaldehyde phenylhydrazones **5** to **10**.

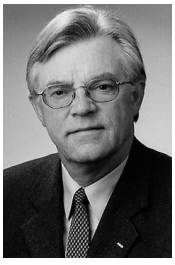
Baldwin extended the scope of this application decisively by the exchange of the phenyl residue for sterically demanding substituents, such as R^1 = *tert*-butyl, trityl, and diphenyl-4-pyridylmethyl in **5**, which block the reactivity of the hydrazone nitrogen atoms.[10] Sterically hindered aldehyde hydrazone anions **6** react under mild conditions ambidoselectively with weak electrophiles such as alkyl halides and aldehydes or ketones to alkanone and hydroxyalkanone hydrazones **9** and **8**, which can be hydrolyzed to the parent ketones.[10a,10b]

Besides reactions via anions **6**, *N*-monosubstituted hydrazones **5** also react under neutral conditions in thermal ene-[10c,10d,9a] or other[9d,9f] type pathways. Common to all of them is the secondary amino group with the NH functional group that can lead to side reactions.[9,10,11,12]

In contrast to hydrazones **5**, aldehyde *N*,*N*-dialkylhydrazones bear a tertiary amino group and they are also capable of nucleophilic acylations. They turned out to be a third type of acyl anion equivalence in the series of the aldehyde hydrazones. This latter type of umpolung chemistry will be fully covered in this review.



Rainer Brehme was born in 1933 in Meißen. He studied chemistry at the Humboldt University in Berlin where he received his Diploma in 1959 and his Dr.rer.nat in 1963 under the supervision of Prof. L. Reichel. He then moved to the pharmaceutical industry and developed procedures for the synthesis of pharmaceuticals on industrial scale. In addition, he dealt with the aza-enamine concept and obtained his Dr.sc.nat. in 1985. From 1993–1995 he worked at the "Max-Plack-Institut für Kolloid und Grenzflächenforschung" in Potsdam on surfactants and the regrowth of raw materials.



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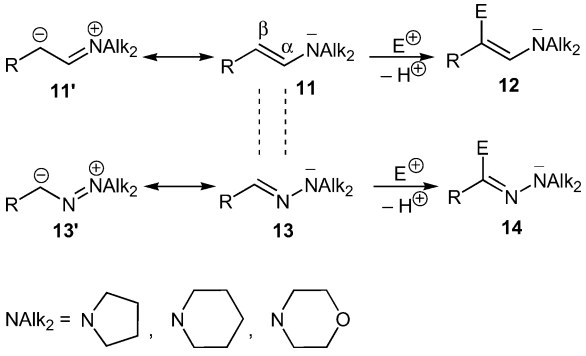
2. The Aza-Enamine Concept

A glance at the formulas shows that both enamines **11** and aldehyde hydrazones **13** are constructed similarly. The basic skeleton consists of a double bond bearing an amino group. They only differ by the isoelectronic exchange of the enamino α-carbon atom for the azomethine nitrogen in the hydrazones (Scheme 2).[13,14]

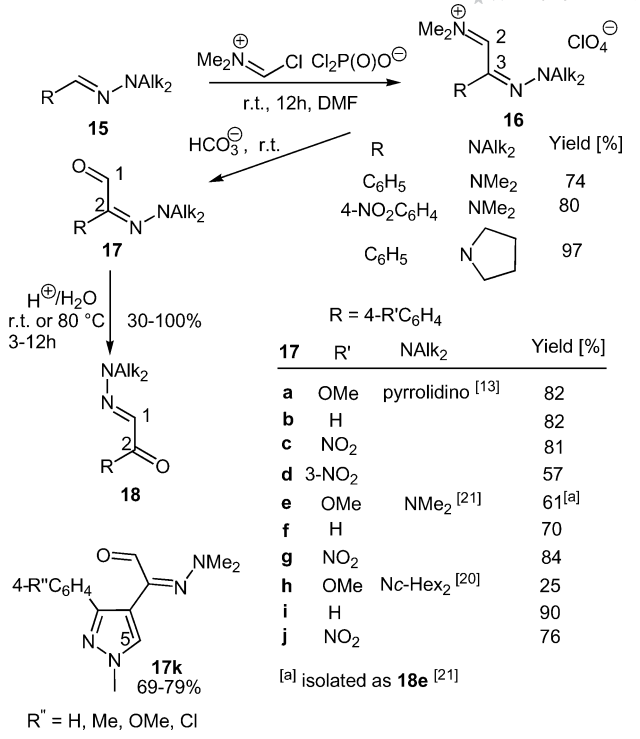


Scheme 2. Comparison of the structures and reactions of enamines and aldehyde *N*,*N*-dialkylhydrazones.

The most important property of enamines is their ability to undergo electrophilic substitutions at the β-carbon atom to afford compounds of type **12**.[15] They owe this property to the conjugative interaction between the C=C bond and the amino lone pair in the sense of mesomeric structure **11′**. The mostly used and most effective electron-donating groups are the pyrrolidino, piperidino, and morpholino moieties.[15] It turned out that analogous reactions also take place with aldehyde hydrazones containing such tertiary electron-donating amino groups instead of the secondary amino ligands NHR[1] in **5**.[13,16] Aldehyde *N*,*N*-dialkylhydrazones **13**,[16,17] especially those with pyrrolidine as the amino group, react with electrophiles to compounds **14** at the azomethine carbon, which corresponds to the enamino β-carbon and thus can indeed be regarded as "aza-enamines".[13,14] Despite the higher electronegativity of the imine nitrogen relative to the α-carbon of enamines, these hydrazones have proved to be important reagents for umpolung, which are in contrast to basic anionic types **1**, **2**, **3**, and **6** *neutral* equivalents of the acyl anion d[1]-synthon **4**.

3. Formylations of Aldehyde *N*,*N*-Dialkylhydrazones with the Vilsmeier Reagent

The Vilsmeier reagent is an often employed well-suited electrophilic formylation reagent.[18] Whereas benzaldehyde monophenylhydrazone **5** provided *N*-formyl product **10**[12] (Scheme 1), benzaldehyde *N*,*N*-dialkylhydrazones **15a**–**j** with the pyrrolidino, the dimethylamino, and the dicyclohexylamino functionalities as the amino moiety were − according to the aza-enamine concept and in analogy to enamines[18,19] − attacked at the azomethine carbon, leading via triaza-pentadienium salts **16** and after hydrolysis to 2-phenylglyoxal hydrazones **17a**–**j**[13,20,21] (Scheme 3).



R	NAlk2	Yield [%]
C6H5	NMe2	74
4-NO2C6H4	NMe2	80
C6H5	N	97

17	R'	NAlk2	Yield [%]
a	OMe	pyrrolidino [13]	82
b	H		82
c	NO2		81
d	3-NO2		57
e	OMe	NMe2 [21]	61[a]
f	H		70
g	NO2		84
h	OMe	Nc-Hex2 [20]	25
i	H		90
j	NO2		76

[a] isolated as **18e** [21]

Scheme 3. Vilsmeier formylation at the azomethine carbon of benzaldehyde- and pyrazolecarbaldehyde *N*,*N*-dialkylhydrazones to **17** and hydrazone shift to **18**.

A few pyrazole-4-carbaldehyde dimethylhydrazones were also examined and yielded 2-pyrazolylglyoxal 2-dimethylhydrazones **17k**. No formylation at the vinylogous 5-position was detected.[22] In contrast, the pyrrolidino, piperidino, and morpholino hydrazones of the furan-2-carbaldehyde and of the aliphatic aldehydes did not furnish isolable compounds in the Vilsmeier reaction.[16,20] The benzaldehyde morpholino and piperidino hydrazones formed the corresponding phenylglyoxal hydrazones only in small amounts (1–25%). Their reactions were not worked up, but the compounds were isolated and determined as phenylglyoxal bis(4-nitrophenylhydrazones).[20] A few 3-phenyl-1,4,5-triaza-1,3-pentadienium salts **16** could be isolated as defined perchlorates.[20,21,23] Under acidic conditions, a hydrazine-transfer takes place from the 2-position in phenylglyoxal 2-hydrazones **17** to the 1-position to give rise to 2-phenylglyoxal 1-hydrazones **18a**–**j**.[20,21] Severin obtained compounds **16**–**18** in a different way and published their preparative significances.[24] The conversion of the hydrazones into the parent aldehydes by ozonolytic cleavage is well known.[25] Compounds **17** and **18** described here were not hydrolyzed.

4. Reactions with Sulfonyl Isocyanates

Sulfonyl isocyanates[26] are highly enough electrophilic compounds to react with aza-enamines. However, the amidation of benzaldehyde *N*,*N*-dialkylhydrazones **19** can proceed in two different directions depending on the $NAlk_2$

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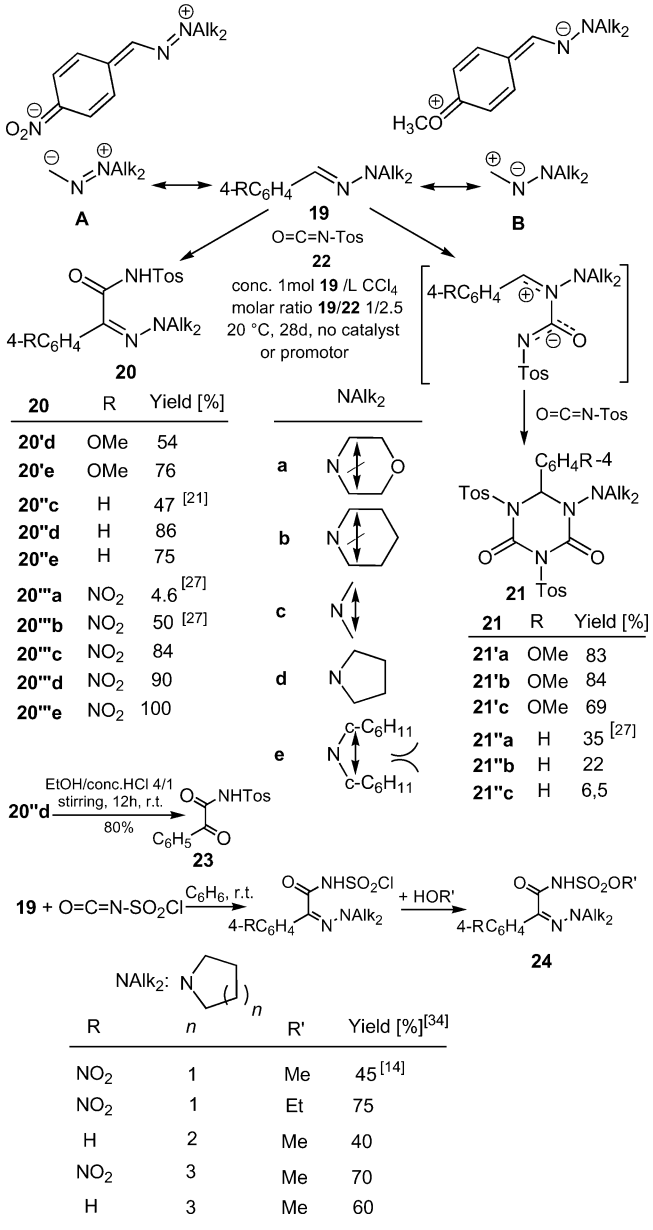
amino ligands and the substituents in the aromatic part. The attack takes place either according to mesomeric structure **A** at the azomethine carbon atom to deliver glyoxylic acid sulfonamido hydrazones **20**[14,21,23,27] or according to reactivity **B** at the azomethine nitrogen atom, which leads via an intermediate 1,4-dipolar cycloaddition to 1,3,5-triazinane-2,4-diones **21**[27,28] as outlined in Scheme 4 (see also ref.[29]). At first, phenyl-, 4-tolyl-, and methylsulfonyl isocyanates were employed as electrophiles. The reactions were performed at room temperature or in boiling benzene or CCl_4 and completed in 1–2 h.[14,27] In order to find out more precisely the direction of the reaction, a trial series was carried out under standardized conditions with 4-tosyl isocyanate **22** as the electrophile and benzaldehyde hydrazones **19a**–**e** with substituents R = OMe, H, and NO_2 in the 4-position.[28,30] The results listed in Scheme 4 show that the reactions proceeded remarkably selectively. It is evident that compounds **21** were formed from hydrazones **19** with R = OMe or H and morpholine, piperidine, or dimethylamine as the amino components. In all other cases, compounds **20** were formed.

Thus, in anisaldehyde hydrazones **19** (R = OMe) the methoxy group as an electron-donating substituent delocalizes the formal positive charge at the azomethine carbon of **B** and favors the imine-like reactivity. The donor potentials of the morpholino, piperidino, and dimethylamino residues are not sufficient to overcome the opposite influence of the methoxy group. That is why the electrophilic attack takes place at the azomethine nitrogen atom to yield **21′a**–**c**. However, the pyrrolidino and dicyclohexylamino substituents as strong electron donors lead to umpolung and therefore to attack at carbon to form **20′d**,**e**.

Umpolung is a little more favored in the case of benzaldehyde hydrazones **19** (R = H). Here the influence of the methoxy susbstituent lacks to give **21"a**,**b** and **20"d**,**e**, respectively, as well as a mixture of **20"c** and **21′′c**. The strong electron-acceptor substituent R = NO_2 in hydrazones **19** increases the contribution of dipolar structure **A** and so favors umpolung, that is, the aza-enamine reactivity gives compounds **20′′′a**–**e** (Scheme 4). The degree of the n–π interaction in dependence of the substituents $NAlk_2$ and R corresponding to canonical structures **A** and **B** parallels with the ^1H,[30] ^{13}C,[13,28] and ^{15}N[31] NMR shifts of the azomethine function and the λ_{max} values[23,30] of the hydrazones **19**.

The following conclusions can be drawn from the results reported so far: The pyrrolidino group **d** is a very efficient electron donor in aza-enamine chemistry, which is in contrast to the morpholino (**a**) and the piperidino (**b**) ligands (compare also Chapter 3); the causes for these differences have been already discussed.[32] Scheibe attributes the conjugative interaction to the state of hybridization of the nitrogen atom of the amino group, which depends on the valence angles at the nitrogen atom.[33] Because of ring strain, these can be spread only insufficiently in the six-membered rings, a fact that leads to less overlap. In contrast, hydrazones with open noncyclic amino groups proved to be very reactive aza-enamines. These compounds can spread their



20	R	Yield [%]
20'd	OMe	54
20'e	OMe	76
20"c	H	47 [21]
20"d	H	86
20"e	H	75
20'''a	NO_2	4.6 [27]
20'''b	NO_2	50 [27]
20'''c	NO_2	84
20'''d	NO_2	90
20'''e	NO_2	100

21	R	Yield [%]
21'a	OMe	83
21'b	OMe	84
21'c	OMe	69
21"a	H	35 [27]
21"b	H	22
21"c	H	6,5

R	n	R'	Yield [%][34]
NO_2	1	Me	45 [14]
NO_2	1	Et	75
H	2	Me	40
NO_2	3	Me	70
H	3	Me	60

Scheme 4. Attack of sulfonyl isocyanates on the azomethine functionality of benzaldehyde *N*,*N*-dialkylhydrazones. Top: substitution and addition with 4-tolylsulfonyl isocyanate **22** to **20** and **21**, respectively, under standard conditions and hydrolysis of **20"d** to **23**; bottom: substitution at the azomethine carbon with chlorosulfonyl isocyanate to **24**.

nitrogen valence angles without hindrance, which thereby achieves good interaction with the azomethine double bond. This applies not only to the *N*,*N*-dicyclohexylhydrazones but also to the dimethylhydrazones demonstrated by compounds **17e**–**g** in Scheme 3 and by many subsequent examples. However, the more effective electron donor is the dicyclohexylamino group as the comparison of **20′e** and **21′c** shows in Scheme 4. The reason may be the sterically demanding bulkiness of the cyclohexyl[12] group and also of the diisopropyl substituents (see subsequent chapters). These could bring about a decrease of the s character of the p(π) orbital and a shielding of the azomethine carbon

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from the competitive reactivity of the azomethine nitrogen atom in Baldwin's sense; thus, the reaction is directed along the desired carbon acylation pathway.

In contrast, the azomethine carbon is also sterically hindered by its aromatic and aliphatic substituents. Therefore, the formaldehyde hydrazones are the most versatile nucleophilic acylation reagents of the series of the aza-enamines (see in detail subsequent chapters). These facts are depicted once more in Figure 2.

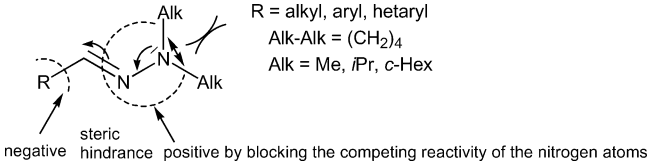
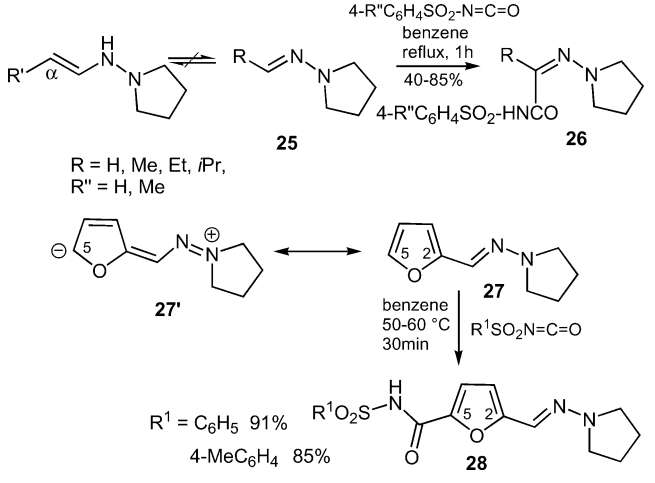


Figure 2. Steric and electronic factors that influence the nucleophilicity of the azomethine carbon of aldehyde *N*,*N*-dialkylhydrazones.

Also, the substituents in the aromatic moiety influence the electronic behavior according to structures **A** and **B** (Scheme 4). However, the main basis for the umpolung of the reactivity is the special intrinsic property of the hydrazone structure element. Here, two centers of the same affinity are directly linked; thus, the natural polarity is reversed.[1]

Scheme 4 also outlines the reaction of **19** with strongly reactive chlorosulfonyl isocyanate to afford **24**[14,34] and also the hydrolysis of **20′′d** to parent ketone **23**.[14] Noteworthy is that aliphatic aldehyde hydrazones **25** were also attacked at the azomethine carbon to afford **26** and not at the imine nitrogen atom, the NH group, or the α-position, which could be a consequence of a possible tautomeric enehydrazine[16] (Scheme 5).

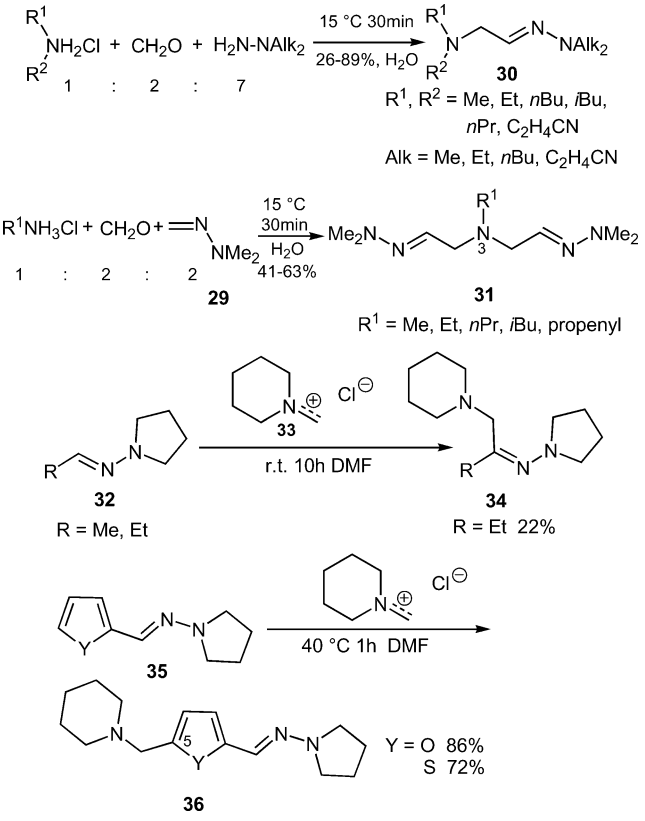


Scheme 5. Reaction of *N*,*N*-tetramethylene hydrazones of aliphatic aldehydes and of furan-2-carbaldehyde with sulfonyl isocyanates.

The reaction of furan-2-carbaldehyde *N*,*N*-tetramethylene hydrazone **27** with sulfonyl isocyanates also proceeded; however, it was not substituted at the azomethine carbon but at the vinylogous 5-position affording **28**[16] (Scheme 5). Thus, it turns out to be a vinylogous aza-enamine (see Chapter 8). With the less reactive phenyl or benzoyl isocyanates neither the benzaldehyde hydrazones nor the saturated aliphatic aldehyde hydrazones delivered compounds carboxylated at the azomethine carbon in contrast to the carboxylation at the β-carbon of the enamines.[15] This can be explained by the stronger electronegativity of the azomethine nitrogen, which reduces n–π overlap. Thus, aza-enamines can be compared with enol ethers in their reactivity.[14,35]

5. Aminomethylations with the Mannich Reagent

Gafarov and Konovalova[36] carried out the aminomethylation of formaldehyde *N*,*N*-dialkylhydrazones **29** by the classic method with ammonium salts and formaldehyde in aqueous solution. The salts of the dialkylamines gave the *N*,*N*-dialkylhydrazones of dialkylamino acetaldehydes **30**, whereas those of the monoalkylamines gave bis(dimethyl)-hydrazones **31** (Scheme 6). The hydrazones of higher aliphatic aldehydes **32** did not provide isolable compounds in aqueous solution. However, with Böhme reagent **33**[37] in anhydrous DMF, 1-piperidinoalkan-2-one hydrazones **34** were formed.[16] Whereas the Böhme reagent was too mild in the reaction with the benzaldehyde *N*,*N*-tetramethylene hydrazones, both furan-2-carbaldehyde and thiophene-2-carbaldehyde *N*,*N*-tetramethylene hydrazones **35** provided **36** in good to very good yields.[16] Despite a few attempts, the reaction of benzaldehyde *N*,*N*-dimethylhydrazones with the Viehe reagent[18] failed.[38] Alkylations occurred pre-



Scheme 6. Aminomethylation of aliphatic and heterocyclic aldehyde *N*,*N*-dialkylhydrazones.

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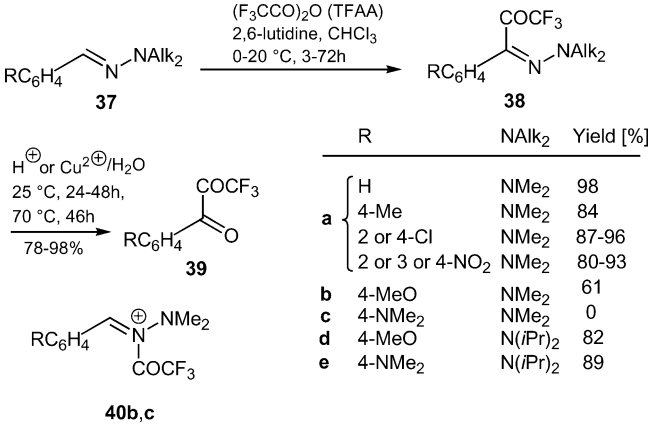
dominantly at the amino nitrogen atom, which is a third nucleophilic center of the hydrazones[39–41](see also **92** and **93** in Scheme 17).

6. Reactions with Trifluoroacetic Anhydride (TFAA)

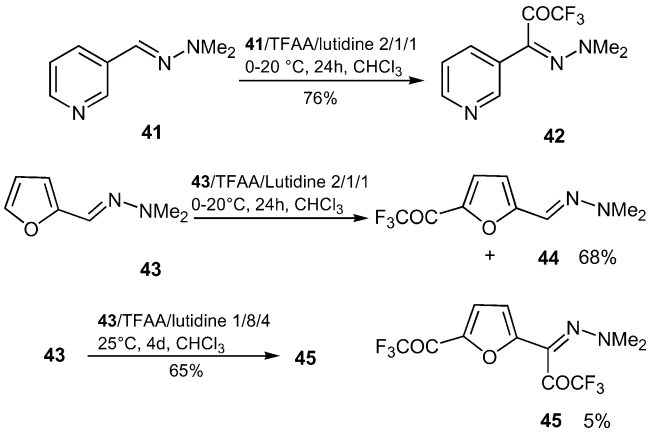
6.1. Acylations of Benzaldehyde and Heterocyclic Aldehyde Dialkylhydrazones

Hojo and colleagues treated benzaldehyde *N*,*N*-dialkylhydrazones **37** with strongly electrophilic trifluoroacetic anhydride to form trifluoromethyl-1,2-diketone hydrazones **38** (Scheme 7).[42] These acylations also proceeded without catalysts and were only partly promoted by added tertiary bases. Whereas the reaction of benzaldehyde dimethylhydrazones **37a** with TFAA furnished compounds **38a** in high yields, **38b**,**c** were only obtained in 61 and 0% yield, respectively. The yields increased again with diisopropylhydrazones **38d**,**e**. This may again be a result of the steric demand of the bulky diisopropyl groups, as was discussed for the reaction between sulfonyl isocyanates and the aza-enamines with the sterically demanding dicyclohexyl ligands at the amino group (Chapter 4).



