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STEREOSELECTIVE CYCLOADDITIONS OF NITRILIMINES AS A SOURCE OF ENANTIOPURE HETEROCYCLES

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Abstract – Stereoselective 1,3-dipolar cycloadditions of nitrilimines represents a useful tool in the obtainment of a number of enantiopure heterocycles containing the 4,5-dihydropyrazole ring. The literature data on this subject are reviewed in a systematic way for both inter-and intramolecular processes, with an emphasis to their versatile potential in heterocyclic synthesis.

CONTENTS

I. INTRODUCTION

Stereoselective 1,3-dipolar cycloadditions represent one of the most productive fields of modern synthetic organic chemistry.[1] As a result, the behaviour of a large array of 1,3-dipolar functionalities have been exploited in the construction of a number of enantiopure five-membered heterocycles.[2] Nitrile oxide and nitrone cycloadditions have played a major role in this field,[3] due to the easy generation of the dipole and to the astonishing array of latent functionalities displayed by the corresponding cycloadducts.[4] Much less work has been done on other kinds of 1,3-dipoles. Despite to the utility of enantiopure pyrazolines in organic synthesis[5] and some interesting applications of related products,[6-9] stereoselective cycloadditions of nitrilimines have become useful only in the last few years. In fact, as is stated in the 1998 review by Gothelf and Jørgensen, "only very few studies have been performed in the field of asymmetric 1,3-dipolar cycloadditions involving nitrile imines" (sic).[2a] Since this situation is now changed, the aim of this paper

is to present the behaviour of nitrilimine cycloadditions towards stereoselectivity in a systematic way, giving emphasis to their versatile potential in the synthesis of enantiopure heterocycles. For this reason the discussion will be restricted to cover cycloadditions in which the product(s) is optically active.

II. INTERMOLECULAR CYCLOADDITIONS

The presentation of intermolecular stereoselective cycloadditions involving nitrilimines is divided into three parts. First, reaction between achiral nitrilimines and enantiopure dipolarophiles, then reactions in which enantiopure nitrilimines undergo cycloaddition onto achiral dipolarophiles and finally reactions between enantiopure nitrilimines and enantiopure dipolarophiles.

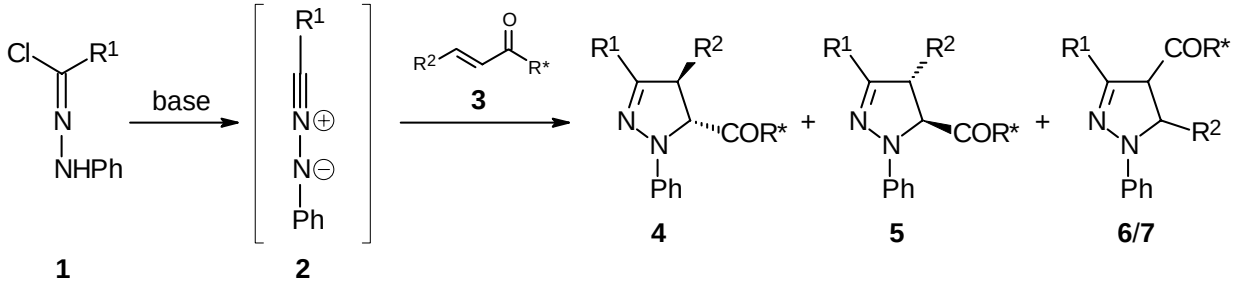
II.1. Nitrilimine cycloadditions onto enantiopure dipolarophiles.

As a general trend, cycloadditions between achiral nitrilimines and enantiopure dipolarophiles proceed efficiently irrespective of the nature of the dipolarophile. However, due to the variety of functionalities presented by the latter, this section is further divided into five parts according to their chemical features.

II.1.1 Enantiopure enones

Base treatment of hydrazonoyl chlorides (**1**) in the presence of enantiopure enones **3** gave the 4,5-dihydropyrazole cycloadducts **4-7** via the labile nitrilimine intermediate (**2**) (Scheme 1, Table 1).[10] The reaction was regioselective except in the case of diphenylhydrazonoyl chloride (Entry 5). The diastereoselectivity ranging from 37:33 to 70:30 was low to moderate; the influence of temperature and base variation on stereoselection were only marginal. Replacement of triethylamine with n-butyllithium as the base caused the drop of the overall yield (Entry 4).

Scheme 1



1 **2** **4** **5** **6/7**

1a: R^1= COOEt; **1b:** R^1= Ph; **1c:** R^1= COMe

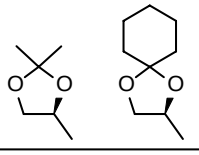
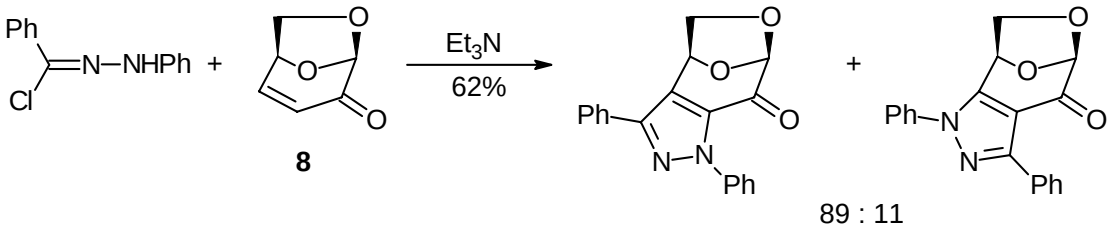
3	**a**	**b**	**c**
R^2	Me	Me	OEt
R*			

Table 1. Cycloaddition between nitrilimines (**2**) and enantiopure enones (**3**).

Entry	**2**	**3**	Temperature (°C)	Base	Overall yields (%)	Stereoselective ratio	
						4:**5**	**6**:**7**
1	**a**	**a**	25	Et_3N	76	70:30	—
2	**a**	