Scheme 7. Reaction of benzaldehyde *N*,*N*-dimethyl and benzaldehyde diisopropylhydrazones with trifluoroacetic anhydride.

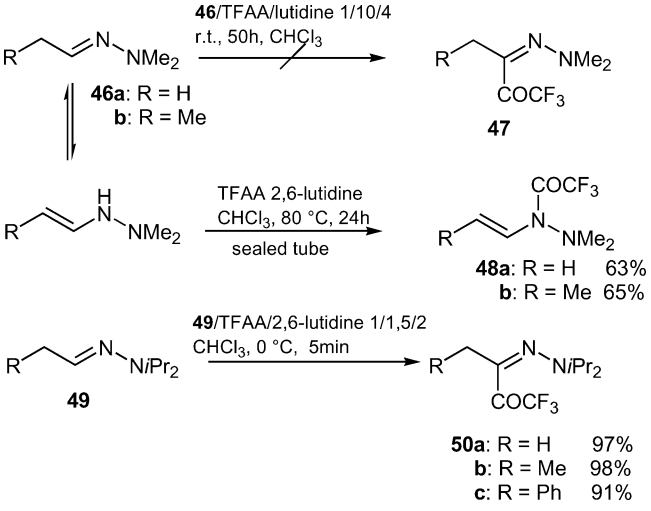
Electrophilic attack at the azomethine nitrogen atom was probably responsible for the poor yield of **38b** and for the failure to obtain **38c**; this supposition was proved by the fact that **40b**,**c** were detected by ^{1}H NMR spectroscopy and indirectly by their instability towards water: both **40b**,**c** could not be isolated; they hydrolyzed during workup to starting hydrazones **37**, so that **37b** provided a mixture of **38b** and **37b** as final product and **37c** a mixture of **37c** and the parent 4-(dimethylamino)benzaldehyde. Compounds **38** and **39** are attractive substrates for fluorine-containing heterocycles.[43] The reaction of TFAA with nicotinaldehyde dimethylhydrazone **41** gave **42** as the sole product acetylated at the azomethine carbon (Scheme 8), whereas the reaction of furancarbaldehyde hydrazone **43** proceeded at the 5-position to afford a mixture of **44** and **45** in 68 and 5% yield, respectively. In order to obtain **45** as the sole product, an eightfold excess of TFAA was necessary.[42]



Scheme 8. Trifluoroacetylation of the dimethylhydrazones of the pyridine- and furancarbaldehydes.

6.2. Trifluoroacylation of Saturated Aliphatic Aldehyde Dialkylhydrazones

Both acetaldehyde and propionaldehyde dimethylhydrazone **46a**,**b** showed remarkable resistance towards TFAA under mild conditions and did not allow substitution at the azomethine carbon to afford **47** at room temperature (Scheme 9). Steric hindrance by the alkyl substituents at the azomethine carbon was supposed to be responsible[44] (see also Chapter 7).



Scheme 9. Reaction of TFAA with acetaldehyde and propionaldehyde dialkylhydrazones.

When **46a**,**b** were treated at 80 °C in a sealed tube, unexpected *N*-acetyl enamines **48a**,**b** were obtained in good yields as a consequence of the enhydrazine character of **46**, but no **47** was formed. The bulky diisopropyl groups at the terminal nitrogen atom suppressed the undesirable N-attack. So, acetaldehyde-, propionaldehyde-, and phenylacetaldehyde diisopropylhydrazones **49** were readily converted

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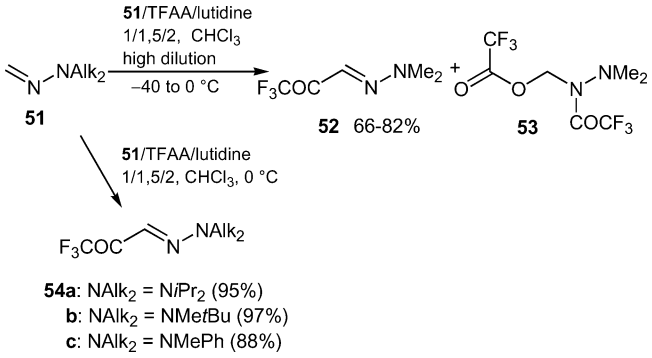
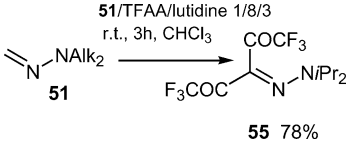
into corresponding hydrazones **50**, acylated at the carbon atom. Formaldehyde dimethylhydrazone **51** ($NAlk_2$ = NMe_2), which is not able to form a tautomeric enhydrazine, was acylated predominantly at the azomethine carbon atom to give **52**, although undesirable adduct **53** was simultaneously formed. Best yields resulted under higher dilution at – 40 °C (Scheme 10).



Scheme 10. Trifluoroacylation of formaldehyde *N*,*N*-dialkylhydrazones bearing methyl or bulky substituents at the amino nitrogen atom.

As expected, by using the bulky *N*,*N*-diisopropylamino group, or the *N*-*tert*-butyl-*N*-methyl and *N*-phenyl-*N*-methylamino substituents, undesirable N-attack was inhibited to yield *C*-acylated compounds **54a**–**c** as the sole products. Hojo and colleagues also examined the bis(trifluoroacetylation) of formaldehyde hydrazones.

The diisopropylhydrazone derivative afforded **55** (Scheme 11), whereas the dimethylhydrazone derivative afforded a mixture of mono and diacetylated formaldehyde hydrazones and heterocyclic compounds.[44]

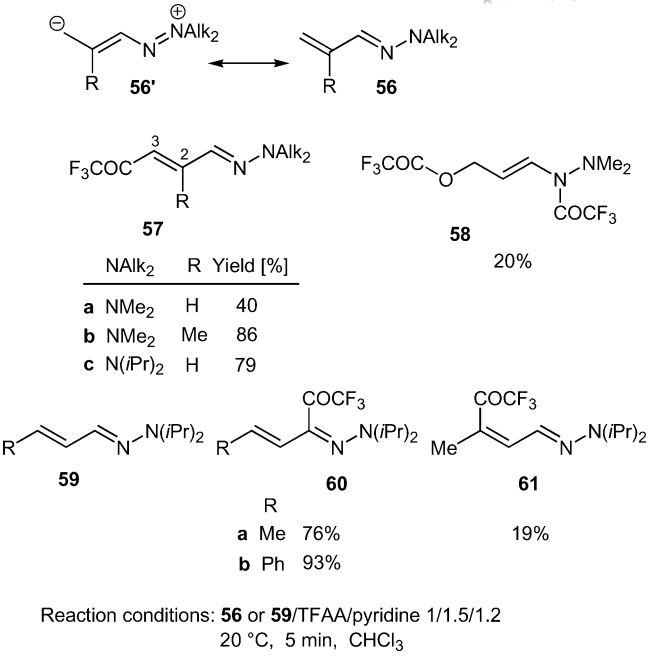


Scheme 11. Bis(trifluoroacylation) of formaldehyde *N*,*N*-diisopropylhydrazone.

6.3. Trifluoroacylation of Unsaturated Aldehyde Hydrazones

α,β-Unsaturated aldehyde hydrazones react, depending on their substituents, either at the azomethine carbon atom or at the vinylogous position. Thus, trifluoroacylation of acrolein and methacrolein hydrazones **56** occurred preferentially at the terminal 3-position to afford **57** (Scheme 12).[44] Compounds **57c**,**b** owe their high yields to the protecting effect of the bulky isopropyl substituents and the methyl group in 2-position, respectively. This protection from *N*-acylation is absent in acrylaldehyde hydrazone **56a**; therefore, adduct **58** also forms alongside **57a**.

In contrast, the diisopropylhydrazone of cinnamaldehyde **59b** was not attacked at the terminal position, and the diisopropylhydrazone of crotonaldehyde **59a** only gave **61** in

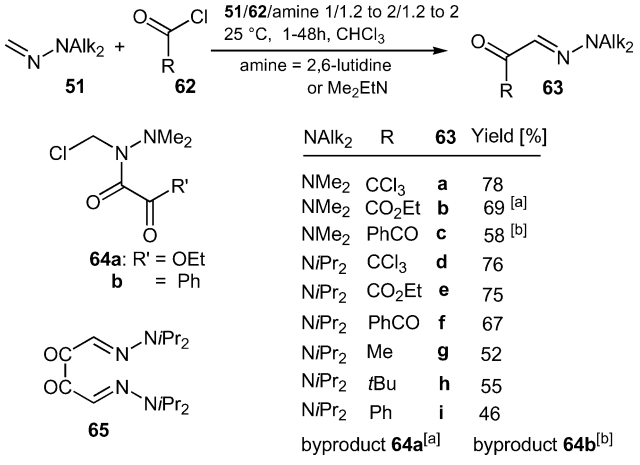


Scheme 12. Trifluoroacylation of α,β-unsaturated aldehyde hydrazones.

19% yield. Both the phenyl and methyl substituents provided steric hindrance to conjugative attack at the terminal olefinic carbons; hence, the reactions at the azomethine carbon atom to give **60a**,**b** was favored.

7. Reactions of Formaldehyde Dialkylhydrazones with Some Other Acylating Reagents

Formaldehyde hydrazones also react with milder acylating agents such as **62a**–**i**[44] (Scheme 13). Thus, the reactions of formaldehyde dimethylhydrazone with trichloroacetyl chloride, ethyl chloroglyoxylate, and phenylglyoxylyl chloride afforded acylated compounds **63a**–**c** and those of formaldehyde diisopropylhydrazone gave **63d**–**f**. The reactions of the diisopropylhydrazones additionally proceeded with ace-



Scheme 13. Reaction of formaldehyde dialkylhydrazones with weaker acylation reagents.

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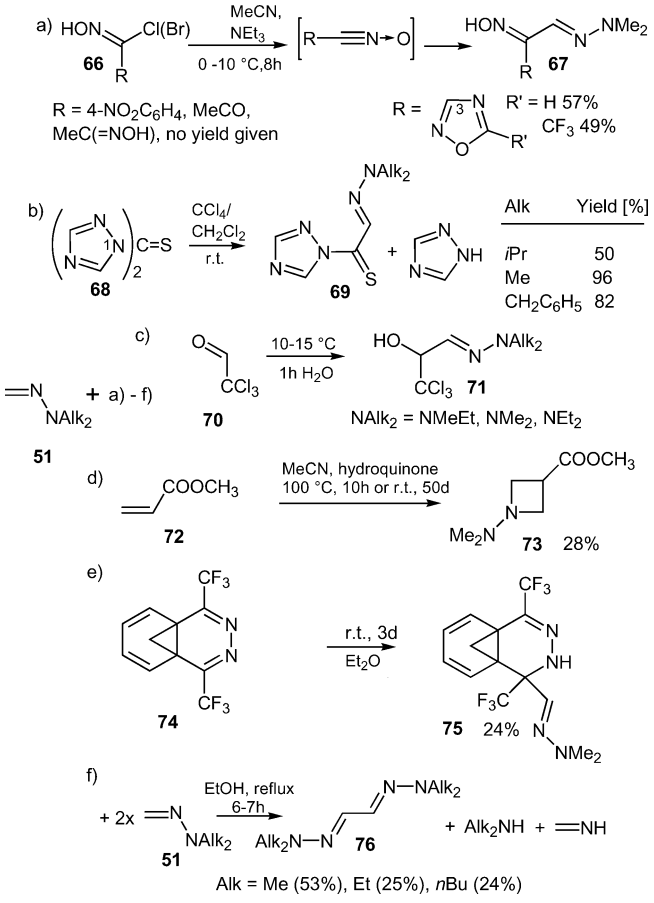
tyl-, pivaloyl-, and benzoyl chloride to form **63g–i**. The reaction of formaldehyde hydrazone (2 equiv.) with oxalyl dichloride delivered compound **65**.

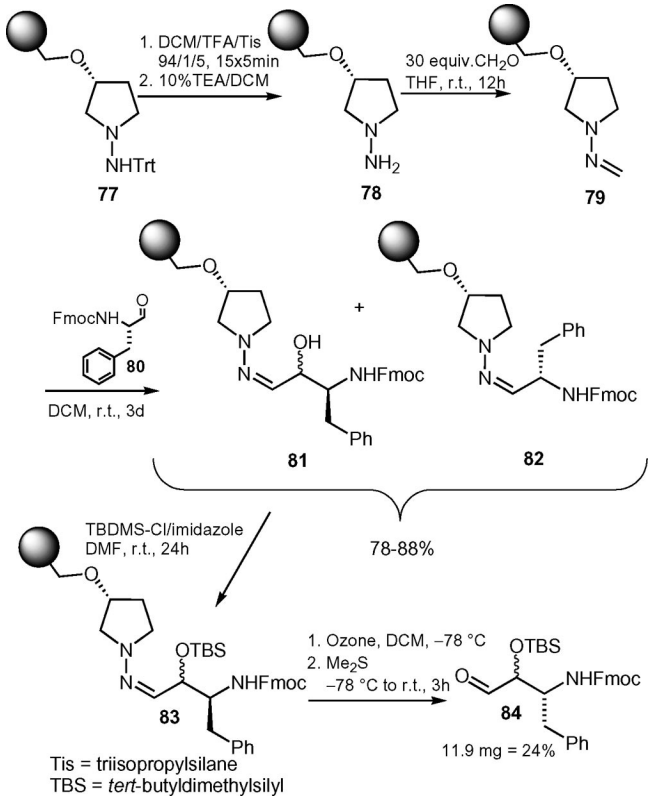
A summary of the results presented so far indicates that the substituents at the amino groups are not entirely responsible for steric influences. Steric hindrance is also caused by substituents at the azomethine carbon atom.[44] Therefore, the reaction of formaldehyde hydrazones lacking substituents proceeds smoothly with milder electrophiles, too, and thus, they rank among the most reactive aza-enamines. This fact is also confirmed by the reactions demonstrated in Scheme 14. They only take place with formaldehyde hydrazones.



Scheme 14. Reactions of formaldehyde dialkylhydrazones **51** with (a) hydroxamic acid halides **66** to form hydroxyimino hydrazones **67**;[45] (b) 1,1′-thiocarbonyl bis(triazole) **68** to form the dimethylhydrazones of thioglyoxalyl-1,2,4-triazole **69**, but no reaction takes place with 1,1′-thiocarbonylbis(imidazole); the reaction of acetaldehyde *N*,*N*-dimethylhydrazone with **68** does not proceed;[46] (c) chloral **70** to form 2-hydroxy-3,3,3-trichloro-1-propanone hydrazones **71**;[47] (d) methyl acrylate **72** to form methyl 1-(dimethylamino)azetidin-3-carboxylate **73**,[48a] but see ref.;[48b] however, the reaction with acrylonitrile 2-dimethylamino propenonitrile results in [2+3] dipolar cycloaddition with urotropine as a byproduct; (e) phthalazine **74** to form addition product **75**;[49] (f) itself to form head-to-head dimer glyoxal bis(hydrazone) **76**; here, **51** acts as both a nucleophile and an electrophile.[50]

For further reactions of formaldehyde dialkylhydrazones, especially in asymmetric syntheses, see Chapters 11–13.

Nucleophilic formylation with immobilized formaldehyde tetramethylene hydrazone was also investigated.[51a,51b] This technique of polymer-assisted solution-phase (PASP) syntheses has advantages over the conventional applications in liquid phase such as the ease of separation of the supported species from a reaction mixture by filtration and washing, the opportunity to use an excess amount of the reagent to force the reaction to completion without causing workup problems, and the adaptability to continuous-flow processes.[51c] Solution synthesized (3*R*)-1-(tritylamino)-3-pyrrolidinol was anchored to the Merrifield methylpolystyrene resin through an ether bridge to afford **77**, which was thus immobilized. Compound **77** was then deprotected to afford 7**8**, which was then treated with formaldehyde to afford **79** (Scheme 15). On the basis of the results of Lassaletta and Fernandez working in the liquid phase,[52] Fmoc-phenylalaninal **80** was used as an electrophilic substrate that gave a mixture of desired α-hydroxyaldehyde hydrazone **81** and byproduct **82** was formed by aldehyde exchange. Compound **83** protected at the OH group by TBS chloride was finally cleaved by oxidation to **84** whose structure was confirmed after purification by preparative HPLC by ^{1}H and ^{13}C NMR spectroscopy.



Scheme 15. Nucleophilic formylation of Fmoc-phenylalaninal **80** by polymer-supported formaldehyde *N*,*N*-tetramethylene hydrazone **79** to afford α-hydroxyaldehyde **84** [probably *anti* product (2*S*,3*S*)].

Now the focus is directed on further nucleophilic acylations through the hydrazone linker strategy, such as an expansion to any α-aminoaldehydes or also an acceleration of these reactions by catalysts.[51a] Also remarkable is the

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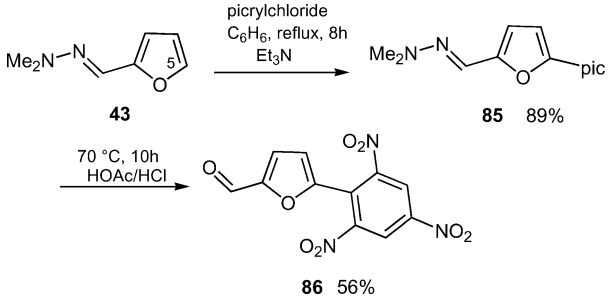
phenylation with mild picryl chloride. However, to date, this reaction has only been performed with the vinylogous aza-enamine furan-2-carbaldehyde dimethylhydrazone[53] and not with the formaldehyde hydrazone itself (Scheme 16).



Scheme 16. Reaction of picryl chloride with furan-2-carbaldehyde dimethylhydrazone.

The pronounced tendency of the hydrazones of five-membered heterocycles for nucleophilic attack of electrophilic substrates at the 5-position may be due to the fact that this ω-position, unlike the azomethine position, is free of sterically hindered substituents, which is in analogy to the free formaldehyde hydrazone.

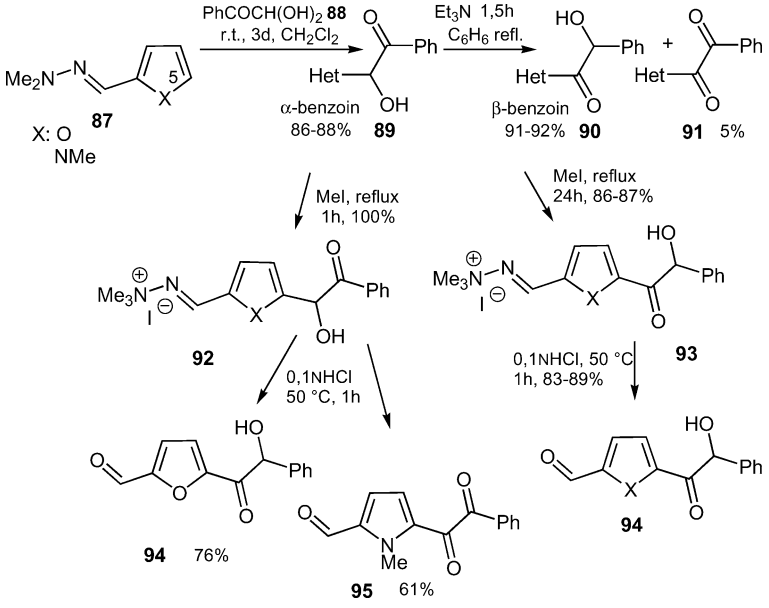
8. Nucleophilic Additions of Vinylogous Aza-Enamines to Activated Double Bonds

Vinylogous aza-enamines are *N*,*N*-dialkylhydrazones of unsaturated aldehydes. To them belong the noncyclic hydrazones of acrylaldehyde-type derivatives as well as the aldehyde hydrazones of the five-membered heterocycles. Bond formation occurs preferentially at the ω-position according to canonical structures **27′** and **56′** to afford unsaturated aldehydes after hydrolysis. Besides the nucleophilic substitution reactions presented in **36**, **44**, **57**, **61**, **85**, and in subsequent examples, nucleophilic additions to activated double bonds are also known. A first example already demonstrated is the addition of furan-2-carbaldehyde hydrazone **27** to the C=N bond of sulfonyl isocyanate, which affords **28** (Scheme 5). Benzoins **89** were formed smoothly by reaction of hydrazones **87** with less-reactive phenylglyoxal hydrate **88** at room temperature (Scheme 17). Such a reaction was found to be impossible with unsubstituted heterocycles.[54]

Less-stable α-benzoins **89** isomerize to β-benzoins **90**; some benzil **91** was formed by atmospheric oxygen. To regenerate the parent carbonyl functionality, both α- and β-benzoins were methylated, and hydrazonium iodides **92** and **93** were hydrolyzed to aldehydes **94** and **95**.

Also described are the addition reactions of **96** to Michael acceptors such as azodicarboxylate **97** to afford **98**.[55] The addition of **96** to acetylenedicarboxylate **99** and to tetracyanoethylene **102** to afford **100**[56] and **101**,[57] respectively, have also been documented, but the latter reaction may possibly proceed by an addition–elimination mechanism (Scheme 18).

This course is remarkable, because both furan-2-carbaldehyde dimethylhydrazone **96** (X = O) as a good diene exemplified by the synthesis of **103**[58] and the three electron-deficient substrates as dienophiles are well-known partners in the Diels–Alder reaction.[59] To his surprise, Potts found that **43** acts similarly towards 1,4-benzo- and 1,4-naphthoquinone **104** as well as towards quinoline-5,8-dione and isoquinoline-5,8-dione **105**. Instead of the expected oxidized Diels–Alder cycloaddition product **106**, Michael adducts



Scheme 17. Formation of benzoins from furan-2-carbaldehyde and *N*-methylpyrrole-2-carbaldehyde dimethylhydrazones and phenylglyoxal hydrate.

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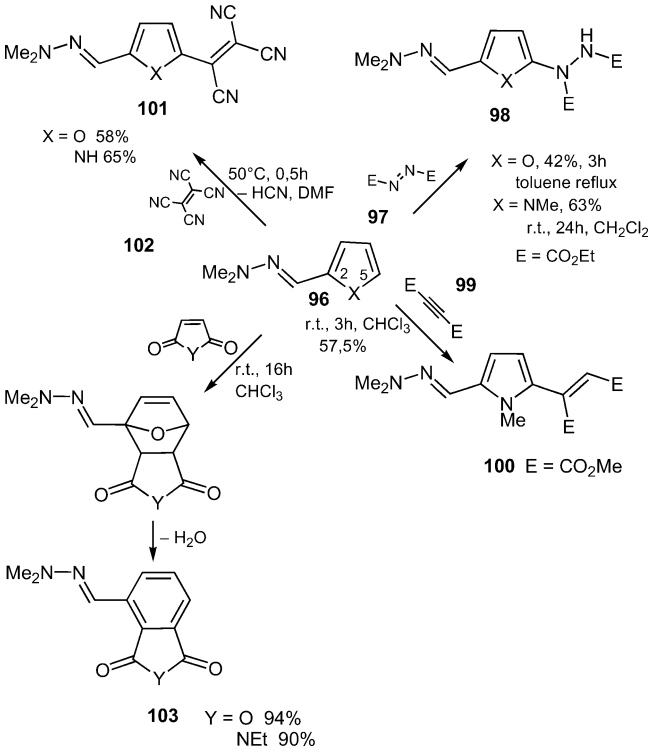
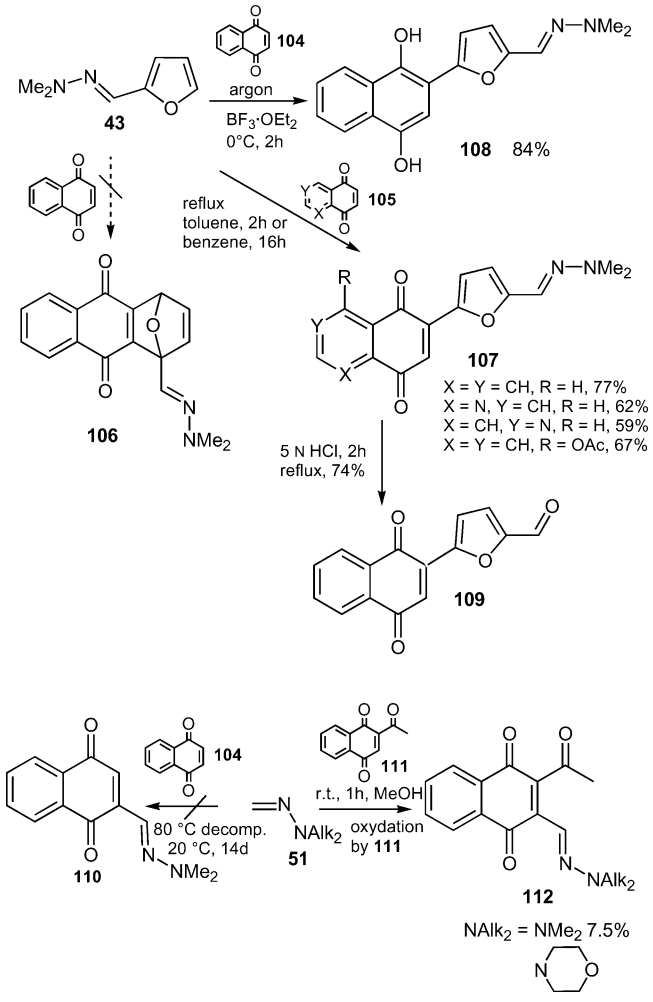


Scheme 18. Nucleophilic formylations by the addition of 2-carbaldehyde dimethylhydrazones of five-membered heterocycles to Michael electrophiles, and the Diels–Alder addition of furan-2-carbaldehyde dimethylhydrazone to maleinanhydride and maleinimide, respectively.



Scheme 19. Michael addition of the dimethylhydrazones of furancarbaldehyde **43** and formaldehyde **51** to quinones: comparison of their reactivities.

107 were obtained without a catalyst in the presence of atmospheric air[58b] (Scheme 19). When **43** was treated with 1,4-naphthoquinone in the presence of a catalyst under an inert atmosphere and at low temperature naphthoquinole **108** was isolated, because oxidation to quinone was avoided. Compound **107** was hydrolyzed with aqueous HCl, which led to aldehyde **109**. It should be pointed out that formaldehyde dimethylhydrazone **51** undergoes Michael addition to conjugated enones under mild conditions, as discovered by Fernandez, Lassaletta et al.[60] but towards naphthoquinone **104** it is inert at room temperature and at 80 °C[61] (Scheme 19), which is in contrast to furan-2-carbaldehyde dimethylhydrazone **43**.

Only activated naphthoquinone **111** bearing two different electron-withdrawing groups on the same carbon atom allows the formaldehyde hydrazone to undergo Michael addition to form **112**[61b] (see also refs.[62a,62b,48b]). These facts suggest that furancarbaldehyde hydrazones − perhaps as a consequence of a free 5-position that is sterically not hindered by a substituent − might react in the same way or even better as an acyl anion equivalent than the corresponding formaldehyde hydrazones in comparable reactions.

Noncyclic vinylogous aza-enamines can also be added to Michael acceptors. Although dialkylhydrazones of unsaturated aldehydes are used very often as 1-amino-1-aza-1,3-dienes in the Diels–Alder reaction (see Chapter 10), they can in certain cases also act as vinylogous acyl anion equivalents to give linear noncyclic Michael adducts with electron-deficient dienophiles. Thus, the reactions of acyloxymethylidene–malonodinitriles **113** with cyclopentadiene, cyclohexadienes, and anthracenes led to the Diels–Alder products, for example, **114**,[63a] but the reactions with acrylaldehyde hydrazones **115** gave Michael adducts **116** with a terminal formyl group after hydrolysis[63b] (Scheme 20). In addition, tricyclic ketone **117** did not provide expected [4+2] cycloadduct **118** with methacrylaldehyde hydrazone, but rather the unusual 1,4-addition product, probably because of the enhanced stability of indoline **119**.[64] Finally, Batty and Langlois found that 2-alkenyl-4*H*-1,3,4-oxadiazines **120**, by the authors also understood as vinylogous aza-enamines, do not react as 1-aza-1,3-dienes to afford cyclic products, but they do react with polar dienophiles to give linear addition products **121** and **122**.[65] With these examples the possibilities of the vinylogous aza-enamines to react as acyl anion equivalents with Michael electrophiles are certainly not exhausted yet.

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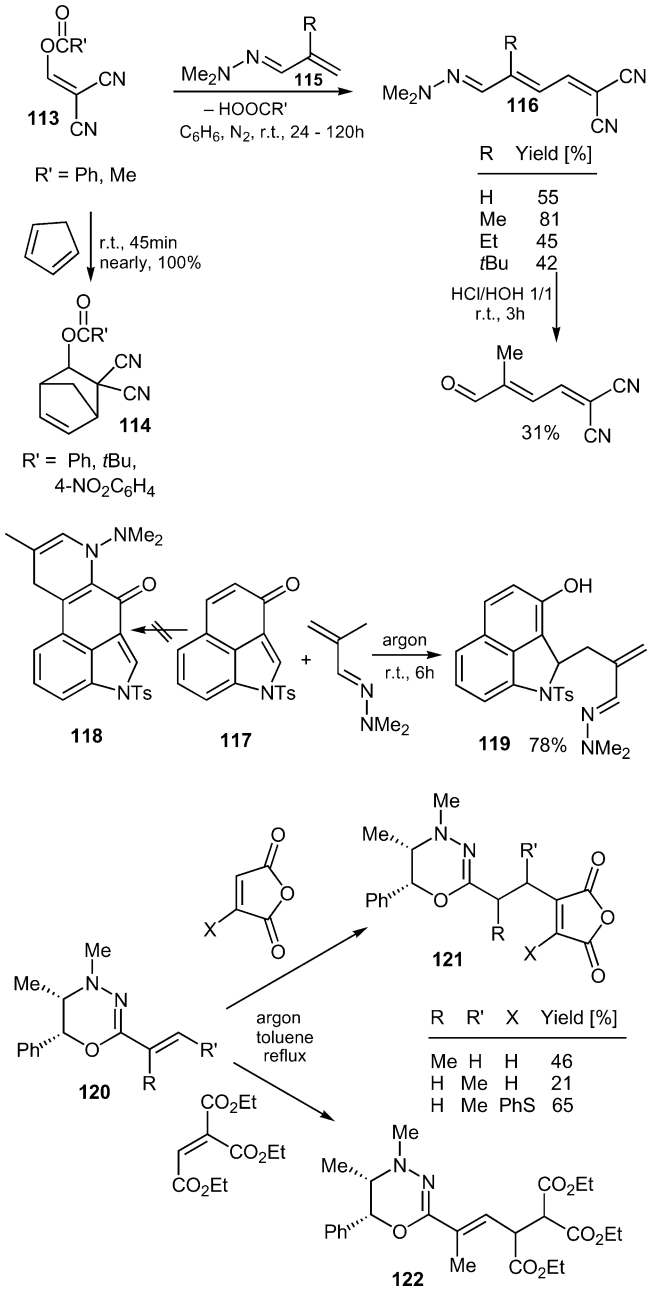
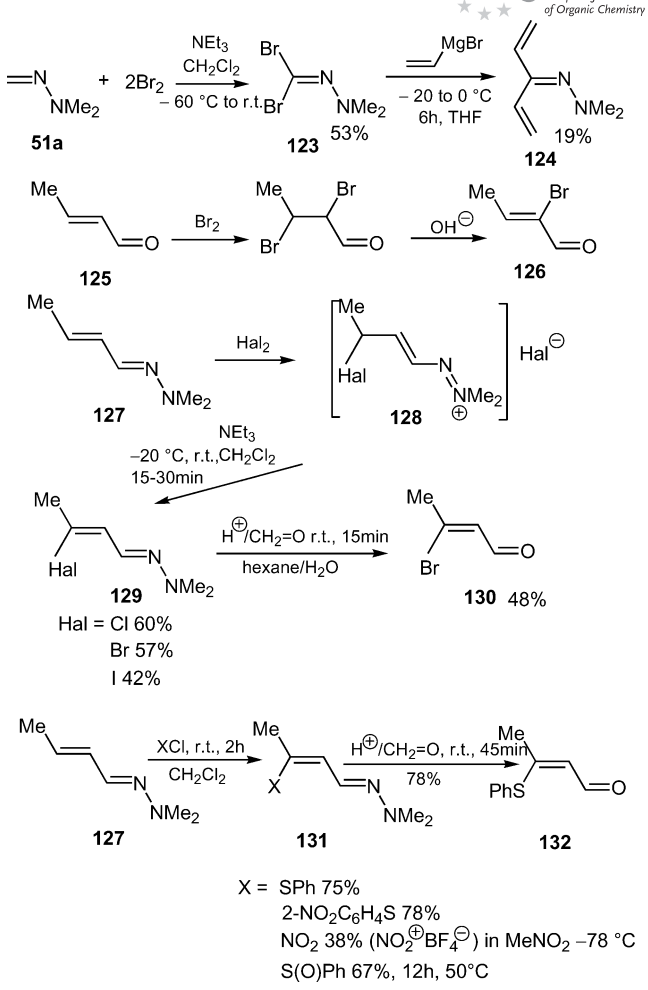


Scheme 20. Vinylogous aza-enamines reacting as acyl anion equivalents with electron-deficient dienophiles to give linear Michael-addition products.



Scheme 21. Bromination of **51a** and subsequent reaction with vinylmagnesium bromide. Reaction of crotonaldehyde dimethylhydrazone (**127**) with halogens and other electrophiles.

9. Carbon–Heteroatom Bond Formations

Koldobskii and Lunin brominated formaldehyde dimethylhydrazone (**51a**) to stable dibromo derivative **123** that was treated with vinylmagnesium bromide to afford **124**[66] (Scheme 21). Whereas crotonaldehyde (**125**) adds bromine at the 2,3-positions to afford after treatment with base 2-bromobut-2-enal (**126**), crotonaldehyde *N*,*N*-dimethylhydrazone (**127**) reacts as a vinylogous aza-enamine at the 3-position to give 3-bromobut-2-enal dimethylhydrazone (**129**), which was hydrolyzed to 3-bromobut-2-enal (**130**).[67]

Here the umpolung caused by the electron-releasing amino component is clearly demonstrated. Severin and coworkers assume **128** to be the intermediate. Analogous products resulted by using Cl_2, *N*-chlorosuccinimide, and I_2. In the same fashion, phenyl- and 2-nitrophenylsulfenyl chloride (PhSCl), phenylsulfinyl chloride (PhSOCl), and nitryl tetrafluoroborate (O_2N^+ BF_4^-) attacked the crotonaldehyde dimethylhydrazone at the same 3-position to afford **131**. Compound **132** was obtained by hydrolysis.

Mühlstädt and Weber treated both cinnamaldehyde and crotonaldehyde tetramethylene hydrazone **133** with disulfur dichloride and obtained 3-imino-3*H*-1,2-dithioles **135**. They supposed an addition–elimination mechanism via intermediate thiosulfenyl chloride **134** in accordance with the aza-enamine character of the hydrazones[68] (Scheme 22). In the opinion of the authors, the unexpected formation of 5-aryl-3-methyl-1,3,4-thiadiazole-2(3*H*)-thiones **137** from dimethylhydrazones of aromatic aldehydes **136** and sulfur dichloride or disulfur dichloride also proceeded by electrophilic attack at the azomethine carbon atom as the first step.[69] From benzaldehyde-*N*,*N*-tetramethylene hydrazones **138a**–**e** and sulfur dichloride, novel pyrrolo[2,1-*b*]-1,3,4-thiadi-

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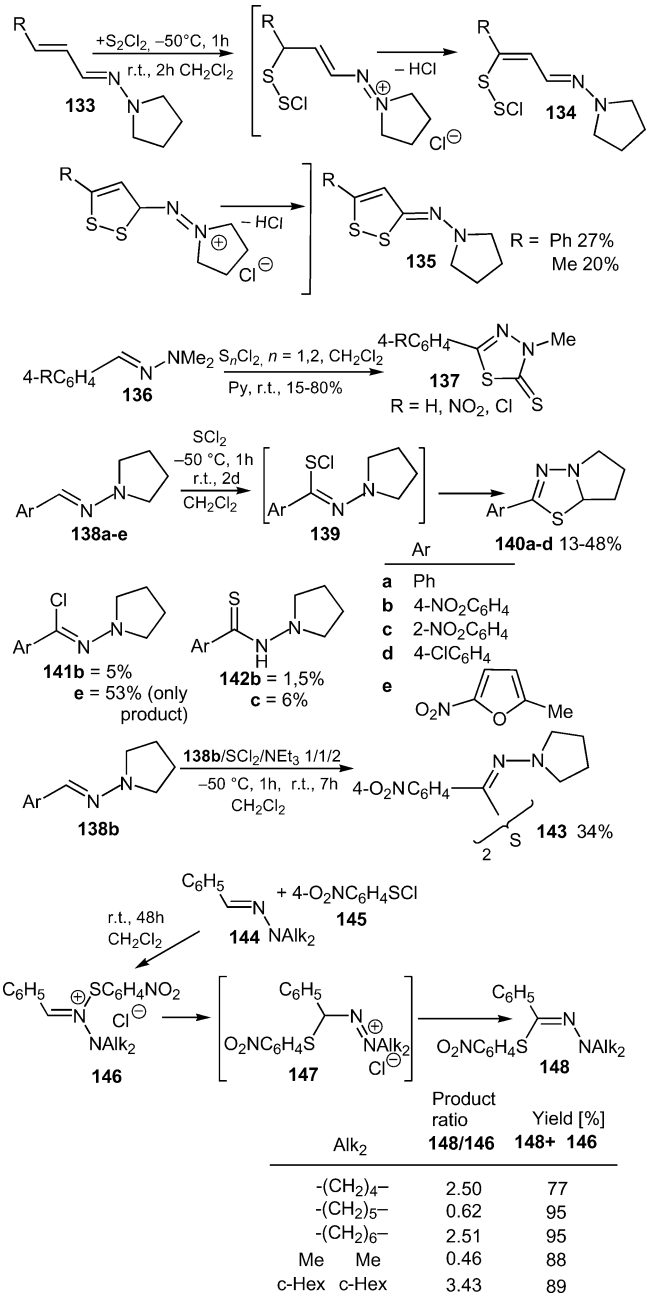
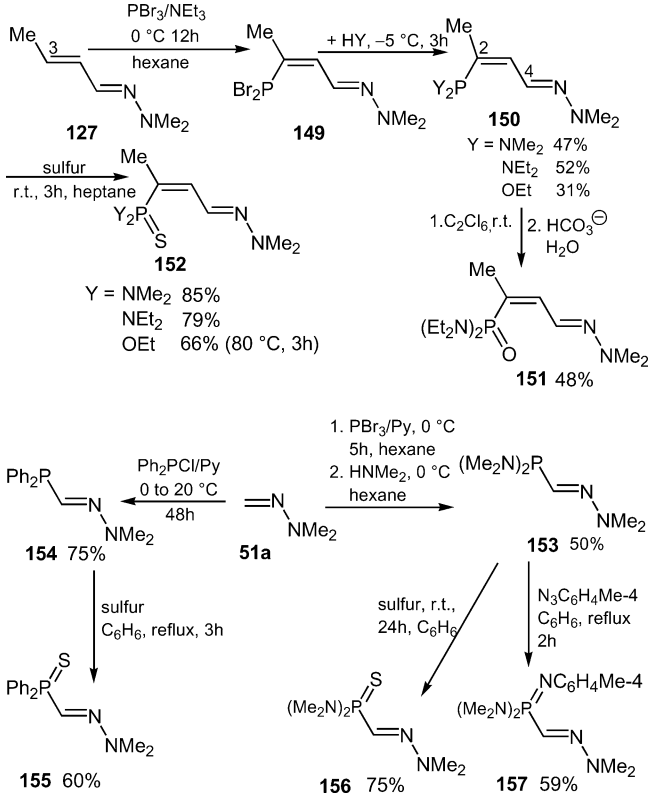
azoles **140a–d** were formed with **141b**,**e** and **142b**,**c** as side products. In the presence of triethylamine (2 equiv.), 2:1 insertion product **143** was obtained from **138b**. Compound **139** is not isolable and may be an intermediate in the formation of **140** and **143**. The reaction between benzaldehyde hydrazones **144** and 4-nitrophenylsulfenyl chloride **145** yielded mixtures consisting of **146** and **147**. The authors concluded from the experimental facts as well as from theoretical considerations and ^{1}H NMR spectroscopic data that the initial attack occurred at the azomethine nitrogen atom to form **146** in contradiction to the aza-enamine concept.



Scheme 22. Reactions of aldehyde *N*,*N*-dialkylhydrazones with sulfur dichloride and disulfur dichloride (top) and with 4-nitrophenylsulfenyl chloride (bottom).

Rearrangement to *C*-sulfenyl diazenium salt **147** allows subsequent HCl elimination to afford **148**.[70]

Tolmachev and colleagues phosphorylated crotonaldehyde dimethylhydrazone (**127**) (Scheme 23). In this case, too, attack with PBr_3 took place at the carbon 3-position and led first to hydrazonoyldibromophosphane **149**, which was stable only in solution. Ethanol and dimethylamine or diethylamine, respectively, as additives yielded stable 4-(*N*,*N*-dimethylhydrazono)but-2-en-2-yl[diethoxy or bis(dialkylamino)]phosphanes **150**.[71]



Scheme 23. Carbon–phosphorus bond formation with crotonaldehyde and formaldehyde dimethylhydrazones.

Formaldehyde dimethylhydrazone **51a** was substituted at the azomethine carbon in the same fashion to furnish **153**. In contrast to the crotonaldehyde hydrazone, **51a** was attacked also by the less reactive diphenyl chlorophosphane to afford **154**, which thus proves its higher nucleophilic potential. Tolmachev and coworkers pointed out that hydrazones **150**, **153**, and **154** (Scheme 23) are the first representatives having a P^{III} atom at an azomethine carbon atom or at a carbon atom vinylogous to it. These compounds can be converted with air, sulfur or phenylazide into oxide **151**, into thiones **152**, **155**, and **156**, or into hydrazonomethylphosphonimidic acid bis(amide) **157**, which are all examples containing a pentavalent phosphorus atom. The authors also posphorylated furan- and thiophene-2-carbaldehyde *N*,*N*-dimethylhydrazones **158** with phosphorus tribromide[72] (Scheme 24). In this case, the aldehyde hydrazono group also directed the electrophile at the vinylogous 5-position to form **159**. Depending on the molar ratios, two or all three bromine atoms can be substituted to afford **162**

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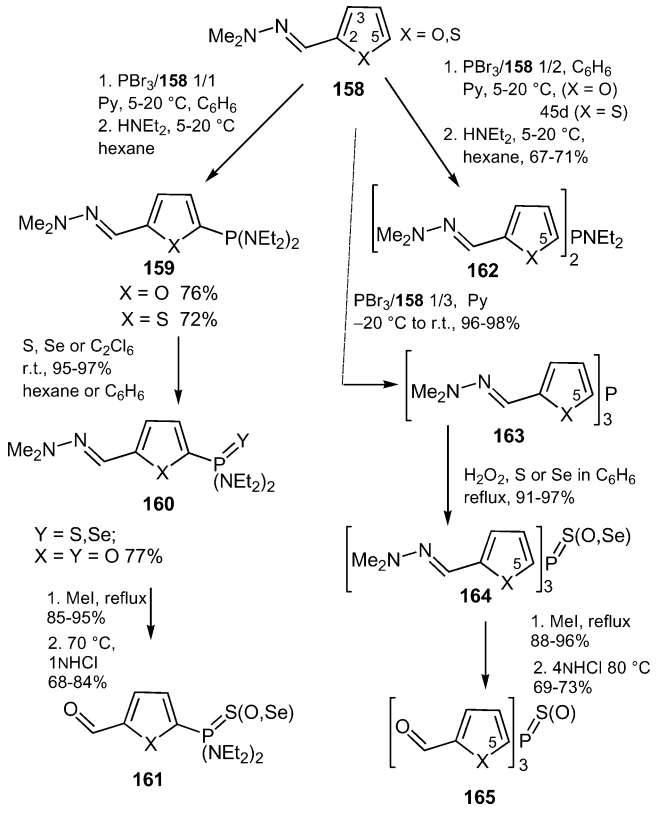
and **163**. The authors emphasized that the unsubstituted furan and thiophene five-membered ring heterocycles do not react with PBr_3 under analogous conditions. In most cases the hydrazones were hydrolyzed to parent aldehydes **165** and **161**.[72] However, this way via the trimethylhydrazonium iodides (see Scheme 17) could only be performed with compounds **164** and **160**, which contain a pentavalent phosphorus atom, otherwise the phosphorus(III) center would be methylated.

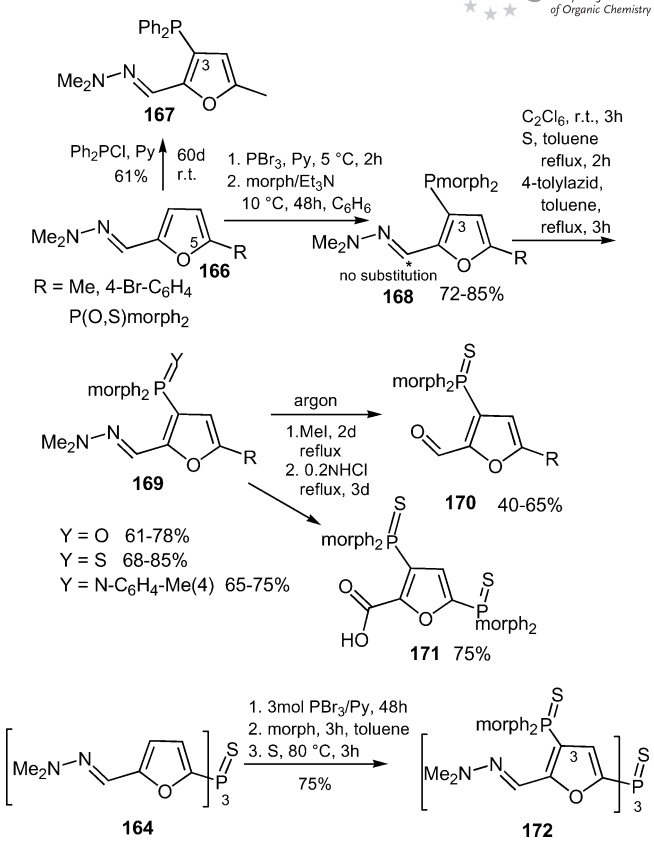


Scheme 24. Reactions of the furan- and thiophene-2-carbaldehyde dimethylhydrazones with phosphorus tribromide and subsequent reactions.

When the 5-position is occupied in compounds such as **166**, electrophilic attack occurs at the vinylogous 3-position of the heterocyclic nucleus to afford **167** and **168**[73a] (Scheme 25). By subsequent reactions, compounds **169**, **170**, and **171** were formed. In **164**, all three heterocyclic nuclei are phosphorylated to provide **172**.

The reactions of *N*-methylpyrrol-2-carbaldehyde dimethylhydrazones with phosphorus tribromide and the subsequent reactions proceed in similar manner.[74] For phosphorylation at the 4-position of the 5-(diethylamino)furancarbaldehyde dimethylhydrazone see ref.[73]

Most of the phosphorylated compounds and subsequent products presented in Schemes 23, 24, and 25 are stable solid substances with defined fluid points. Several of them are even distillable. Finally, anthracene-9-carbaldehyde *N*,*N*-dimethylhydrazone was also phosphorylated and yielded, after treatment with morpholine and sulfur, 10-dimorpholidothiophosphoryl derivative **173** (Figure 3).[75]



Scheme 25. PBr_3 attack at the 3-position of furan-2-carbaldehyde hydrazone containing a blocked 5-position.

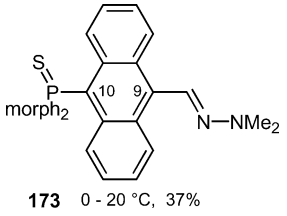


Figure 3. Anthracene-9-carbaldehyde *N*,*N*-dimethylhydrazone phosphorylated at the 10-position.

10. Aza-Enamines as Electron-Rich Dienes and Dienophiles in the Diels–Alder Reaction

In the previous chapters, the aza-enamines were presented as acyl anion equivalents that were capable of forming linear noncyclic products, but these compounds are also valuable substrates in the Diels–Alder reaction as both electron-rich dienes and electron-rich dienophiles. Before concluding this part of our review, this interesting variant must be mentioned briefly. However, it does not concern a reversible umpolung, but an irreversible one. Whereas methacrylaldehyde **174** reacts as an electron-deficient dienophile with electron-rich dienes such as cyclopentadiene to afford **175**,[76] Ghosez revealed that the aldehyde in the form of dimethylhydrazone **115** acts as an electron-rich 1-amino-1-aza-1,3-diene and furnishes Diels–Alder cycloadducts with electron-deficient dienophiles. Thus, the reaction of meth-

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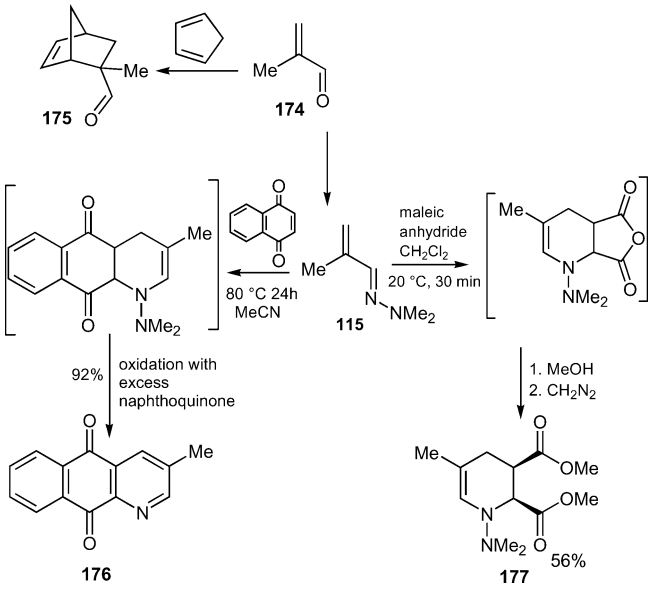
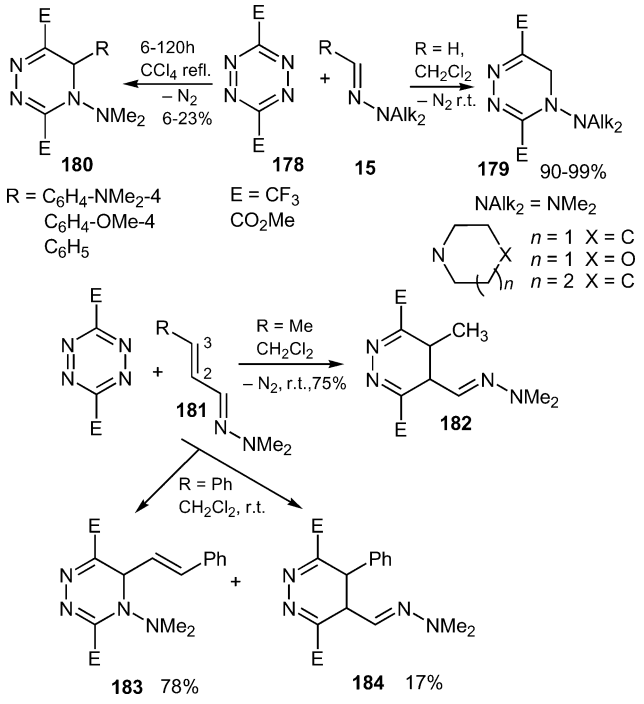
acrylaldehyde *N*,*N*-dimethylhylhydrazone **115** proceeded smoothly with naphthoquinone and maleic anhydride to afford **176** and **177**[77] (Scheme 26).



Scheme 26. Diels–Alder addition of electron-rich aza-enamine methacrylaldehyde *N*,*N*-dimethylhydrazone as diene to electron-deficient maleic anhydride and naphthoquinone.

This synthetic principle has frequently been applied. The dimethylhydrazones of crotonaldehyde,[78] acrylaldehyde, as well as 2-fluoroacrylaldehyde were examined and led especially with quinones as dienophiles to interesting fused polycyclic aza-heterocycles.[79] Fillion and coworkers gave a good survey of this field.[80] Ghosez also presented asymmetric Diels–Alder reactions with chiral 1-amino-1-azadienes using SAMP-hydrazones.[81]

A significant difference does not exist in the properties of the aza-enamines used either for the Diels–Alder reactions or for the nucleophilic acylations: in both cases the system profits from the electron density caused by the electron-donor effect of the dialkylamine ligand. In both cases the hydrazones react with electron-deficient species. The only difference is that the electron-density is formally localized at the azomethine carbon atom or at a vinylogous position in the case of the nucleophilic acylation and delocalized over the π-electron system in the case of the Diels–Alder additions. The examples presented are Diels–Alder additions with normal electron demand in the sense of the Alder rule. This rule states that in many cases electron-donating ligands in the diene and electron-withdrawing ligands in the dienophile accelerate the reaction.[82] However, the aza-enamines can react not only as electron-rich dienes but also in reactions with inverse electron demand as electron-rich dienophiles. Thus, both electron-rich formaldehyde[84c,84d] and benzaldehyde hydrazones[84b,83] **15** undergo [4+2] addition with acceptor-substituted tetrazine **178**, which leads to nitrogen gas evolution and to triazine derivatives **179** and **180**[83] (Scheme 27; see also Scheme 14, point e). Whereas with crotonaldehyde dimethylhydrazone **181** (R = Me) the C=C bond in the 2,3-position is incorporated into the heterocyclic ring to yield **182**, cinnamaldehyde hydrazone **181** (R = Ph) provided a mixture of **183** and **184**. Thus, both the 2,3-double bond and the azomethine double bond can be involved in the heterocyclic ring.[84a]



Scheme 27. Electron-rich aza-enamines as dienophiles in Diels–Alder reactions with inverse electron demand.

11. Formaldehyde *N*,*N*-Dialkylhydrazones as Formyl Anion and Cyanide Equivalents: Applications in Conjugate Additions

Formaldehyde *N*,*N*-dialkylhydrazones **51** constitute a case of particular importance in the context of their use as umpolung (d^1) reagents for two main reasons: (1) the aza-enamine reactivity seems to be particularly affected by steric factors, and therefore, there is an enhanced nucleophilicity in formaldehyde derivatives that enables the reactions with a much broader variety of electrophiles, (2) relative to other acyl anion equivalents, there are fewer alternatives for the nucleophilic formylation reaction, particularly in the field of asymmetric synthesis.

In addition to the information collected in the chapters presented so far, it was during early investigations in the cycloaddition reactions of monosubstituted hydrazones **185** with nitroalkenes **186** that we first recognized the particular behavior of formaldehyde derivatives.[85] In these reactions, the regioselectivity is assumed to be controlled by the first nucleophilic attack. In general, the attack by the NH group to the electron-deficient β-carbon of the nitroalkene resulted in the regioselective formation of pyrazoles **187**, presumably through hydrazonium–nitronate intermediates **A** (Scheme 28). In sharp contrast, we found that reaction of

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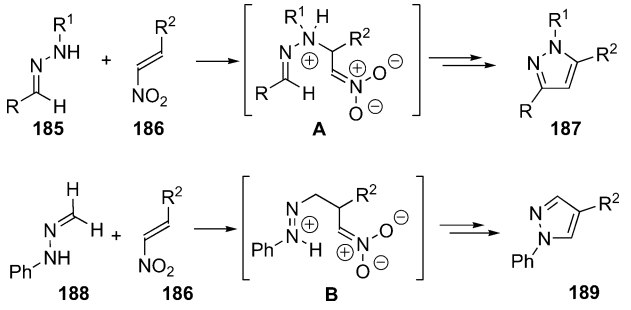
formaldehyde phenylhydrazone **188** unexpectedly led to regioisomeric pyrazole product **189**. Assuming a stepwise (asynchronous) cycloaddition pathway, this result suggested that the initial attack takes place at the azomethine carbon atom, which leads to the final product via diazenium–nitronate intermediates **B**. Thus, this was not only one more example of the aza-enamine reactivity of hydrazones, but it also provided an indication of a much higher nucleophilic reactivity that exceeds even that of the NH group. Stimulated by these unexpected results, we decided to explore the synthetic potential of these compounds as d^1 synthons.



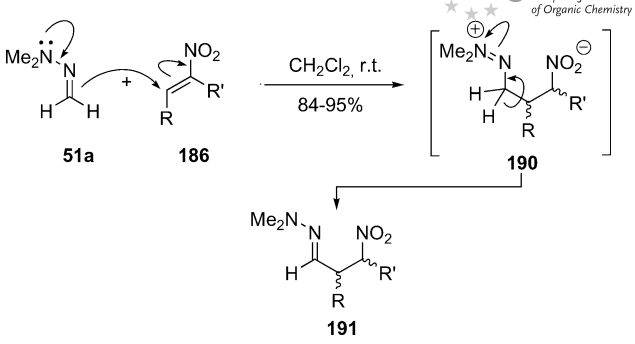
Scheme 28. Regioselective cycloaddition of hydrazones and nitroalkenes.

11.1. Michael Addition to Nitroalkenes

In order to avoid competitive reactivity at nitrogen, *N*,*N*-dialkyl-substituted formaldehyde hydrazones **51** were chosen as the reagents in further studies. With these compounds, reactions at this center would expectedly lead to *reversible* formation of hydrazonium adducts. On the basis of the above-mentioned observations, their reactivity toward conjugated nitroalkenes **199** was investigated first. These readily available compounds exhibit extraordinary electrophilic reactivity (among the strongest neutral π-electrophiles known) that has been extensively exploited in Michael-addition reactions of many different nucleophiles,[86] whereas the rich chemistry of the nitro group has enabled the synthesis of an impressive array of compounds. Noteworthy, however, is that the nucleophilic formylation has never been reported.

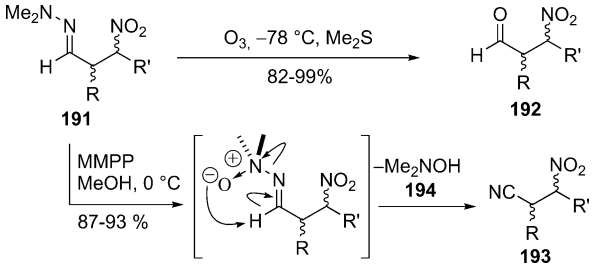
Simplest formaldehyde *N*,*N*-dimethylhydrazone **51a** and several simple aliphatic and aromatic nitroalkenes **186** were used in the first studies. The results fully confirmed the expected reactivity, as desired β-nitrohydrazone adducts **191** were obtained in excellent yields.[87] The reaction is thought to proceed via diazenium intermediates **190**, which are acidic compounds that are known to readily regenerate the hydrazone moiety as depicted[88] (Scheme 29). Interestingly, the addition reaction takes place spontaneously at room temperature in the absence of any catalyst or promoter; a fact that reflects the nucleophilicity of the neutral reagent.

β-Nitrohydrazones **191** obtained as products are interesting bifunctional compounds, which can be considered as masked 1,3-dicarbonyl compounds, as both the nitro group and the hydrazone moiety can be transformed into carbonyl



Scheme 29. Reaction of formaldehyde *N*,*N*-dimethylhydrazone **51a** with nitroalkenes **186**.

groups by means of the Nef reaction and hydrazone cleavage, respectively.[25a] The synthetic equivalence of reagent **51a** with a "formyl anion" was demonstrated after removal of the hydrazone moiety by ozonolytic cleavage of the C=N bond of adducts **191**, which afforded corresponding β-nitroaldehydes **192** in good yields (Scheme 30).



Scheme 30. Synthesis of β-nitroaldehydes **192** and β-nitronitriles **193**.

Additionally, the oxidative transformation of the hydrazone moiety of **191** into β-nitronitriles **193** was also accomplished cleanly by applying the method previously developed for simple *N*,*N*-dimethylhydrazones.[89,96] The method uses commercially available magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) as the oxidant and proceeded under very mild conditions (MeOH, 0 °C) to afford nearly quantitative yields of products **193**. The proposed mechanism consists of the N-oxidation of the amino nitrogen atom followed by an aza-Cope-type elimination, supported by the detection of *N*,*N*-dimethylhydroxylamine **194** in the reaction mixtures.

This is also a valuable result that demonstrates the synthetic equivalence of reagent **51a** with the cyanide anion and, in this particular case, provides an indirect method for the conjugate cyanation of nitroalkenes. Therefore, the neutral and soft character of the nucleophile is the key for the cyanation reaction of nitroalkenes that was not previously performed in a direct fashion, probably due to the easy polymerization of these substrates under more basic conditions. This formylation and cyanation method was also extended to some carbohydrate-derived nitroalkenes for the synthesis of branched-chain sugars.[90,91]

Once the conditions for the new acylation and cyanation of nitroalkenes were established, we decided to study the asymmetric version of the key addition reaction. To this

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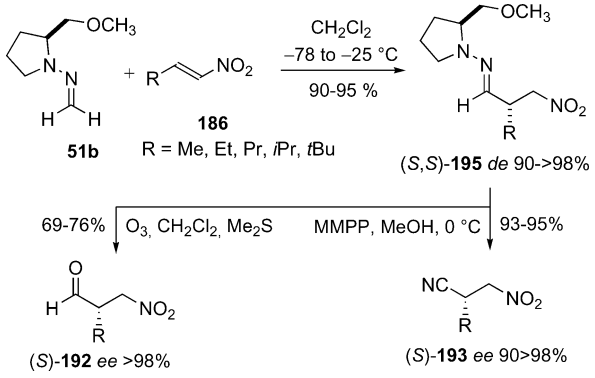
aim, commercially available (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) was chosen as the chiral auxiliary. The corresponding formaldehyde hydrazone, (*S*)-**51b**, was readily prepared by reaction with paraformaldehyde[92] and used as the reagent in the reaction with a series of prochiral nitroalkenes **186**. We were glad to observe that the reaction took place as for the achiral reagent to afford exclusively the expected (*E*) configured α-substituted β-nitroaldehyde SAMP-hydrazones (*S*,*S*)-**195** in excellent yields (Scheme 31).[91,92b,93] High diastereoselectivities (*de* 90→98%) were achieved for aliphatic substrates by carrying out the addition reaction at low temperatures without affecting the yields (90–95%). The reaction at such low temperatures indicates a higher reactivity of **51b** relative to that of achiral reagent **51a**, a structural effect that can be explained, as in related enamines with the more efficient n→π conjugation associated with the pyrrolidine ring.[94]



Scheme 31. Asymmetric synthesis of β-nitroaldehydes **192** and β-nitronitriles **193**.

β-Nitro-SAMP-hydrazones (*S*,*S*)-**195** were transformed into corresponding β-nitroaldehydes (*S*)-**192** by ozonolytic cleavage of the hydrazone moiety, in full analogy with the *N*,*N*-dimethyl derivatives, and the auxiliary can be recycled through a well-known procedure.[95] Additionally, the method developed for the cleavage of *N*,*N*-dimethylhydrazones **191** by MMPP proved to be also suitable for the cleavage of SAMP-hydrazones **195**,[91,92b,89b] which afforded optically enriched nitriles (*S*)-**193** in excellent yields (Scheme 31). Thanks to the mild conditions required, both transformations were found to proceed without racemization, in spite of the sensibility of the stereogenic centers of the products. Therefore, formaldehyde SAMP-hydrazone **51b** proved to be not only a neutral, *chiral* formyl anion equivalent, but a *chiral* cyanide anion equivalent as well.

The high degree of diastereoselectivity originated by the remote chiral center in the auxiliary is difficult to understand unless a closed, chair-like transition state stabilized by attractive electrostatic interaction of the developing charges $N^{\delta+}/NO_2^{\delta-}$ is assumed. The diastereomeric transition state that minimizes steric CH_2OMe/NO_2 interactions is consistent with the absolute configuration observed for the products (Figure 4).

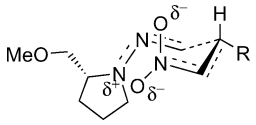
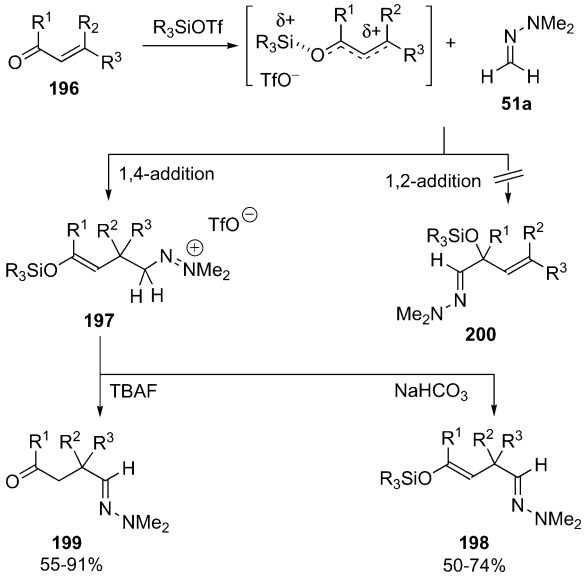


Figure 4. Stereochemical model for the reaction of **51b** and **186**.

11.2. Conjugate Addition to α,β-Unsaturated Ketones

In terms of synthetic value, α,β-unsaturated ketones **196** are among the most attractive targets for the nucleophilic formylation procedure via formaldehyde *N*,*N*-dialkylhydrazones **51**. In fact, 1,4-dicarbonyl products are not easy to obtain by alternative methods, in particular in enantiomerically enriched form.

We started again by studying the reactivity of the simplest, achiral formaldehyde *N*,*N*-dimethylhydrazone **51a** as a model for the "racemic version" of this reaction.[60a] In contrast to the related addition to the more electrophilic nitroalkenes, the reactivity was not high enough for the uncatalyzed additions to enones **196**. In contrast, the activation of the latter by means of Lewis acids proved to be a difficult task, as most of the reagents commonly used for this purpose led to the irreversible formation of hydrazone–Lewis acid complexes, as occurs with many other nitrogen-containing compounds. This problem was solved by using *bulky* trialkylsilyl [TBS or dimethyl(1,1,2-trimethylpropyl)-silyl (TDS)] triflates in diethyl ether as promoters.[97] Thus, the 1,4-addition of **51a** to silyl precomplexed enones gave rise to the formation of the desired adducts trapped as their corresponding silyl enol ethers **197** (Scheme 32).



Scheme 32. Addition of **51a** to trialkylsilyl-precomplexed enones **196**.

The oxophilic character and the great steric hindrance of the silicon acidic center make the complexation of the small carbonyl oxygen of ketone **196** much easier than that of the more-hindered nitrogen atoms of **51a**. Interestingly, primary 1,4-adducts **198** were stable enough for chromato-

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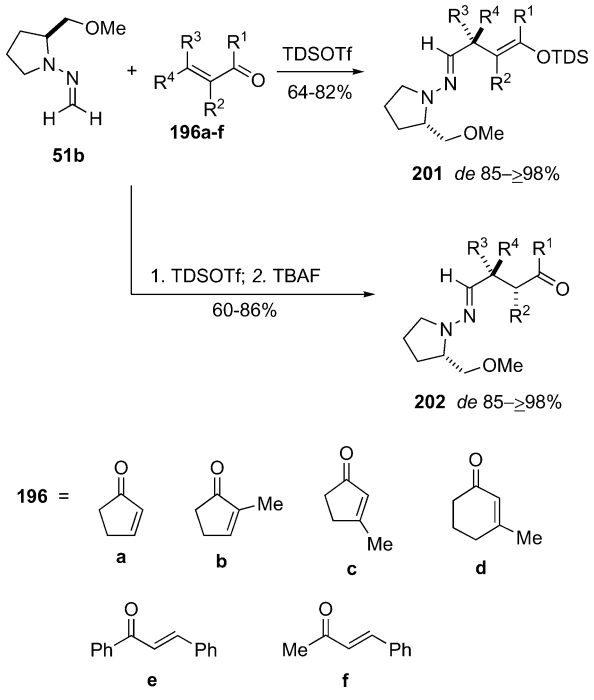
graphic purification. Moreover, corresponding deprotected adducts **199** could also be obtained alternatively in a "one-pot" operation by simply quenching the reaction mixtures with tetrabutylammonium fluoride (TBAF), so that further use of the rich chemistry of silyl enol ethers can be envisaged.[98] The absence of 1,2-adducts **200**, which are usually formed as byproducts in this type of reaction, can be explained as a consequence of the neutral and extremely soft character of the nucleophile on the one hand, and the great steric hindrance around the silyl-activated carbonyl group on the other hand. Thus, the contribution to the observed regioselectivity constitutes a second reason for the choice of such sterically demanding promoters.

Having established the optimal conditions for the addition reaction in the racemic series, studies were directed toward an asymmetric version of the reaction.[60b] To this end, SAMP hydrazone **51b** was chosen again as the reagent. The reactions with a variety of prochiral enones **196** activated by TDSOTf gave rise, in full analogy to the foregoing reaction, to corresponding silyl enol ethers **201** or to free 4-oxohydrazones **202**, depending on the quenching conditions (Scheme 33).



Scheme 33. Asymmetric Michael addition of **51b** to conjugated enones **196**.

Again, the higher reactivity exhibited by SAMP-derived formaldehyde hydrazone **51b** with respect to that of acyclic dimethylhydrazone **51a** allows very fast reactions at temperatures as low as –78 °C. Consequently, the diastereoselectivity of the reaction, which during preliminary experiments proved to be strongly dependent on the temperature, could be improved to excellent levels.

Thus, the reaction proved to be highly selective (85→98% *de*) for different kinds of substrates, including five- (**196a**–**c**) and six-membered (**196d**) cyclic enones, as well as aryl (**196e**) and alkyl-substituted (**196f**) acyclic enones. The addition to β,β-disubstituted substrates (**196c** and **196d**) led to products **201c**,**d** and **202c**,**d** containing all-carbon, quaternary stereogenic centers (bearing four differently functionalized alkyl chains) in good yields and with excellent diastereomeric excesses. This result is particularly interesting, as such centers are commonly encountered in a variety of natural products, and the range of methodologies for their stereoselective generation is one of the most restricted in organic synthesis.[99]

The attack of **51b** occurs always at the same face of the enone, regardless of its structure and of the geometry of the C=C bond. A compact, cyclic, chair-like geometry for the transition state was proposed (Figure 5). According to this model, the steric repulsion between the CH_2OMe group in the pyrrolidine ring and both the highly demanding TDS^+-complexed oxygen atom and the R^1 substituent should result in an energy much higher for **II** than for **I**, which is in agreement with the absolute configuration and the high induction observed.[100]

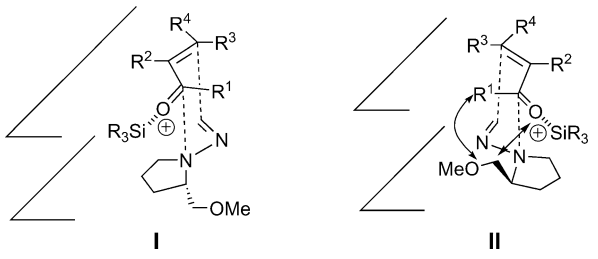


Figure 5. Stereochemical model.

The transformation of the hydrazone functionality of adducts **199** or **202** afforded a series of bifunctional building blocks of synthetic interest. Ozonolytic cleavage and/or HCl-mediated hydrolysis of the hydrazones in a two-phase system afforded 4-oxoaldehydes in excellent yields, proving again the synthetic equivalence of reagents **51a**,**b** with the formyl anion (Scheme 34). In addition, Jones oxidation of the crude compounds was also carried out to yield 4-oxoacids **204**. The oxidative cleavage by MMPP·$6H_2O$ proved again to be an efficient transformation, which afforded 4-oxonitriles **205** in excellent yields. Additionally, dithioketals **206** were also obtained in high yields and without racemization from corresponding compounds **202**. These BF_3·Et_2O-promoted hydrazone to dithioketal transformations are examples of a more general study,[101] whose main interest arises from the fact that the chemistry of dithioketals (carbanion chemistry, desulfuration, etc.) is complementary to that of hydrazones themselves, and also to that of the deprotected products (aldehydes and nitriles, i.e. electrophiles) usually obtained from them. When adducts **202** were used as starting materials, these transformations were found to proceed without racemization of labile stereogenic centers. Finally, a selective, racemization-free cleavage of the hydrazone moiety of silyl enol ethers **201** to afford nitriles **207**

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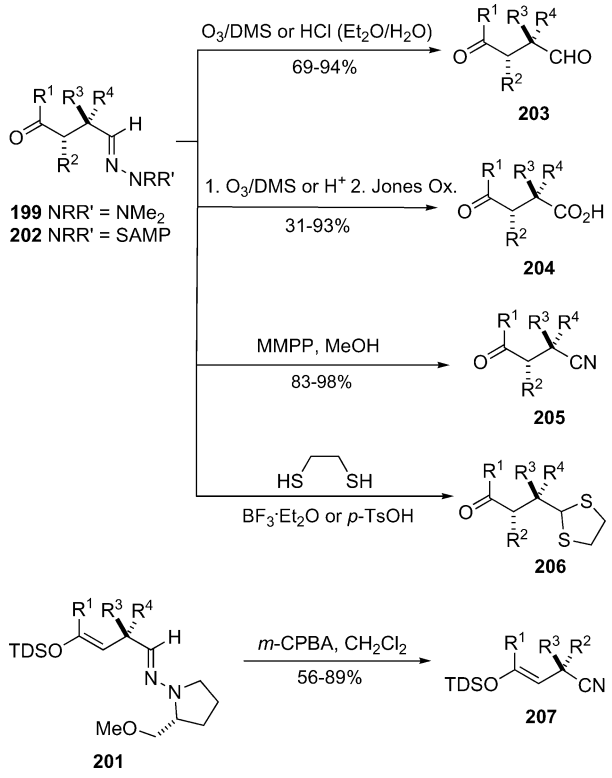
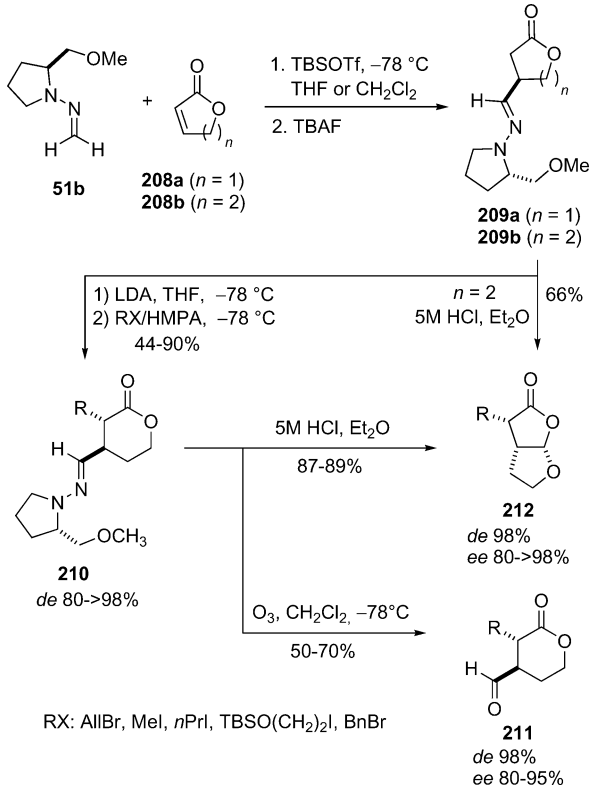
(Scheme 34) was satisfactorily accomplished by means of *m*-CPBA in the presence of a small amount of suspended solid $NaHCO_3$, which was necessary to prevent partial cleavage of the silyl enol ether moiety.[102]



Scheme 34. Synthesis of bifunctional derivatives **203**–**207**.

11.3. Conjugate Addition to α,β-Unsaturated Lactones

The strategy developed above for the conjugate addition of formaldehyde SAMP-hydrazone **51b** to conjugated enones has also been applied to α,β-unsaturated lactones **208a**,**b**[103] A Lewis acid proved to be necessary to activate the substrates towards the attack of reagent **51b**. As observed previously in the enone case,[60a,60b,104] only the use of trialkylsilyl triflates (SiR_3 = TBS or TMS) as promoters led to the formation of desired Michael adducts (*S*,*R*)-**209a**,**b** (Scheme 35). The lactone ring size had a marked effect on the reactivity, and hence, it was not possible to establish a general method for both types of lactones. In the case of 5-hydro-2*H*-furan-2-one (**208a**), addition of the reagent to a solution of the precomplexed lactone in THF at –78 °C afforded desired product **209a** in poor yield (20%) but in excellent diastereoisomeric excess (*de* >95%). In the case of 2-pentenolide (**208b**), addition of the TBSOTf promoter to a cooled (–78 °C) mixture of reagent **51b** and the substrate in CH_2Cl_2 afforded adduct **209b** in moderate yield (54%) and good diastereomeric excess (*de* 80%). Compound **209b** was used in a subsequent deprotonation/α-alkylation step. LDA at –78 °C in the presence of HMPA afforded better results than other bases tested (TMPLi, *t*BuLi). The alkylation of the aza-enolate formed under these conditions afforded *trans* α-substituted lactone hydrazones **210** in variable yields (44–90%) and with satisfactory diastereomeric excesses (*de* 80→98%) (Scheme 35). Interestingly, the use of potassium diisopropylamide (KDA) had a marked effect on the *trans*/*cis* ratio of the alkylated products in all cases, which even led to the formation of the *cis* isomer as the major product in the methylation reaction (RX = MeI).



Scheme 35. Asymmetric synthesis of β-formyl-δ-lactones and furofuran lactones.

Again, ensuing deprotection by ozone afforded a series of α-alkyl β-formyl δ-lactones **211** in acceptable yields (50–70%) and high diastereo- and enantiomeric excesses (*de* ≥98%, *ee* 80–95%). These are useful building blocks, as illustrated by their behavior upon hydrolytic cleavage.[103b] Acidic hydrolysis with 5 N HCl in a two-phase system rapidly initiated a domino reaction that afforded furofuran lactone derivatives **212** in excellent yields (87–98%) and with high stereoisomeric purities (*de* ≥98%, *ee* 80–98%). The reaction cascade involves cleavage of the hydrazone moiety, opening of the lactone ring, and formation of the furofuran lactone system through the corresponding hemiacetal intermediate.[105] These furo[2,3-*b*]furan lactones **212** are particularly interesting substructures present at various levels of oxidation in a number of insect antifeedant clerodanes,[106] such as clerodin [**I**, R = H and caryoptin (**I**, R = OAc) or mycotoxins like aflatoxin B_1 (**II**) (Figure 6)].

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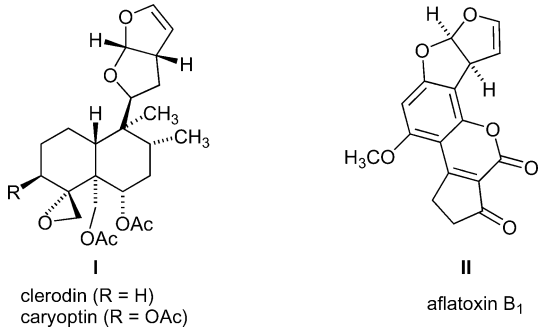


Figure 6. Furofuran motif in biologically active compounds.

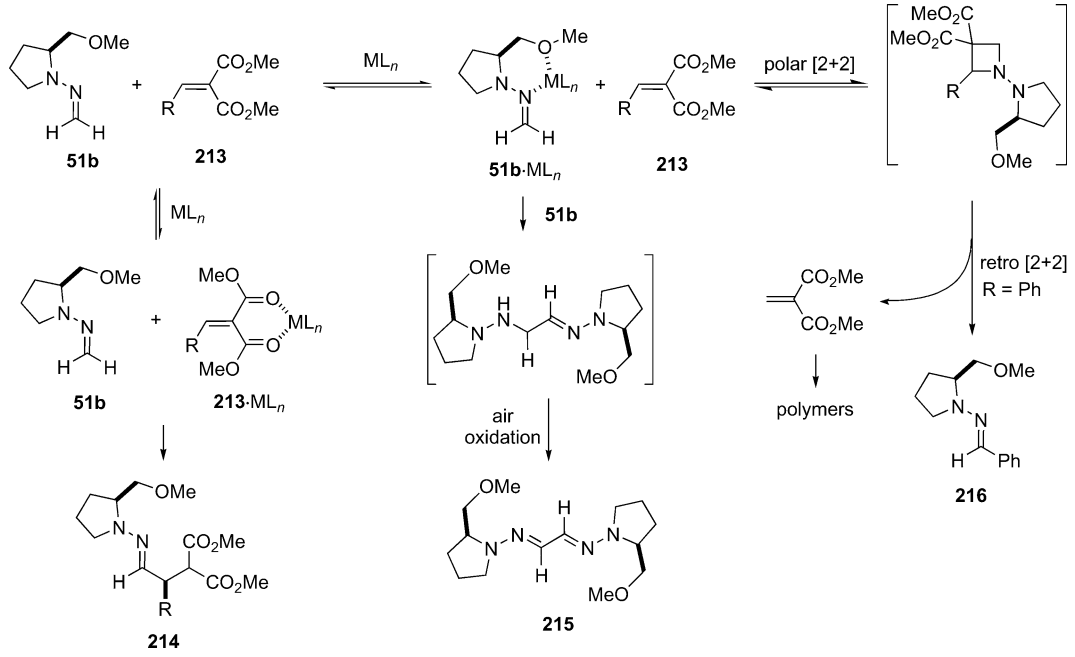
11.4. Conjugate Addition to Alkylidenemalonates

The method developed for the addition of reagents **51** to α,β-unsaturated enones or lactones could not be extended to the formylation of simple enoates, an unfortunate fact that is attributed to the combination of the limited reactivity of the neutral nucleophile and the lower electrophilic character of enoates. Considering the synthetic interest for this particular reaction, alternative enoate surrogates with a higher electrophilic reactivity were investigated.

Alkylidenemalonates **213** appear as suitable candidates in this context, and they present with a series of interesting characteristics: (1) they are easily available through Knoevenagel condensation of malonates and different carbonyl compounds, (2) for the most common type of malonates, the presence of two identical carboxyl groups at the same olefinic carbon eliminates the *Z*/*E* isomerism, which constitutes a synthetic problem in other classes of substrates, (3) the enhanced electrophilic reactivity provided by the geminal carboxylate functions allows the addition reactions to be carried out with poorer nucleophiles and/or under milder conditions with respect to other Michael acceptors, and (4) the presence of two geminal carbonyl groups provides chelating ability to these substrates, which is an essential tool for the control of the stereochemistry in metal-promoted or -catalyzed additions. These characteristics have stimulated extensive use of these compounds as enoate surrogates for the addition of a variety of nucleophiles, but only a few reports have been written on their acylation reactions,[107] none of them dealing with *asymmetric* acylation or formylation reactions. The precedent of the addition of **51b** to nitroalkenes,[91,92b,93] which exhibit similar levels of reactivity,[108] suggested that the addition of reagents **51** to alkylidenemalonates **213** should also be possible under uncatalyzed conditions or, at least, under mild conditions compatible with the hydrazone moiety.

Disappointingly, however, **51b** did not react with dimethyl alkylidenemalonates **213** under a variety of uncatalyzed conditions. Again, it was necessary to activate substrates **213** by means of a Lewis acid as the catalyst or promoter.[48b,62b] Taking into account the chelating ability of **51b**, the reaction was expected to proceed after achieving an equilibrium between metal-hydrazone **51b**·ML_n and metal-malonate **213**·ML_n complexes (Scheme 36).

The selection of a suitable catalyst, however, presented some difficulties because some common Lewis acids, such as $ZnCl_2$, $AlCl_3$, $Ti(OiPr)_4$, or trialkylsilyl triflates, either in catalytic or stoichiometric amounts, afforded desired hydrazono dicarboxylates **214** in low yields, due to the formation of variable amounts of glyoxal bis(hydrazone) **215** as an undesired byproduct. The formation of this product can be explained after formation of complex **51b**·ML_n by nucleophilic attack of a second molecule of the free reagent, followed by air oxidation of the α-hydrazinohydrazone intermediate.[109] In the case of aromatic substrate **213** (R = Ph),



Scheme 36. Lewis acid catalyzed reactions and side reactions of **51b** with alkylidenemalonates **213**.

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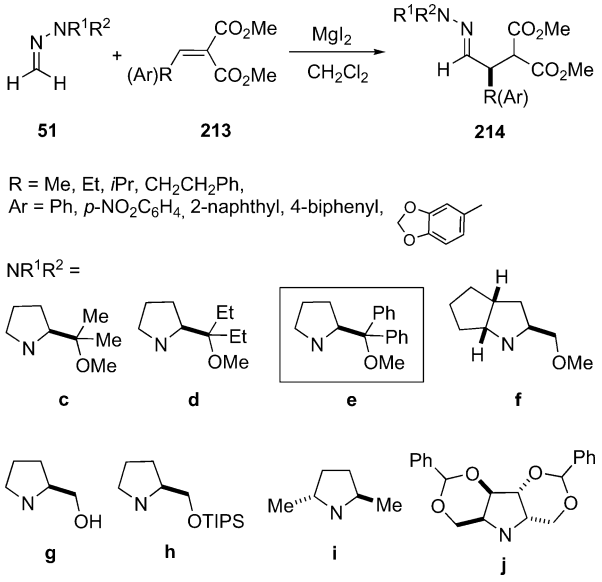
benzaldehyde SAMP-hydrazone **216** was also isolated as a byproduct, even in dry media. Its formation can be explained by [2+2] cycloaddition[110] of the hydrazone to the activated alkylidenemalonate followed by retro-cycloaddition to the observed byproduct, along with dimethyl methylidenemalonate, which is unstable against polymerization.

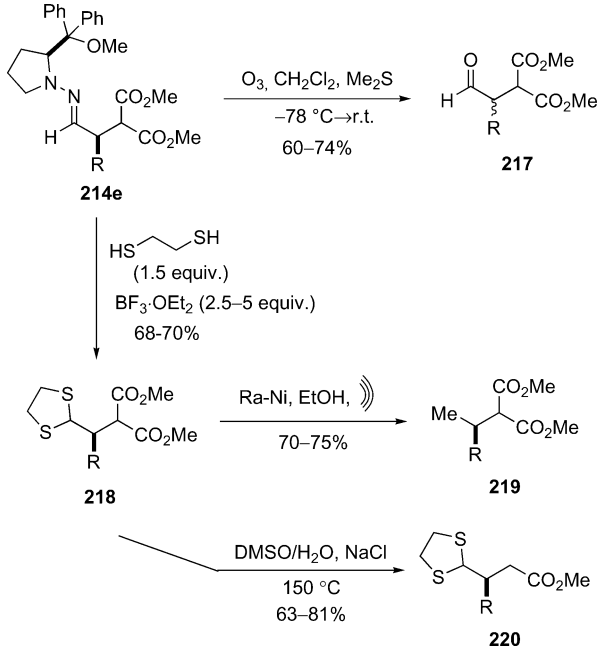
Fortunately, it was found that catalytic amounts of MgI_2 or $MgBr_2$ in CH_2Cl_2 as solvent minimized the side reactions mentioned above and led to the almost exclusive formation of adducts **214**. The observed diastereoselectivities, however, were disappointing in all cases. In light of these results, formaldehyde hydrazones **51c**–**j** were synthesized and used in a second screening performed to analyze the effect of the modified auxiliaries in the stereochemical outcome of the conjugate addition (Scheme 37).



Scheme 37. Asymmetric addition of hydrazones **51b** to alkylidenemalonates **213**.

In order to keep the reactivity of the reagent as high as possible, the pyrrolidine ring was maintained as a common characteristic in these reagents, as we had previously noticed that this structural motif confers a high nucleophilicity to the aza-enamine system. From this screening, pyrrolidine **51e** emerged as the most convenient reagent. In the presence of a stoichiometric amount of MgI_2, compounds **214e** were obtained in excellent yields (70–98%) and variable stereoselectivities (*dr* 58:42 to 95:5). A high reactivity was found for both aliphatic and aromatic substrates, though the optimized experimental conditions were different for the two groups of substrates. For example, optimal reaction temperatures of –78 and 0 °C were applied to the addition to aliphatic and aromatic substrates, respectively. Better inductions (*de* 78–90%) were observed in the aromatic series, even when the higher reaction temperature (0 °C) was applied to achieve high yields of adducts. Moreover, the resolving properties of the selected diphenylmethoxymethyl pyrrolidine auxiliary allowed easy chromatographic separation for many of the diastereomeric mixtures obtained, and this behavior proved to be uniform for the aromatic adducts investigated. In this way, good yields (77–93%) of optically pure (*de* >98%) adducts **214e** were obtained in a single reaction step.

Regeneration of the formyl group to obtain aldehydes **217** was accomplished by ozonolytic cleavage of the hydrazone C=N bond in moderate yields (55–74%, Scheme 38). Unfortunately, even aliphatic aldehydes racemized partially during the chromatographic purification, and therefore, alternative methods for the removal of the auxiliary were investigated. Fortunately, it was found again that the direct dithioketalization of the hydrazone moiety was a suitable reaction to this aim. Thus, treatment of adducts **214e** with ethanedithiol in the presence of an excess amount of $BF_3{\cdot}OEt_2$ (2.5–5 equiv.) as the promoter afforded desired dithioketals **218**. These are versatile intermediates, which can also be transformed into other useful derivatives by making use of the chemistry of the dithioketal moiety. As an illustrative example, ultrasound-assisted Ra-Ni-mediated desulfuration of **218** (R = Et and 2-naphthyl) was effected to afford known malonates **219** (R = Et[111] and 2-naphthyl[112]) in 75 and 71% yield, respectively. As the overall result, hydrazone **51e** was used as a chiral reagent for the asymmetric nucleophilic methylation of alkylidenemalonates with the racemization-free direct dithioketalation as the key step in this process. Other useful compounds can also be obtained upon typical transformations of the malonate terminus. For instance, optically pure adducts **218** readily undergo decarboxylation under Krapcho conditions[113] (NaCl, wet DMSO, 150 °C) to afford succinic semialdehyde derivatives **220** in moderate-to-good yields (63–81%).



Scheme 38. Asymmetric synthesis of derivatives **217**–**220**.

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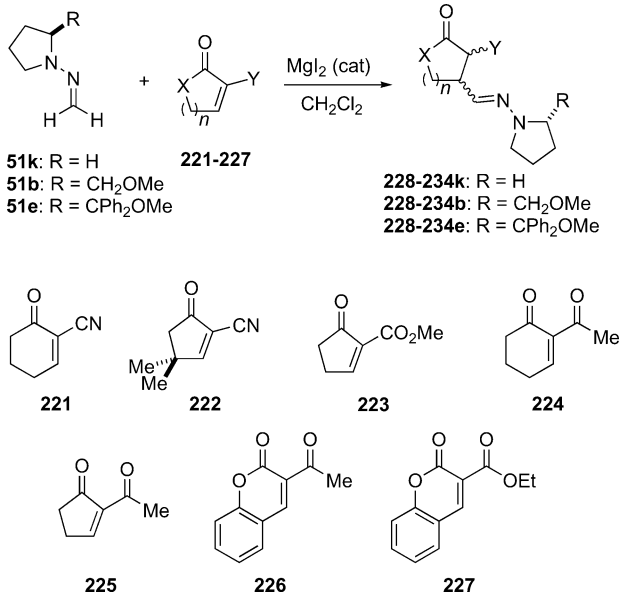
11.5. Addition to Activated Cyclic Alkenes

Continuing our studies, we decided to investigate reactions with cyclic alkenes bearing two electron-withdrawing groups on the same olefinic carbon. They should a priori show similar reactivity as alkylidenemalonates. The tested substrates include α-alkylidene-β-ketonitriles (**221**, **222**),[114] 2-methoxycarbonyl-cyclopent-2-enone (**223**),[115] five- and six-membered α-alkylidene-β-diketones (**224**, **225**),[116] commercially available 3-acetylcumarine (**226**), and 3-ethoxycarbonylcumarine (**227**). These compounds were chosen as substrates taking into account that some of the expected addition products are precursors of natural carbocyclic compounds with important biological activity. Particularly interesting are cyclopentenone derivatives, as the resulting adducts possess substructures present in a large number of natural products of interest[117] including jasmonoids, and prostaglandins, and cyclopentenoid antibiotics, such as methylenomycin A,[118] methylenomycin B, xanthocydin,[119] cyclosarkomycin,[120] and sarkomycin.[121] Additionally, compounds **221**–**227** have the practical advantage of a stable C=C configuration, which simplifies their synthesis and avoid considering eventual *E*/*Z* isomerization (Scheme 39).



Scheme 39. Addition of reagents **51** to cyclic alkenes **221**–**227** activated by two electron-withdrawing groups.

Pyrrolidine-derived formaldehyde hydrazone **51k** (R = H)[91] showed a much higher reactivity than **51a** and when treated with compounds **221**, **222**, **223**, and **224** the reaction proceeded spontaneously to afford corresponding adducts **228**–**230k** and **233k** in moderate-to-good yields (50–85%).[62a] Only the less reactive ethoxycarbonylcumarine **227** required external activation (MgI_2) to afford adduct **234k** in 80% yield as a 17:1 *trans*/*cis* mixture of isomers. The products were isolated as *trans*/*cis* mixtures, obtained in variable ratios ranging from 3:1 in six-membered ketonitrile **228k** to >99:1 for the less-reactive cumarine derivative **233k**.

Bearing in mind the good stereocontrol observed in the addition of bulky hydrazone **51e** to alkylidenemalonates,[48b,62b] the asymmetric version of the precedent addition was carried out by using this reagent in most cases. Thus, the addition of hydrazone **51e** to alkenes **222**, **224**, and **225** in the presence of MgI_2 as the catalyst afforded only the two *trans* diastereoisomers **229e**, **231e**, and **232e** (*dr* 2:1 to 5:1) in good yields (71–80%) (Figure 7). Only alkene **221** afforded a mixture of the four possible diastereomers of **228e**. In the case of **223**, more-hindered hydrazone **51e** did not improve the diastereoisomeric ratio obtained by the simplest one **51b**. Less-reactive cumarine derivatives **226** and **227** required the employment of formaldehyde SAMP hydrazone **51b**, which led in both cases to *trans* adducts **233b** and **234b** in a 1.3:1 diastereoisomeric ratio (*dr* >99:1 after column chromatography). Polymerization of cumarine **226** in the presence of MgI_2 did not allow its use as a promoter. Fortunately, the reaction with hydrazone **51b** proceeded spontaneously at room temperature (84% yield) and 2-ethoxycarbonylcumarine **227**, which is less reactive than keto ester **226**, gave the desired adduct in 75% yield.

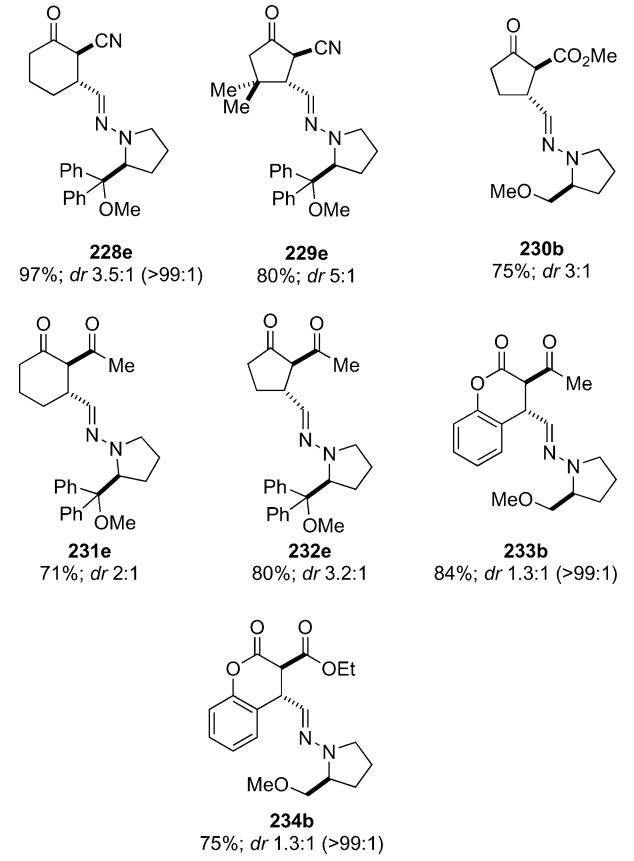


Figure 7. Adducts **228**–**234**.

Ozonolytic cleavage of adducts **228**–**234** led to corresponding aldehydes **235**–**241** in pure form, according to ^1H NMR spectroscopic analysis of the crude reaction mixtures.

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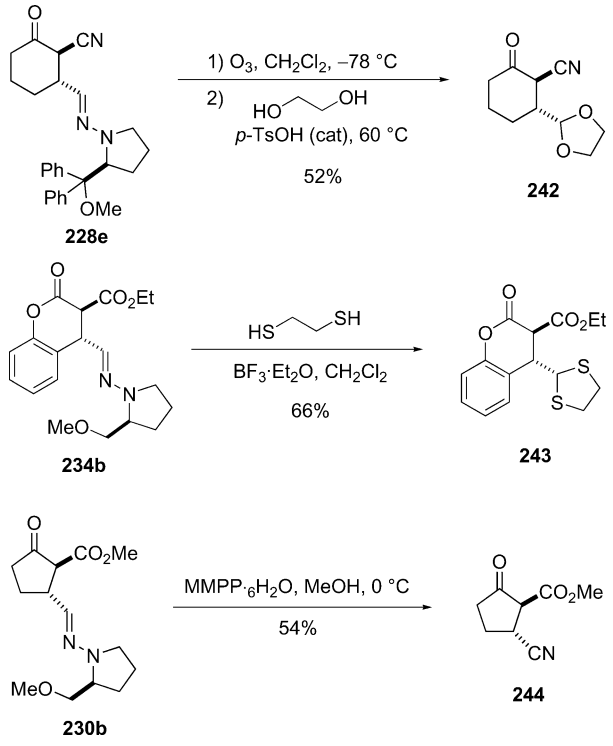
The aldehydes, however, are highly sensitive and any attempt to purify these compounds by column chromatography by using either silica gel or florisil led to extensive decomposition. Nevertheless, the crude aldehydes could be used in further reactions. For instance, **228e**, in spite of its tendency to undergo β-elimination of hydrogen cyanide, was successfully transformed into acetal **242** through the corresponding aldehyde and isolated after protection in a 52% yield over two steps (Scheme 40). Alternative transformations have also been used to remove the chiral auxiliary. For instance, direct dithioacetalation of adduct **234b** was achieved by reaction with ethanedithiol in the presence of an excess amount of $BF_3{\cdot}Et_2O$ (2.5 equiv.) to afford desired dithioacetal **243** in 66% yield. Finally, adduct **230b** was transformed into corresponding nitrile **244** in 54% yield by treatment with MMPP. This compound is an interesting precursor of the cyclopentenoid antibiotic sarkomycin.[122]

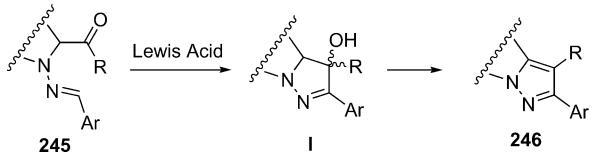


Scheme 40. Representative transformations.

12. Nucleophilic Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to Carbonyl Compounds

The addition of carbon nucleophiles to the carbonyl group of aldehydes and ketones constitutes one of the keystones of modern organic synthesis. Therefore, studies on the synthetic utility of formaldehyde *N*,*N*-dialkylhydrazones **51** as d^1 synthons were completed by analyzing their (asymmetric) addition to a variety of carbonyl compounds, and the transformation of the resulting α-hydroxy *N*,*N*-dialkylhydrazones into several bifunctional compounds.

In addition to the antecedents mentioned in the precedent chapters for the aza-enamine reactivity of higher hydrazones, Katayama et al.[123] reported in 1993 that Lewis acids catalyze the cyclization of hydrazones **245** to pyrazole products **246** (Scheme 41). In some cases, intermediate alcohols **I** could be isolated, which indicates that the reaction proceeds by intramolecular nucleophilic addition of the azomethine carbon atom to the neighbor carbonyl group. Though the reaction was reported to fail in an intermolecular fashion, the lack of success was most probably associated to the limited nucleophilicity of aromatic hydrazones. Trusting again the difference of reactivities exhibited by formaldehyde derivatives **51**, we decided to explore their addition to carbonyl compounds.



Scheme 41. An early precedent for the intramolecular addition of the hydrazone azomethine carbon to carbonyl groups.

12.1. Addition to Simple Aldehydes

An initial set of experiments carried out with simple aliphatic and aromatic aldehydes **247** revealed that, as in the case of most α,β-unsaturated carbonyl compounds, there is no spontaneous addition of reagents **51** to the carbonyl group in the absence of catalysts or promoters. The activation by Lewis acids proved not to be a trivial solution, not only because of the formation of strong complexes with the hydrazone nitrogen atoms, but also for the undesired side reactions catalyzed by them. Thus, an unexpected competing hydrazo transfer reaction (to **248**) and/or a dimerization of the reagent (to **249**, as in the case of alkylidenemalonates) was observed, depending on the Lewis acid used (Scheme 42).[47b] The formation of products **248** has been classically explained by assuming the catalytic effect of trace amounts of water present in the medium, which hydrolyze the C=N bond of the hydrazone and allow the subsequent condensation of the liberated hydrazine with the aldehyde. However, experimental conditions as the rigorous exclusion of water, as well as theoretical ab initio MO calculations,[124] suggest an alternative mechanism consisting of successive [2+2] and retro-[2+2] cycloadditions. Thus, only small amounts of desired adducts **250** were detected under most conditions.

Fortunately, desired products **250** could be isolated in reasonable yields (52–81%) by using $ZnCl_2$ or Et_2AlCl as suitable promoters and 1-methyleneaminopyrrolidine (**51k**) as the reagent (Scheme 43). Noteworthy, when *p*-nitrobenzaldehyde (**247**, R = *p*-$C_6H_4NO_2$) was treated with **51k** in the absence of any promoter, the corresponding 1,2-adduct was obtained, albeit in lower yield (33%) than that obtained for the $ZnCl_2$-promoted reaction (81%). This last result prompted us to investigate the uncatalyzed addition of

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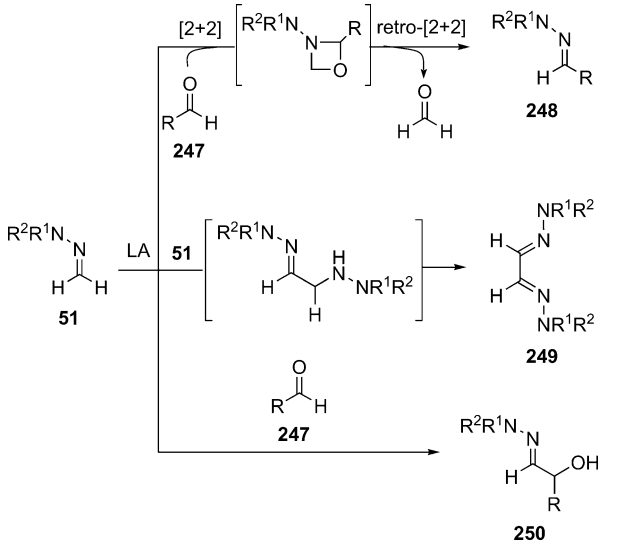
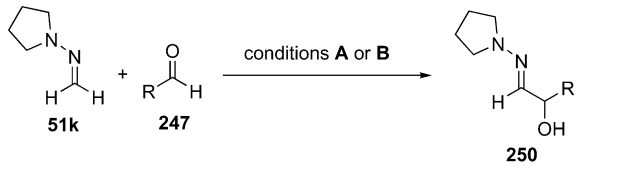


Scheme 42. Reactions and side reactions between formaldehyde *N*,*N*-dialkylhydrazones **51** and aldehydes **247**.

reagents **51** to more reactive aromatic or aliphatic aldehydes intrinsically activated by the inductive *–I* effects of electronegative heteroatoms.



A: R = *n*Bu, *n*-C_5H_{11}, Cy, Bn, Ph, *p*-C_6H_4-Br, *p*-C_6H_4-NO_2

⇩

Activation by promoters (Et_2AlCl in THF or $ZnCl_2$ in CH_2Cl_2): 33–81%

B: R = $BnOCH_2$, $TBSOCH_2$, $(MeO)_2CH$, Cl_3C, F_3C, *p*-$C_6H_4NO_2$, F_5C_6

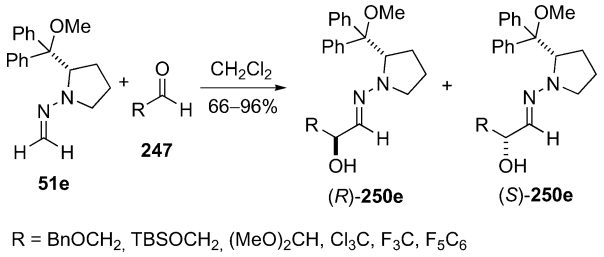
⇩

Spontaneous addition in CH_2Cl_2 enabled by inductive effects: 60–95%

Scheme 43. Substrate-dependent spontaneous or Lewis acid promoted addition of **51k** to aldehydes **247**.

The inductive effect of a single alkoxy group in the α-position to the carbonyl group was found to increase the reactivity of these substrates up to the level needed for the spontaneous addition. In the initial experiments, the reaction of α-monoalkoxy (R = $BnOCH_2$, $TBSOCH_2$) and α,α-dialkoxy [R = $(MeO)_2CH$] aldehydes, as well as chloral (R = CCl_3) and fluoral (R = CF_3) also with **51k** in the absence of promoters also proceeded to afford corresponding α-hydroxy hydrazones **250** in good-to-excellent yields. In general, reasonable reaction rates were observed for all substrates at room temperature, which led through clean reactions to the desired adducts. Interestingly, the commercial forms of dimethoxyacetaldehyde (60% in H_2O), chloral (monohydrate), and fluoral (ethyl hemiacetal) could be used without any previous treatment.

The development of an asymmetric version of these uncatalyzed additions was studied with limited success. Though all available chiral hydrazones **51** showed excellent reactivities, the diastereoselectivities were disappointing in all cases. Once again, however, the (2*S*)-(1,1-diphenyl-1-methoxymethyl) auxiliary of **51e** operated as a resolving agent that made easy chromatographic separation of diastereomeric adducts (*R*)-**250e** and (*S*)-**250e** possible (Scheme 44).

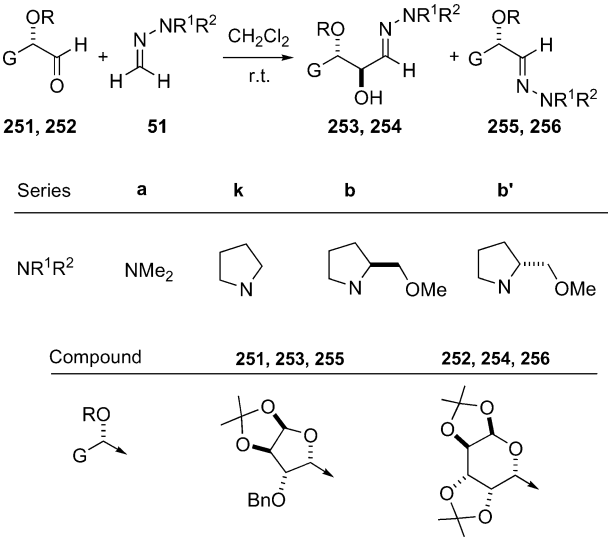


R = $BnOCH_2$, $TBSOCH_2$, $(MeO)_2CH$, Cl_3C, F_3C, F_5C_6

Scheme 44. Addition of **51e** to reactive aldehydes **247**.

12.2. Homologation of Carbohydrates and α-Amino Acid Derivatives

Carbohydrate-derived aldehydes constitute a particular group of carbonyl compounds that, generally bearing protected hydroxy groups at the α-position, should be able to undergo the uncatalyzed reaction with hydrazones **51**. This is an interesting reaction because of the mild conditions required (an aspect of special value when handling polyfunctional substrates such as carbohydrates) and for the interest of the expected products. Therefore, we were pleased to see that the addition of **51** to sugar-derived aldehydes **251** and **252** proceeded smoothly in dichloromethane at room temperature to afford corresponding α-hydroxyhydrazones **253** and **254** (Scheme 45).[52,125]



Scheme 45. Diastereoselective addition of hydrazones **51** to carbohydrate-derived aldehydes **251** and **252**.

As for simple aldehydes, hydrazone **51k** gave better results than the simplest dimethyl analogue **51a**, which afforded products mixed with hydrazono transfer byproducts

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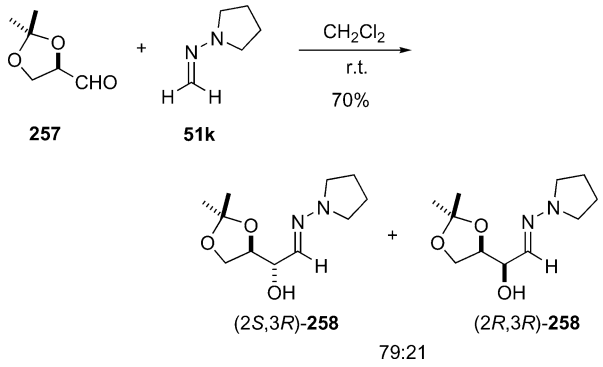
255 and **256**, even in the absence of acids. The high diastereoselection for the addition of **51k** makes the use of chiral reagents **51b** or **51b'** superfluous unless an additional diastereoselective reaction on the chiral hydrazone is envisaged. Double induction experiments also revealed that the influence of the stereogenic α-center in substrate **251** or **252** is stronger than that of **51b** or **51b′**, and therefore, the products with the opposite configuration at the newly created center cannot be prepared directly.

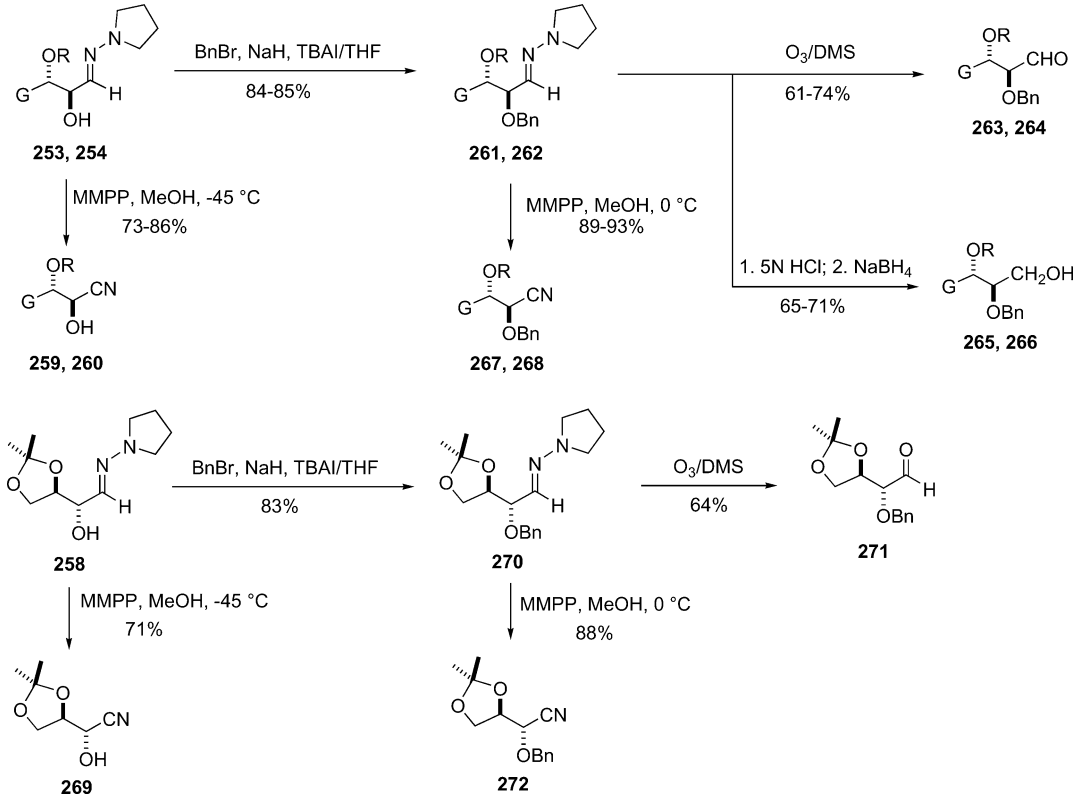
Lower asymmetric induction was observed for the addition of **51k** to 2,3-*O*-isopropylidene-D-glyceraldehyde (**257**). Corresponding adduct **258** was obtained in 70% yield as a 79:21 mixture of (2*S*,3*R*) and (2*R*,3*R*) diastereomers, which could be easily separated by flash chromatography (Scheme 46).



Scheme 46. Asymmetric addition of **51k** to 2,3-*O*-isopropylidene-D-glyceraldehyde **257**.

Starting from adducts **253** and **254**, direct oxidative cleavage by MMPP under the usual conditions afforded corresponding unprotected cyanohydrins **259** and **260** in good yields (Scheme 47). Additionally, the protection of the newly created hydroxy group as benzyl ethers afforded compounds **261** and **262**, which were efficiently transformed into a variety of derivatives, including α-benzyloxy aldehydes **263** and **264** (either by ozonolysis or HCl-mediated hydrolysis), monoprotected diols **265** and **266** (by acid hydrolysis and subsequent "one-pot" reduction with $NaBH_4$), and benzyl-protected cyanohydrins **267** and **268** (by oxidative cleavage promoted by MMPP). Starting from **258**, the same transformations were applied to the synthesis of cyanohydrin **269**, aldehyde **271**, and protected cyanohydrin **272**. Hence, the addition of **51k** to aldehydo sugars constitutes a valuable alternative to the few existing methods for their selective homologation.

In order to explore the desirable extension of this methodology to α-amino aldehydes **273**, the addition of **51k** to *N*-Boc-L-phenylalaninal (R = Bn) and *N*-Boc-L-leucinal (R = *i*Bu) was also investigated (Scheme 48). Considering the lower electronegativity of the nitrogen atom, the *N*-Boc protecting group was chosen as the first option in order to procure a reasonable inductive effect (higher aldehyde reactivity), while still maintaining a relatively low steric hindrance with respect to other common derivatives, such as α-dibenzylamino aldehydes. The 1,2-addition of **51k** to **273**



Scheme 47. Synthesis of carbohydrate derivatives.

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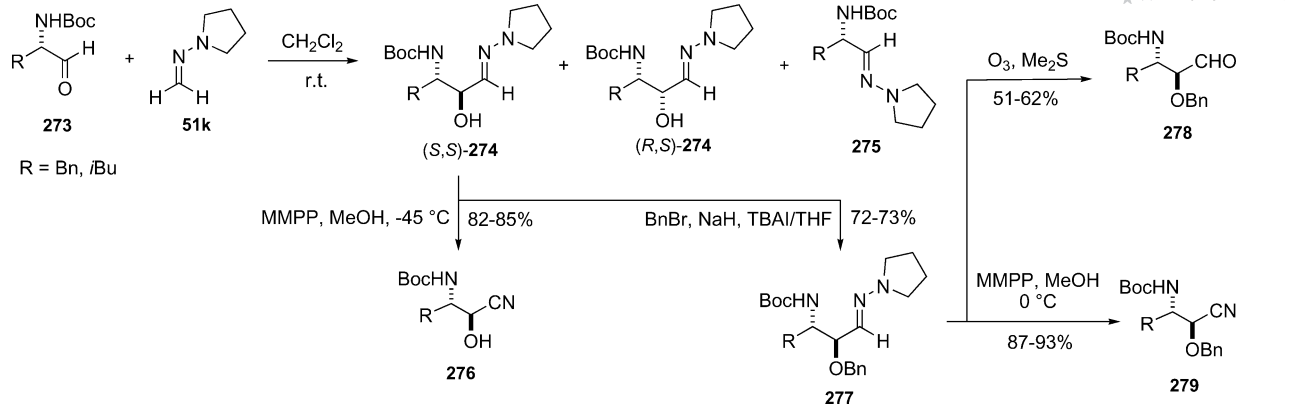


Scheme 48. Addition of **51k** to α-amino aldehydes **273** and synthesis of derivatives **276**–**279** therefrom.

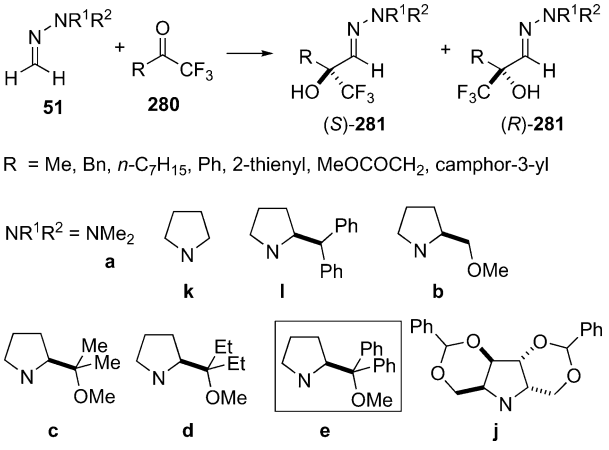
proceeded smoothly to afford expected adducts **274** in good yields and moderate-to-good *anti* selectivities, along with small amounts (8 and 6%, respectively) of hydrazono transfer byproducts **275** (Scheme 48). Both the major (2*S*,3*S*) and minor (2*R*,3*S*) diastereomers of **274** could easily be separated by flash chromatography to get pure compounds.

A variety of densely functionalized derivatives can be synthesized from adducts **274** upon manipulation of their hydrazono terminus. Again MMPP was successfully used for the racemization-free oxidative cleavage of the hydrazone moiety of major isomers (*S*,*S*)-**274** to afford corresponding β-amino cyanohydrins **276**. In addition to the advantages mentioned above for the choice of *N*-Boc protecting groups, a supplementary benefit for this protection comes now into view: the low nucleophilic carbamate nitrogen of **274** easily survives the oxidative conditions needed for the synthesis of these cyanohydrins. Standard benzylation of compounds (*S*,*S*)-**274** yielded derivatives **277**, which were transformed into protected β-amino-α-hydroxy aldehydes **278** and β-amino-*O*-benzyl cyanohydrins **279** by applying the usual hydrazone cleavage procedures.

For both α-alkoxy and α-amino aldehydes, *erythro*-configured compounds were isolated as major or sole products. The *anti* selectivities observed for the 1,2-addition to the aldehyde are in agreement with the nonchelated Felkin–Anh model for nucleophilic addition to chiral carbonyl compounds.[126] It should be mentioned here that *erythro*-α-amino-β-hydroxy acids are important components of several biologically active compounds.[127,128]

12.3. Addition to Trifluoromethyl Ketones

In view of the observed effect of electronegative atoms on the reactivity of aldehydes, we decided to investigate the behavior of trifluoromethyl ketones in this context. It was predicted that the strong activation by three fluorine atoms in the α-position should balance the lower reactivity toward related nucleophiles usually observed for ketones than for aldehydes. Accordingly, hydrazones **51** were treated with several kinds (aliphatic, aromatic, and heteroaromatic) of trifluoromethyl ketones **280**. The 1,2-addition took place smoothly in all cases, again in a spontaneous manner (Scheme 49).



Scheme 49. Addition of hydrazones **51** to trifluoromethyl ketones **280**.

As for aldehydes, the addition of **51k** occurred faster and in better yields than that of **51a** and afforded corresponding pyrrolidine-derived α-trifluoromethyl-α-hydroxyhydrazones **281k** in good-to-excellent yields.[129] The development of a reasonable enantioselective version of this reaction presented some more difficulties. SAMP-formaldehyde hydrazone **51b** afforded high yields of adducts **281b**, but the *de* values were disappointing and the mixtures could not be separated easily. The screening with modified, sterically more demanding reagents **51c**–**e**,**i**,**j** indicated a direct correlation between the size of the residues at the 2′-position of the pyrrolidine ring and the observed selectivity for the addition; the best asymmetric inductions were achieved for **51d** and **51e**, which have bigger (quaternary) substituents at this position. As in many precedent cases, crystalline **51e** proved to be the reagent of choice once again due to its resolving properties. By using this hydrazone, all diastereomeric mixtures could be easily separated by flash chromatography, which thus allowed the isolation of both diastereomers (*S*,*S*)- and (*R*,*S*)-**281e** in enantiomerically

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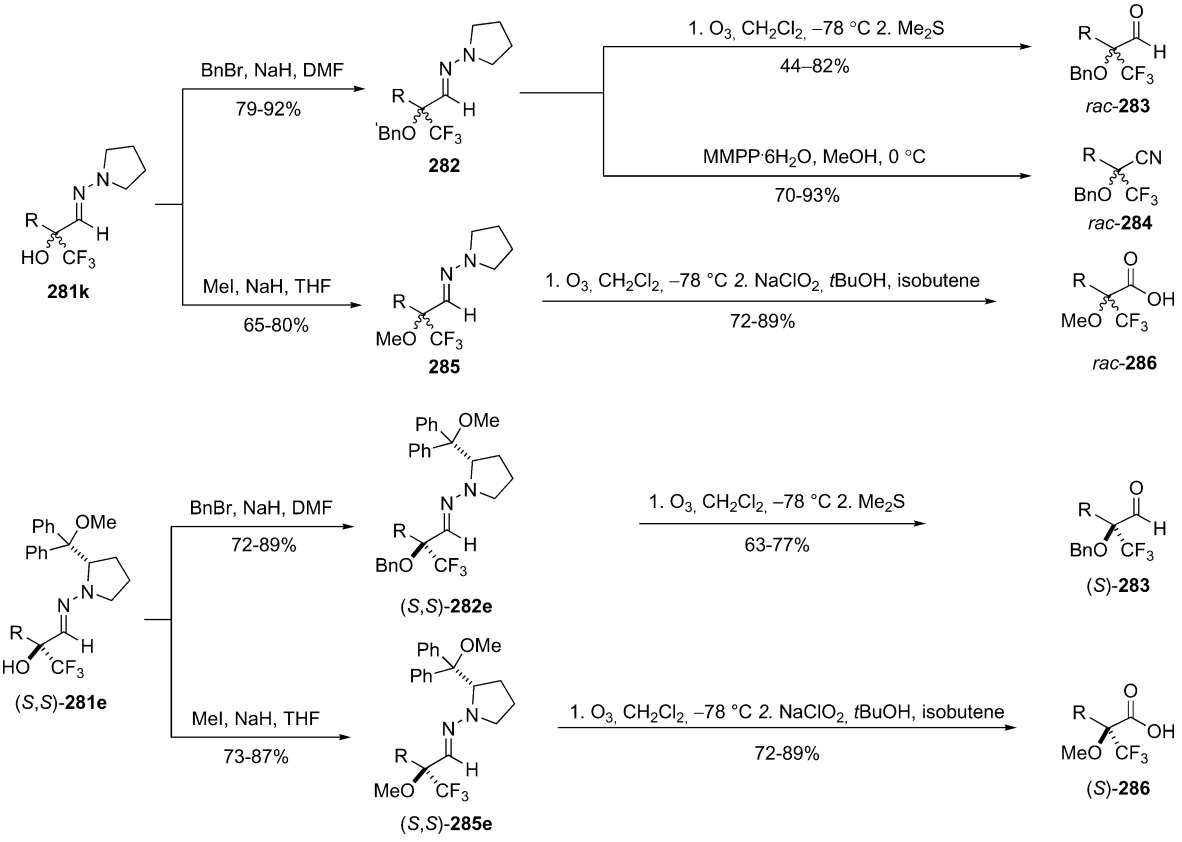

Scheme 50. Synthesis of α-trifluoromethyl functionalized carbinols **283**, **284**, and **286**.

pure forms. Though the *de* values were not very high, the overall result for these additions can be considered as satisfactory, as the combination of excellent yields (82–92%) and moderate *ee* values (51–81%), together with the easy chromatographic separations, resulted in moderate-to-good yields (42–75%) of the pure (*de* >98%) major (*S*,*S*)-**281e** diastereomers in a single step.

The newly created hydroxy group of adducts **281k** was protected by benzylation under standard conditions (NaH, BnBr, DMF), and products **282** were then transformed into α-benzyloxy-α-trifluoromethyl aldehydes **283** by ozonolysis and into benzyl-protected α-trifluoromethyl cyanohydrins **284** by MMPP oxidative cleavage (Scheme 50). Alternatively, adducts **281k** were methylated to **285** and transformed into the corresponding α-methoxy-α-trifluoromethyl carboxylic acids **286** by successive ozonolysis and in situ oxidation ($NaClO_2$, *t*BuOH, isobutene) of the crude α-methoxy aldehydes. The same reactions were applied for the transformation of (*S*,*S*)-**281e** into benzyl [(*S*,*S*)-**282e**] or methyl [(*S*,*S*)-**285e**] ethers, and for the synthesis of enantiopure pure α-benzyloxy-α-trifluoromethyl aldehydes (*S*)-**283** and α-methoxy-α-trifluoromethyl carboxylic acids (*S*)-**286**. As a limitation in this case, the MMPP-mediated transformation into nitriles was ineffective from (*S*,*S*)-**282e**, presumably due to the presence of the bulky methoxydiphenylmethyl group, which hinders the required oxidation of the neighbor amino nitrogen atom. Enantiopure trifluoromethylated compounds such as (*S*)-**283** and (*S*)-**286** are valuable building blocks, some of them with direct applications. For example, (*S*)-**286** (R = Ph) is a well-known chiral derivatizing reagent for the determination of the absolute configuration of alcohols and amines,[130] whereas (*S*)-**286** (R = Me) has been used as a derivatizing reagent for GC separation of enantiomeric amino acids.[131] In addition, enantiomerically pure, long-chain trifluoromethylated compounds of this type possess promising structures as precursors of liquid crystals.

13. Catalytic Activation of Electrophiles for the Enantioselective Addition of Formaldehyde *N*,*N*-Dialkylhydrazones

Within the last decade, the synthetic possibilities of hydrazones **51** in asymmetric synthesis have been associated with the efficiency of SAMP and related proline-derived auxiliaries. The difficult compatibility of these reagents with Lewis acids has probably delayed the arrival of metal-catalyzed enantioselective reactions, whereas the activation by milder species as organocatalysts appears a priori to be particularly appropriate for the characteristics of these reactions. In this chapter, very recent reports employing achiral reagents **51** in the field of asymmetric catalysis are covered.

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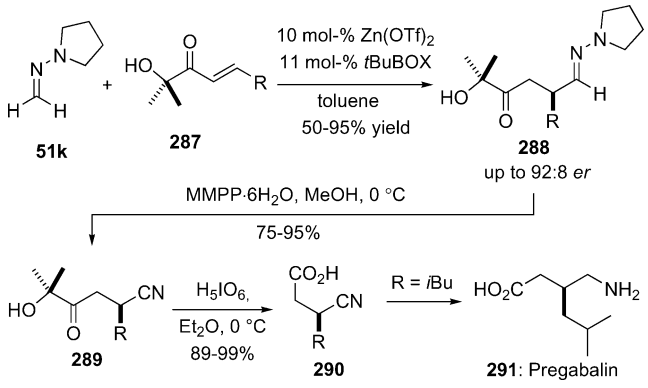
13.1. Catalytic Activation by Lewis Acids

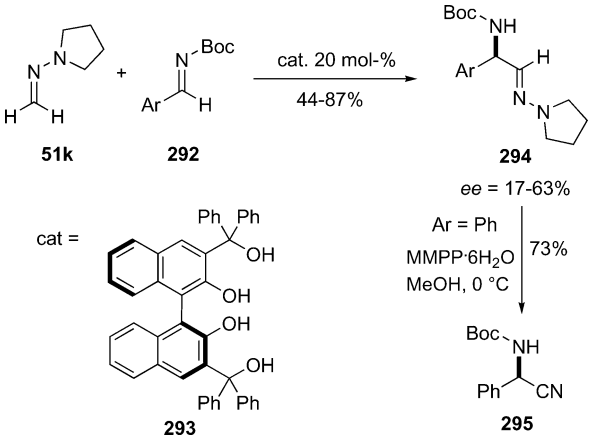
As mentioned, the activation of electrophilic substrates by Lewis acids (in particular in catalytic amounts) is troublesome due to the deactivation by the nitrogenated reagent and/or the competence of undesired side reactions.[62b,47b] Moreover, the addition of hydrazones **51** to acyclic enoates could not be accomplished under the conditions developed for enones[60] or α,β-unsaturated lactones[103] probably due to the lower reactivity of these substrates. Therefore, an effort was made to develop an efficient catalytic system for this particular reaction. After several screenings performed to identify an adequate enoate surrogate, Lewis acid, and chiral ligand, it was found that α-hydroxy enones **287** can be efficiently activated by the $Zn(OTf)_2$/*t*BuBOX catalyst (Scheme 51) to afford products **288** in high yields and moderate-to-good enantioselectivities.[132] Oxidative cleavage of these products by MMPP·$6H_2O$ readily afforded nitriles **289**. Further oxidation by periodic acid led to cyano acids **290** in good overall yields. These compounds are direct precursors of γ-amino butyric acids (GABAs), which are relevant bioactive compounds. In particular, the formal synthesis of pregabalin **291**, an anticonvulsant drug used for treatment of neuropathic pain, can be accomplished from **290** (R = *i*Bu) according to a known procedure.[133]



Scheme 51. Catalytic asymmetric addition of **51k** to α-hydroxyenones **287**.

13.2. Activation by Brønsted Acids or H-Bonding Organocatalysts

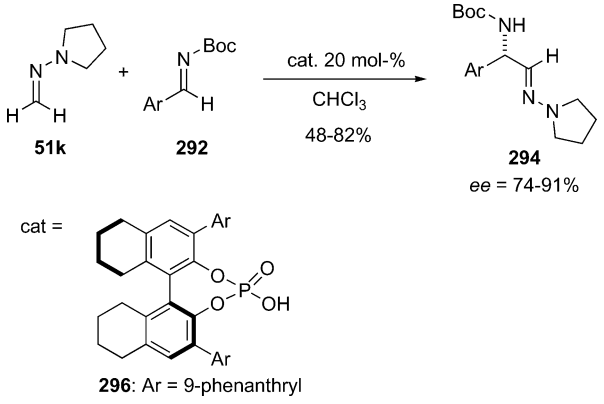
Recently, the first enantioselective Brønsted acid catalyzed addition of 1-methyleneaminopyrrolidine **51k** to *N*-Boc imines **292** was achieved in the presence of chiral BINOL-derived catalysts (Scheme 52). By using 3,3′-bis(methanol)-2,2′-binaphthol catalysts (BIMBOLs, **293**) in this asymmetric imino-ene-type reaction, desired adducts **294** were obtained in moderate-to-good yields and enantiomeric excesses.[134] No reaction was observed in the absence of catalysts, whereas BINOL itself showed little catalytic activity. It was observed that the additional hydroxy groups in the BIMBOL catalysts were required to increase the acidity of the catalytic system. Additionally, the diaryl functionalities in the 3,3′-positions were also found to be essential to the effectiveness of the catalyst.



Scheme 52. Organocatalytic addition of **51k** to *N*-Boc imines **292**.

The mild oxidation of product **294** (Ar = Ph) by using MMPP·$6H_2O$ gave corresponding nitrile adducts **295** cleanly, in good yield without any observable racemization. This provides an alternative route to enantiomerically enriched Strecker adducts without having to resort to the use of highly toxic HCN.

Better results were obtained in the same reaction by using phosphoric acids derived from binaphthols as catalysts. A survey of hydrazones **51**, imine protecting groups, solvents, and catalyst structure was performed to reach finally products **294** with good yields and enantiomeric excesses up to 91% by using **51k**, *N*-Boc-protected aldimines **292**, and 3,3′-bis(phenanthryl)-H8-BINOL **296** in $CHCl_3$ (Scheme 53).[135]



Scheme 53. Enantioselective Brønsted acid catalyzed addition of **51k** to imines **292**.

Hydrogen-bonding organocatalysts were also considered as an alternative strategy to the approach described above for the catalytic activation of enoate surrogates. By using in this case β,γ-unsaturated α-keto esters **297** as enoate surrogates, it was found that the addition of **51k** was strongly accelerated by catalytic amounts of thioureas. The best results in terms of selectivity were achieved by employing (1*S*,2*R*)-aminoindan-2-ol-derived thiourea **298**,[136] which

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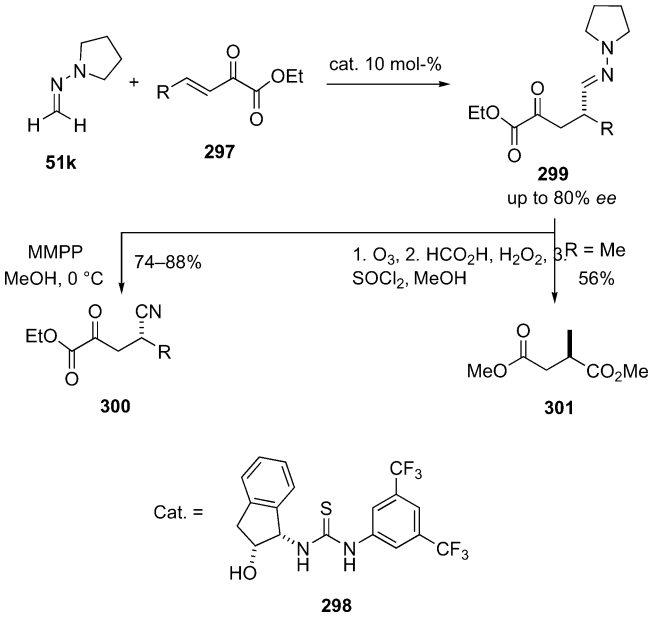
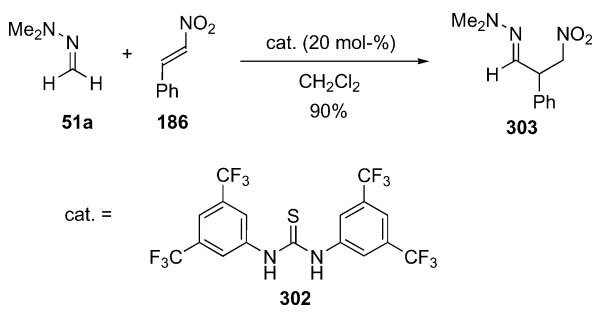
led to adducts **299** in good yields and enantioselectivities (Scheme 54).[137] These compounds are versatile 1,4-dicarbonyl compounds that can be transformed into nitriles **300** by MMPP·6H_2O. Additionally, ozonolytic cleavage of **299** (R = Me) afforded an unstable intermediate that was further oxidized by a HCO_2H/H_2O_2 mixture and treated with $SOCl_2$/MeOH to obtain succinate **301** resulting from deoxidative decarboxylation.



Scheme 54. Enantioselective catalytic addition of **51k** to β,γ-unsaturated α-keto esters **297**.

In addition, thioureas were also used as H-bonding organocatalysts to accelerate the addition of formaldehyde *N*,*N*-dimethylhydrazone (**51a**) to nitroalkenes. Thus, whereas the uncatalyzed addition of **51a** to β-nitrostyrene proceeded to yield the expected adduct with incomplete conversion (<50%) after 18 h, the use of thiourea **302** (20 mol-%) as the catalyst resulted in full conversion of nitrostyrene (**186**, R = Ph), which led to the isolation of **303** in 90% yield after the same reaction time (Scheme 55).[138] The use of chiral thioureas for the enantioselective activation of nitroalkenes **186**, as well as of other electrophilic substrates is a current object of study in our laboratories.



Scheme 55. Thiourea-catalyzed addition of **51a** to nitrostyrene **186**.

Conclusions

The field of the aza-enamine chemistry, started nearly four decades ago, has emerged as a powerful tool for the umpolung of classical carbonyl reactivity. Aldehyde *N*,*N*-dialkylhydrazones constitute an important class of acyl, formyl, and cyanide anion equivalents. The most interesting features of the title compounds lies in their *neutral* character, which makes them compatible with many functional groups, and their efficiency in the transformations that release masked carbonyl functionalities or the cyano group. A second aspect that contributed to the successful application of the aldehyde hydrazones is the availability of different proline-derived chiral auxiliaries, which can easily be incorporated for the development of asymmetric syntheses of a variety of densely functionalized compounds, usually in enantiomerically pure form. Additionally, it should be mentioned that the primary products obtained in the addition reactions retain the (chiral) hydrazone moiety. Thus, they can be used a second time for (stereoselective) C–C bond forming processes such as the well-established *S*AMP/*R*AMP methodology,[139] the addition of organometallic reagents[140] and nucleophilic free radicals,[141] and [2+2] cycloadditions with alkoxy or amino ketenes.[142]

Finally, the neutral character of the reagent appears to be particularly well suited for the development of new catalytic, enantioselective reactions where Brønsted acids or H-bonding catalysts can be used for the activation of the substrates. Therefore, we are convinced that many more applications based on the combination of such organocatalysts and formaldehyde hydrazones will appear in the near future.

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[1] D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[2] a) D. Seebach, *Angew. Chem.* **1969**, *81*, 690–700; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 639; b) D. Seebach, *Synthesis* **1969**, 17–36.
[3] a) D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359–373; b) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541; c) J. S. Johnson, *Angew. Chem.* **2004**, *116*, 1348–1350; *Angew. Chem. Int. Ed.* **2004**, *43*, 1326; d) A. B. Smith, C. M. Adams, *Acc. Chem. Res.* **2004**, *37*, 365–377; e) C. Kison, N. Meyer, T. Opatz, *Angew. Chem.* **2005**, *117*, 5807–5809; *Angew. Chem. Int. Ed.* **2005**, *44*, 5662–5664; f) H. Stetter, H. Kuhlmann, *Org. React.* **1991**, *40*, 407–496; g) T. A. Hase, *Umpoled Synthons*, Wiley, New York, **1987**.
[4] H. Staudinger, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2217–2219.
[5] E. J. Corey, D. Seebach, *Angew. Chem.* **1965**, *77*, 1134–1136; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1065.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[6] a) D. Seebach, M. Kolb, *Chem. Ind. (London)* **1974**, 687–692; b) A. B. Callear, I. Fleming, R. H. Ottewill, K. Waiwright, S. G. Warren, R. H. Prince, *Chem. Ind. (London)* **1974**, 910–913.

[7] O. W. Lever Jr., *Tetrahedron* **1976**, *32*, 1943–1971.

[8] Carbon–heteroatom bond formation: a) R. Pütter (Ed.), *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed., Thieme, Stuttgart, **1965**, vol. 10/3, pp. 633–642; halogenations: b) E. Enders (Ed.), *Methoden der Organischen Chemie (Houben-Weyl)*, Thieme, Stuttgart, **1967**, vol. 10/2, pp. 379–381; c) P. Bouchet, J. Elguero, R. Jacquier, *Bull. Soc. Chim. Fr.* **1967**, 4716–4728; d) F. D. Chattaway, H. Irving, *J. Chem. Soc.* **1935**, 90–92; e) J. Kosary, P. Sohar, *Acta Chim. Acad. Sci. Hung.* **1980**, *103*, 405; f) R. S. Tewari, P. Parihar, *J. Chem. Eng. Data* **1981**, *26*, 418; nitration: g) H. Feuer, L. F. Spinicelli, *J. Org. Chem.* **1976**, *41*, 2981–2984; h) A. S. Shawali, H. M. Hassaneen, S. M. Sherif, *J. Heterocycl. Chem.* **1980**, *17*, 1745–1749; nitrosation: i) R. Pütter (Ed.), *Methoden der Organischen Chemie: (Houben-Weyl)*, 4th ed., Thieme, Stuttgart, **1965**, vol. 10/3, pp. 622–623; j) J. P. Kitaev, B. J. Busykin, *Usp. Khim.* **1972**, *41*, 995–1037; k) A. S. Shawali, *J. Heterocycl. Chem.* **1977**, *14*, 185–189; acyloxylation: l) R. N. Butler, *Chem. Ind. (London)* **1976**, 499–500; m) R. N. Butler, W. B. King, *J. Chem. Soc. Perkin Trans. 1* **1975**, 61–65; n) R. N. Butler, W. B. King, *J. Chem. Soc. Perkin Trans. 1* **1977**, 282–286; o) J. B. Aylward, *J. Chem. Soc. C* **1970**, 1494–1497; p) E. Enders (Ed.), *Methoden der Organischen Chemie (Houben-Weyl)*, Thieme, Stuttgart, **1967**, vol. 10/2, p. 686; azides: q) O. Dimroth, S. Merzbacher, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2899–2904; azodicarbonic and phenylazocarbonic acid ester: r) E. Fahr, H.-D. Rupp, *Angew. Chem.* **1964**, *76*, 684; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 693; s) E. Fahr, H. Lind, *Angew. Chem.* **1966**, *78*, 376–388; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 372–383.

[9] Carbon–carbon bond formation: methyl methacrylate, methyl acrylate, and acrylonitrile: a) B. B. Snider, R. S. E. Conn, S. Sealfon, *J. Org. Chem.* **1979**, *44*, 218–221; styrene, acrylic ester, trimethyl ethylenetricarboxylate, dimethyl maleate and fumarate: b) G. Le Fevre, J. Hamelin, *Tetrahedron* **1980**, *36*, 887–891; methyl propiolate: c) R. Baumes, R. Jacquier, G. Tarrago, *Bull. Soc. Chim. Fr.* **1974**, 2547–2555; quinones: d) V. M. Lyubchanskaya, L. M. Alekseeva, V. G. Granik, *Tetrahedron* **1997**, *53*, 15005–15010; e) V. M. Lyubchanskaya, L. M. Alekseeva, V. G. Granik, *Chem. Heterocycl. Compd.* **1999**, *35*, 570–574; nitrovinylation: f) Th. Severin, Th. Wieland, *Synthesis* **1973**, 613–614; intramolecular cyclization reactions: g) B. Fouchet, M. Joucla, J. Hamelin, *Tetrahedron Lett.* **1981**, *22*, 1333–1336; Mannich Reaction: h) L. El Kaim, L. Gautier, L. Grimaud, V. Michaut, *Synlett* **2003**, *12*, 1844–1846; i) V. Atlan, H. Bienayme, L. El Kaim, A. Majee, *Chem. Commun.* **2000**, 1585–1586; j) E. Enders (Ed.), *Methoden der Organischen Chemie (Houben-Weyl)*, Thieme, Stuttgart, **1967**, vol. 10/2, pp. 461–462; hydroxymethylation: k) K. Bodendorf, W. Wössner, *Justus Liebigs Ann. Chem.* **1959**, *623*, 109; formylation: l) S. O. Abdallah, N. H. Metwally, H. F. Anwar, M. H. Elnagdi, *J. Heterocycl. Chem.* **2005**, *42*, 781–786; reaction with heterocyclic salts: m) A. M. Richter, C. K. J. Tschötsch, E. Fanghänel, *Synthesis* **1983**, 840–842; Michael addition: n) S. A. S. Ghozlan, J. A. Abdelhamid, H. M. Hassaneen, M. H. Elnagdi, *J. Heterocycl. Chem.* **2007**, *44*, 105–108; o) S. A. S. Ghozlan, J. A. Abdelhamid, M. H. Elnagdi, *ARKIVOK* **2006**, 147–157.

[10] a) R. M. Adlington, J. E. Baldwin, J. C. Bottaro, M. W. D. Perry, *J. Chem. Soc. Chem. Commun.* **1983**, 1040–1041; b) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, W. D. Matthew, P. A. U. Jain, *Tetrahedron* **1986**, *42*, 4223–4234; c) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, A. U. Jain, J. N. Kolhe, M. W. D. Perry, I. M. Newington, *J. Chem. Soc. Chem. Commun.* **1984**, 1095–1096; d) J. E. Baldwin, R. M. Adlington, A. U. Jain, J. N. Kolhe, M. W. D. Perry, *Tetrahedron* **1986**, *42*, 4247–4252; e) J. E. Baldwin, J. C. Bottaro, J. N. Kolhe, R. M. Adlington, *J. Chem. Soc. Chem. Commun.* **1984**, 22–23; f) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, I. M. Newington, M. W. D. Perry, *Tetrahedron* **1986**, *42*, 4235–4246.

[11] M. A. Berghot, D. S. Badaway, *Chem. Pap.* **2003**, *57*, 342–349.

[12] R. Brehme, *Schrift zur Promotion B*, Akademie der Wissenschaften der DDR, Berlin, **1985**.

[13] R. Brehme, H. E. Nikolajewski, *Z. Chem.* **1968**, *8*, 226–227.

[14] R. Brehme, H. E. Nikolajewski, *Tetrahedron* **1969**, *25*, 1159–1163.

[15] a) P. W. Hickmott in *The Chemistry of Enamines, Part 1* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1994**, pp. 727–871; b) G. H. Alt, A. G. Cook in *Enamines* (Ed. A. G. Cook), Dekker, New York, **1988**, pp. 181–246; c) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207–222; d) J. Szmuszkovicz in *Advances in Organic Chemistry*, Wiley, New York, **1963**, vol. 4, pp. 1–113.

[16] R. Brehme, H. E. Nikolajewski, *Tetrahedron* **1976**, *32*, 731–736.

[17] a) E. Müller (Ed.), *Methoden der Organischen Chemie (Houben Weyl)*, 4th ed., Thieme, Stuttgart, **1967**, vol. 10/2, pp. 36–37; b) R. Gösl, A. Meuwsen, *Chem. Ber.* **1959**, *92*, 2521–2525.

[18] H. Böhme, H. G. Viehe, "Iminium Salts in Organic Chemistry" in *Advances in Organic Chemistry Part 1* (Ed.: E. C. Taylor), Wiley Interscience, New York, **1976**, vol. 9, .

[19] W. Ziegenbein, *Angew. Chem.* **1965**, *77*, 380; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 358.

[20] R. Brehme, *Chem. Ber.* **1990**, *123*, 2039–2046.

[21] R. Brehme, H. E. Nikolajewski, *Tetrahedron Lett.* **1982**, *23*, 1131–1134.

[22] R. Brehme, E. Gründemann, M. Schneider, R. Radeglia, G. Reck, B. Schulz, *Synthesis* **2003**, 1615–1619.

[23] R. Brehme, R. Radeglia, E. Gründemann, *J. Prakt. Chem./Chem.-Ztg.* **1990**, *332*, 911–921.

[24] a) T. Severin, R. Adam, *Chem. Ber.* **1975**, *108*, 88–94; b) L. Mayring, T. Severin, *Chem. Ber.* **1981**, *114*, 3863–3877; c) T. Severin, R. Adam, H. Lerche, *Chem. Ber.* **1975**, *108*, 1756–1767; d) T. Severin, H. Lerche, *Chem. Ber.* **1976**, *109*, 1171–1178.

[25] a) D. Enders, R. Peters, L. Wortmann, *Acc. Chem. Res.* **2000**, *33*, 157–169; b) R. Fernandez, J. M. Lassaletta, *Synlett* **2000**, 1228–1240; c) D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *112*, 2933–2960; d) M. Avaro, J. Levisalles, H. Rudler, *J. Chem. Soc. C* **1969**, 445–446.

[26] a) R. Richter, H. Ulrich, "Syntheses and Preparative Applications of Isocyanates" in *The chemistry of Cyanates and Their Thio Derivatives Part 2* (Ed.: S. Patai), Wiley, New York, **1977**, ch. 17, pp. 619–818; b) J. W. McFarland, *Int. J. Sulfur Chem. B* **1972**, *7*, 319; c) J. W. McFarland, *Sulfur Rep.* **1981**, *1*, 215.

[27] R. Brehme, B. Stroede, *J. Prakt. Chem./Chem.-Ztg.* **1987**, *329*, 246–258.

[28] R. Brehme, A. Klemann, *Tetrahedron* **1987**, *43*, 4113–4118.

[29] R. Brehme, G. Reck, B. Schulz, R. Radeglia, *Synthesis* **2003**, 1620–1625.

[30] E. Gründemann, R. Brehme, H. E. Nikolajewski, *J. Prakt. Chem./Chem.-Ztg.* **1982**, *324*, 575–580.

[31] L. Weber, M. Mühlstädt, *Z. Chem.* **1988**, *28*, 26–27.

[32] R. Radeglia, S. Dähne, H. Hartmann, *J. Prakt. Chem./Chem.-Ztg.***1970**, *312*, 1081–1086.

[33] G. Scheibe, D. Grosse, J. Heiß, *Angew. Chem.* **1964**, *76*, 187; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 374.

[34] H. Suschitzky, R. E. Walrond, R. Hull, *J. Chem. Soc. Perkin Trans. 1* **1977**, 47–52.

[35] F. Effenberger, R. Gleiter, *Chem. Ber.* **1964**, *97*, 1576–1583.

[36] A. N. Gafarov, S. A. Konovalova, *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 1569–1573; *Zh. Org. Khim.* **1970**; *6*, 1556–1561.

[37] H. Böhme, K. Hartke, *Chem. Ber.* **1960**, *93*, 1305–1309.

[38] R. Brehme, unpublished results.

[39] a) R. F. Smith, L. E. Walker, *J. Org. Chem.* **1962**, *27*, 4372–4375; b) M. Th. Nguyen, L. F. Clarke, A. F. Hegarty, *J. Org. Chem.* **1990**, *55*, 6177–6183.

[40] S. F. Nelsen, *J. Org. Chem.* **1969**, *34*, 2248–2250.

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[41] V. N. Yelokhina, A. S. Nakhmanovich, R. V. Karnaukhova, L. I. Larina, V. A. Lopyrev, *Russ. J. Org. Chem. (Engl. Transl.)* **2000**, *36*, 479–481; *Zh. Org. Khim.* **2000**, *36*, 502–504.
[42] Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, T. Yokoyama, *J. Org. Chem.* **1988**, *53*, 129–135.
[43] a) Y. Kamitori, T. Sekiyama, *Heterocycles* **2004**, *63*, 707–713 and ref. cited therein; b) Y. Kamitori, *Heterocycles* **2003**, *60*, 1185–1190; c) Y. Kamitori, *J. Heterocycl. Chem.* **2001**, *38*, 773–775; d) Y. Kamitori, M. Hojo, R. Masuda, T. Takahashi, M. Wada, T. Hiyama, Y. Mimura, *Heterocycles* **1994**, *38*, 803–809; e) M. Medebielle, K. Kato, W. R. Dolbier Jr., *Tetrahedron Lett.* **2003**, *44*, 7871–7874.
[44] Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, K. Yamada, N. Yoshikawa, *J. Org. Chem.* **1988**, *53*, 519–526.
[45] a) V. G. Andrianov, E. N. Rozhkov, A. V. Eremeev, *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 1834–1835; *Zh. Org. Khim.* **1989**, *25*, 2028–2029; b) V. G. Andrianov, V. G. Semenichina, A. V. Eremeev, *Khim. Geterosikl. Soedin.* **1991**, 976–978.
[46] Ch. Larsen, D. N. Harpp, *J. Org. Chem.* **1981**, *46*, 2465–2466.
[47] a) F. E. Condon, J. P. Trivedi, *J. Org. Chem.* **1972**, *37*, 3960–3961; b) R. Fernandez, E. Martin Zamora, C. Pareja, M. Alcarazo, J. Martin, J. M. Lassaletta, *Synlett* **2001**, 1158–1160.
[48] a) A. B. Koldobskii, J. N. Lusikov, V. V. Lunin, *J. Org. Chem. USSR (Engl. Transl.)* **1986**, *22*, 570- 572; *Zh. Org. Khim.* **1986**, *22*, 636–638; b) J. M. Lassaletta, J. Vazquez, A. Prieto, R. Fernandez, G. Raabe, D. Enders, *J. Org. Chem.* **2003**, *68*, 2698–2703.
[49] a) J. Laue, G. Seitz, H. Waßmuth, *Z. Naturforsch., Teil B* **1996**, *51*, 348–358; b) G. Seitz, S. Dietrich, R. Dhar, W. Massa, G. Baum, *Arch. Pharm.* **1986**, *319*, 798–807.
[50] a) F. E. Condon, D. Farkcasiu, *J. Am. Chem. Soc.* **1970**, *92*, 6625–6630; b) A. N. Gafarov, *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 1565–1568; *Zh. Org. Khim.* **1970**, *6*, 1552–1556.
[51] a) S. Weik, Dissertation, Universtität Tübingen **2004**; b) S. Weik, J. Rademann *Angew. Chem.* **2003**, *115*, 2595–2598; *Angew. Chem. Int. Ed.* **2003**, *42*, 2491–2494; c) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem.* **2001**, *113*, 670–701; *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679.
[52] R. Fernandez, E. Martin-Zamora, C. Pareja, J. M. Lassaletta, *J. Org. Chem.* **2001**, *66*, 5201–5207.
[53] a) S. P. Ivonin, A. A. Anishchenko, M. V. Voevudskii, L. V. Dmitrikova, *Khim. Geterosikl. Soedin.* **1998**, *C*, 1265–1266.
[54] a) S. P. Ivonin, A. V. Lapandin, A. A. Anishchenko, V. G. Shtamburg, *Eur. J. Org. Chem.* **2004**, 4688–4693; b) S. P. Ivonin, A. V. Lapandin, V. G. Shtamburg, *Chem. Heterocycl. Compd.* **2005**, *41*, 1484–1493; *Khim. Geterosikl. Soedin.* **2005**, 1805–1814.
[55] B. Abarca, R. Ballesteros, E. Gonzalez, P. Sancho, J. Sepulveda, C. Soriano, *Heterocycles* **1990**, *31*, 1811–1817.
[56] M. E. Gonzalez, P. Sancho, C. Soriano, R. Ballesteros, B. Abarca, J. Sepulveda, *Heterocycles* **1988**, *27*, 1227–1231.
[57] J. R. Roland, B. C. McKusick, *J. Am. Chem. Soc.* **1961**, *83*, 1652–1657.
[58] a) K. T. Potts, E. B. Walsh, *J. Org. Chem.* **1984**, *49*, 4099–4101; b) K. T. Potts, E. B. Walsh, *J. Org. Chem.* **1988**, *53*, 1199–1202; c) A. Grondin, D. C. Robson, W. E. Smith, D. Graham, *J. Chem. Soc. Perkin Trans. 2* **2001**, 2136–2141; d. A. B. Koldobskii, V. V. Lunin, S. A. Wosnesenskii, *Zh. Org. Khim.* **1992**, *28*, 809–826.
[59] J. Sauer, *Angew. Chem.* **1966**, *78*, 233–252; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 211.
[60] a) E. Diez, R. Fernandez, C. Gasch, J. M. Lassaletta, J. M. Llera, E. Martin-Zamora, J. Vazquez, *J. Org. Chem.* **1997**, *62*, 5144–5155; b) J. M. Lassaletta, R. Fernandez, E. Martin-Zamora, E. Diez, *J. Am. Chem. Soc.* **1996**, *118*, 7002–7003.
[61] a) H. Buff, Dissertation, University of Düsseldorf, **2001**; b) H. Buff, U. Kuckländer, *Tetrahedron* **2000**, *56*, 5137–5145.
[62] a) J. Vazquez, E. Christea, E. Diez, J. M. Lassaletta, A. Prieto, R. Fernandez, *Tetrahedron* **2005**, *61*, 4115–4128; b) J. Vazquez, A. Prieto, R. Fernandez, D. Enders, J. M. Lassaletta, *Chem. Commun.* **2002**, 498–499.
[63] a) M. Dees, H.-H. Otto, *Monatsh. Chem.* **1998**, *129*, 689–696; b) C. Orlewska, R. M. Shaker, M. Dees, H.-H. Otto, *Monatsh. Chem.* **2000**, *131*, 889–893.
[64] L. S. Hegedus, M. R. Sestrick, E. T. Michaelson, P. J. Harrington, *J. Org. Chem.* **1989**, *54*, 4141–4146.
[65] D. Batty, Y. Langlois, *Tetrahedron Lett.* **1993**, *34*, 457–460.
[66] a) A. B. Koldobskii, V. V. Lunin, *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 462–464; *Zh. Org. Khim.* **1991**, *27*, 533–536; b) W. Walter, H. Weiss, *Justus Liebigs Ann. Chem.* **1972**, *758*, 162–172.
[67] T. Severin, G. Wanninger, H. Lerche, *Chem. Ber.* **1984**, *117*, 2875–2885.
[68] M. Mühlstädt, L. Weber, *Z. Chem.* **1985**, *25*, 400.
[69] M. Mühlstädt, L. Weber, *Z. Chem.* **1985**, *25*, 323.
[70] M. Mühlstädt, L. Weber, P. Birner, *J. Chem. Soc. Perkin Trans. 2* **1988**, 821–825.
[71] A. A. Tolmachev, A. S. Merkulov, A. A. Yurchenko, M. G. Semenova, A. M. Pinchuk, *Russ. Chem. Bull.* **1998**, *47*, 1749–1754.
[72] A. A. Tolmachev, S. P. Ivonin, A. A. Anishchenko, A. M. Pinchuk, *Heteroat. Chem.* **1998**, *9*, 461–470.
[73] a) S. P. Ivonin, A. A. Anishchenko, A. F. Kurochkin, A. A. Tolmachev, *Heteroat. Chem.* **1998**, *9*, 559–563; b) S. P. Ivonin, A. A. Anishchenko, A. F. Kurochkin, A. A. Tolmachev, *Russ. J. Org. Chem. (Engl. Transl.)* **1999**, *35*, 1406–1407; *Zh. Organicheskoi Khimii* **1999**, *35*, 1434–1435.
[74] S. P. Ivonin, A. A. Tolmachev, T. E. Terikovska, A. A. Anishchenko, A. A. Chaikovskaya, A. A. Pinchuk, *Heteroat. Chem.* **2003**, *14*, 258–261.
[75] A. A. Tolmachev, A. C. Merkulov, A. A. Jurchenko, A. M. Pinchuk, *Zh. Obshch. Khim.* **1997**, *67*, 1033–1034.
[76] a) S. Beckmann, R. Bamberger, *Justus Liebigs Ann. Chem.* **1953**, *580*, 198–204; b) H. Brunner, F. Henning, M. Weber, M. Zabel, D. Carmona, F. J. Lahoz, *Synthesis* **2003**, 1091–1099.
[77] B. Serckx-Poncin, A.-M. Hesbain-Frisque, L. Ghosez, *Tetrahedron Lett.* **1982**, *23*, 3261–3264.
[78] Z. Bouaziz, A. Gherardi, F. Regnier, M.-E. Sarciron, X. Bertheau, B. Fenet, N. Walchshofer, H. Fillion, *Eur. J. Org. Chem.* **2002**, 1834–1838.
[79] a) M. Alvarez, L. Feliu, W. Ajana, J. A. Joule, J. L. Fernandez-Puentes, *Eur. J. Org. Chem.* **2000**, 849–855; b) J. Gentili, R. Barret, *Tetrahedron Lett.* **2005**, *46*, 1639–1641; c) S. Ghoshand, M. Schlosser, *J. Fluorine Chem.* **1994**, *67*, 53–56.
[80] F. Pautet, P. Nebois, Z. Bouaziz, H. Fillion, *Heterocycles* **2001**, *54*, 1095–1138.
[81] a) R. Beaudegnies, L. Ghosez, *Tetrahedron: Asymmetry* **1994**, *5*, 557–560; b) J. Tailor, D. G. Hall, *Org. Lett.* **2000**, *2*, 3715–3718.
[82] a) J. Sauer, *Angew. Chem.* **1967**, *79*, 76–94; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16; b) J. Sauer, R. Sustmann, *Angew. Chem.* **1980**, *92*, 773–801; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779–805.
[83] G. Seitz, R. Dhar, W. Hühnermann, *J. Prakt. Chem./Chem.-Ztg.* **1982**, *106*, 100–101.
[84] a) G. Seitz, W. Overheu, *Arch. Pharm.* **1981**, *314*, 376–378; b) G. Seitz, R. Mohr, *Arch. Pharm.* **1986**, *319*, 690–694; c) G. Seitz, R. Dhar, S. Dietrich, *Arch. Pharm.* **1983**, *316*, 472–474; d) G. Seitz, W. Overheu, *Arch. Pharm.* **1979**, *312*, 452–455.
[85] M. Gómez-Guillén, J. M. Lassaletta, *Carbohydr. Res.* **1991**, *210*, 175–189.
[86] O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
[87] J. M. Lassaletta, R. Fernández, *Tetrahedron Lett.* **1992**, *33*, 3691–3694.
[88] M. A. Kuznetsov, *Russ. Chem. Rev.* **1979**, *48*, 563–581.
[89] a) R. Fernández, C. Gasch, J. M. Lassaletta, J. M. LLera, J. Vázquez, *Tetrahedron Lett.* **1993**, *34*, 141–144; b) D. Enders, A. Plant, *Synlett* **1994**, 1054–1056.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[90] J. M. Lassaletta, R. Fernández, C. Gasch, J. Vázquez, *Tetrahedron* **1996**, *52*, 9143–9160.

[91] R. Fernández, C. Gasch, J. M. Lassaletta, J. M. Llera, *Synthesis* **1996**, 627–632.

[92] a) H. Eichenauer, Dissertation, University of Giessen, **1980**; b) D. Enders, R. Syrig, G. Raabe, R. Fernández, J. M. Lassaletta, J. M. Llera, *Synthesis* **1996**, 48–52.

[93] R. Fernández, C. Gasch, J. M. Lassaletta, J. M. Llera, *Tetrahedron Lett.* **1994**, *35*, 471–472.

[94] P. W. Hickmott in *The Chemistry of Enamines* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1994**, p. 727.

[95] D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *121*, 2933–2960.

[96] D. Enders, A. Plant, D. Backhaus, U. Reinhold, *Tetrahedron* **1995**, *51*, 10699–10714.

[97] For other trialkylsilyl-promoted conjugate additions of soft carbon nucleophiles to enones, see: a) S. Kim, J. H. Park, *Synlett* **1995**, 163–164; b) M. Eriksson, T. Iliefski, M. Nilsson, T. Olsson, *J. Org. Chem.* **1997**, *62*, 182–187; c) A. R. Katritzki, J. Soloducho, R. P. Musgrave, J. C. Breytenbach, *Tetrahedron Lett.* **1995**, *31*, 5491–5494.

[98] Following well-established procedures, this position could be alkylated, used as a nucleophile in the Mukaiyama aldol reaction, or hydroxylated (the Rubottom reaction). Additionally, the introduction of a nitrogenated functionality has been described: J. Du Bois, J. Hong, E. M. Carreira, M. W. Day, *J. Am. Chem. Soc.* **1996**, *118*, 915–916.

[99] a) E. J. Corey, A. Guzmán-Pérez, *Angew. Chem. Int. Ed.* **1998**, *37*, 389–401; b) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482.

[100] This compact geometry, stabilized by secondary orbital interactions, has also been proposed for the closely related reaction of enamines with α,β-unsaturated carbonyl compounds: M. Pfau, A. Tomas, S. Lim, G. Revial, *J. Org. Chem.* **1995**, *60*, 1143–1147. See also: C. Cavé, D. Desmaële, J. d'Angelo, C. Riche, A. Chiaroni, *J. Org. Chem.* **1996**, *61*, 4361–4368, and references cited therein.

[101] E. Díez, A. M. López, C. Pareja, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *Tetrahedron Lett.* **1998**, *39*, 7955–7958. This procedure allows recovery of the chiral hydrazine in 70–75% yield.

[102] E. Díez, R. Fernández, E. Martín-Zamora, C. Pareja, A. Prieto, J. M. Lassaletta, *Tetrahedron: Asymmetry* **1999**, *10*, 1145–1151.

[103] a) D. Enders, J. Vázquez, *Synlett* **1999**, 629–631; b) D. Enders, J. Vázquez, *Chem. Commun.* **1999**, 701–702; c) D. Enders, J. Vázquez, G. Raabe, *Eur. J. Org. Chem.* **2000**, 893–901.

[104] D. Enders, E. Díez, R. Fernández, E. Martín-Zamora, J. M. Muñoz, R. R. Pappalardo, J. M. Lassaletta, *J. Org. Chem.* **1999**, *64*, 6329–6336.

[105] This final step was described previously by Yoshikoshi et al., who obtained 7-methyl furofuran lactones by hydrolysis of 6-methyl-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde in the presence of *p*-toluenesulfonic acid: F. Kido, S. C. Sinha, T. Abiko, M. Watanabe, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun.* **1990**, 418–420.

[106] For reviews, see: a) T. A. van Beek, Ae. de Groot, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 513–527; b) A. T. Merritt, S. V. Ley, *Nat. Prod. Rep.* **1992**, *9*, 243–287.

[107] a) H. Stetter, F. Jonas, *Chem. Ber.* **1981**, *114*, 564–580; b) H. Cerfontain, P. C. M. van Noort, *Synthesis* **1980**, 490–492.

[108] The electrophilic reactivity of nitroalkenes and malonates can be a priori correlated with the pK_a values in nonaqueous solvent of the anions generated upon addition. See also: W. N. Olmstead, F. G. Bordwell, *J. Org. Chem.* **1980**, *45*, 3299–3305.

[109] A similar explanation was offered for the dimerization of formaldehyde dimethylhydrazone promoted by Bronsted acids: F. E. Condon, D. Farcasiu, *J. Am. Chem. Soc.* **1970**, *92*, 6625–6630.

[110] For a related Lewis acid catalyzed polar [2+2] cycloaddition, see: A. Gautier, J. Renault, C. Fauran, *Bull. Soc. Chim. Fr.* **1963**, 2738–2741.

[111] K. Mori, A. Kamada, M. Kido, *Liebigs Ann. Chem.* **1991**, 775–781.

[112] J.-Y. Legros, M. Toffano, J.-C. Fiaud, *Tetrahedron* **1995**, *51*, 3235–3246.

[113] A. P. Krapcho, *Synthesis* **1982**, 805–822.

[114] F. F. Fleming, A. Huang, V. A. Sharief, Y. Pu, *J. Org. Chem.* **1997**, *62*, 3036–3037.

[115] J. N. Marx, J. H. Cox, L. R. Norman, *J. Org. Chem.* **1972**, *26*, 4489–4491.

[116] J. M. Renga, H. J. Reich, *Org. Synth.* **1980**, *59*, 58 and references cites therein.

[117] a) L. S. Liebeskind, D. Mitchell, B. S. Foster, *J. Am. Chem. Soc.* **1987**, *109*, 7908–7910 and references cited therein; b) L. S. Liebeskind, A. Bombrun, *J. Org. Chem.* **1994**, *59*, 1149–1159.

[118] a) P. Balczewski, M. Mikolajczyk, *Org. Lett.* **2000**, *2*, 1153–1155; b) F. T. Hong, K. S. Lee, C. C. Liao, *J. Chin. Chem. Soc.* **2000**, *47*, 77–82.

[119] D. Boschelli, A. B. Smith III, *Tetrahedron Lett.* **1981**, *22*, 3733–3736.

[120] a) G. Linz, J. Weetman, A. Hady, G. Helmchen, *Tetrahedron Lett.* **1989**, *30*, 5599–5602; b) O. Kitagawa, T. Inoue, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 1059–1062; c) K. Konigsberger, H. Griengl, *Bioorg. Med. Chem.* **1994**, *2*, 595–604; d) I. Ikeda, K. Kanematsu, *J. Chem. Soc. Chem. Commun.* **1995**, 453–454; e) L. Andrau, J. Lebreton, P. Viazzo, V. Alphand, R. Furtoss, *Tetrahedron Lett.* **1997**, *38*, 825–826; f) K. Weinges, H. J. Ziegler, H. Schick, *Liebigs Ann. Chem.* **1992**, 1213–1216.

[121] M. Mikolajczyk, R. Zurawinski, P. Kielbasinski, M. W. Wieczorek, J. Blaszczyk, W. R. Majzner, *Synthesis* **1997**, 356–365 and references cited therein.

[122] J. N. Marx, G. Minaskanian, *J. Org. Chem.* **1982**, *47*, 3306–3310.

[123] J. K. Shen, H. Katayama, N. Takatsu, I. Shiro, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2087–2097.

[124] J. Muñoz, PhD Thesis, University of Seville, **2006**.

[125] J. M. Lassaletta, R. Fernández, E. Martín-Zamora, C. Pareja, *Tetrahedron Lett.* **1996**, *37*, 5787–5790.

[126] a) M. Cherest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *9*, 2199–2204; b) T. A. Nguyen, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61–70.

[127] a) T. Mimoto, J. Imai, S. Kisanuki, H. Enomoto, N. Hattori, K. Akaji, Y. Kiso, *Chem. Pharm. Bull.* **1992**, *40*, 2251–2253; b) S. Kageyama, T. Mimoto, Y. Murakawa, M. Nomizu, H. Ford Jr., T. Shirasaka, S. Gulnik, J. Erickson, K. Takada, H. Hayashi, S. Broder, Y. Kiso, H. Mitsuya, *Antimicrob. Agents Chemother.* **1993**, *37*, 810–817.

[128] W. Yuan, B. Munoz, C.-H. Wong, J. Z. Haeggström, A. Wetterholm, B. Samuelsson, *J. Med. Chem.* **1993**, *36*, 211–220.

[129] a) R. Fernández, E. Martín-Zamora, C. Pareja, J. Vázquez, E. Díez, A. Monge, J. M. Lassaletta, *Angew. Chem. Int. Ed.* **1998**, *37*, 3428–3430; b) C. Pareja, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *J. Org. Chem.* **1999**, *64*, 8846–8854.

[130] a) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; c) G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143–2147.

[131] F. Yasuhara, M. Takeda, Y. Ochiai, S. Miyano, S. Yamaguchi, *Chem. Lett.* **1992**, 251–252.

[132] D. Monge, E. Martín-Zamora, J. Vázquez, M. Alcarazo, E. Álvarez, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, 2867–2870.

[133] G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443.

[134] D. J. Dixon, A. L. Tillman, *Synlett* **2005**, 2635–2638.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[135] M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Ko1ckritz, A. Pews-Davtyan, N. Nemati, M. Beller, *Org. Lett.* **2007**, *9*, 1065–1068.
[136] R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, in press, DOI 10.1021/ol071292c.
[137] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579.
[138] D. Pettersen, R. P. Herrera, L. Bernardi, F. Fini, V. Sgarzani, R. Fernández, J. M. Lassaletta, A. Ricci, *Synlett* **2006**, 239–242.
[139] a) D. Enders in *Asymmetric Synthesis* (Eds.: J. D. Morrison), Academic Press, Orlando, **1984**, vol. 3, ch. 4, pp. 275–339; b) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.
[140] a) H. Takahashi, K. Tomita, H. Otomasu, *J. Chem. Soc. Chem. Commun.* **1979**, 668–669; b) D. A. Claremon, P. K. Lumma, B. T. Phillips, *J. Am. Chem. Soc.* **1986**, *108*, 8265–8266; c) M. Thiam, F. Chastrette, *Tetrahedron Lett.* **1990**, *31*, 1429–1432; d) A. Alexakis, N. Lensen, J.-P. Tranchier, P. Manganey, J. Feneau-Dupont, J. P. Declercq, *Synthesis* **1995**, 1038–1050; e) Y. H. Kim, J. Y. Choi, *Tetrahedron Lett.* **1996**, *37*, 5543–5546; f) P. Bataille, M. Paterne, E. Brown, *Tetrahedron: Asymmetry* **1998**, *9*, 2181–2192; g) Y.-T. Hsieh, G.-H. Lee, Y. Wang, T.-Y. Luh, *J. Org. Chem.* **1998**, *63*, 1484–1490; h) D. Enders, H. Schubert, C. Nübling, *Angew. Chem.* **1986**, *98*, 1118–1119; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1109–1110; i) D. Enders, R. Funk, M. Klatt, G. Raabe, E. R. Hovestreydt, *Angew. Chem.* **1993**, *105*, 418–420; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 418–421; j) D. Enders, C. Nübling, H. Schubert, *Liebigs Ann./Recueil* **1997**, 1089–1100, and references cited therein; k) S. E. Denmark, T. Weber, D. W. Piotrowski, *J. Am. Chem. Soc.* **1987**, *109*, 2224–2225; l) V. Cerè, F. Peri, S. Pollicino, A. Ricci, *Synlett* **1999**, 1585–1587.
[141] a) C. F. Sturino, A. G. Fallis, *J. Am. Chem. Soc.* **1994**, *116*, 7447–7448; b) G. K. Friestad, *Org. Lett.* **1999**, *1*, 1499–1501; c) L. El Kaim, A. Gacon, A. Perroux, *Tetrahedron Lett.* **1998**, *39*, 371–374; d) S. Kim, I. S. Kee, S. Lee, *J. Am. Chem. Soc.* **1991**, *113*, 9882–9883; e) J. Marco-Contelles, G. Balme, D. Bouyssi, C. Destabel, C. D. Henriet-Bernard, J. Grimaldi, J. M. Hatem, *J. Org. Chem.* **1997**, *62*, 1202–1209; f) O. Miyata, K. Muroya, J. Koide, T. Naito, *Synlett* **1998**, 271–272; g) G. K. Friestad, J. Qin, *J. Am. Chem. Soc.* **2000**, *122*, 8329–8330.
[142] a) R. Fernández, A. Ferrete, J. M. Lassaletta, J. M. Llera, A. Monge, *Angew. Chem. Int. Ed.* **2000**, *39*, 2893–2897; b) R. Fernández, A. Ferrete, J. M. Lassaletta, J. M. Llera, E. Martín-Zamora, *Angew. Chem. Int. Ed.* **2002**, *41*, 831–833; c) E. Díez, R. Fernández, E. Marqués-López, E. Martín-Zamora, J. M. Lassaletta, *Org. Lett.* **2004**, *6*, 2749–2752; d) A. Ferrete, J. M. Llera, J. M. Muñoz, R. R. Pappalardo, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2004**, *10*, 6111–6129.

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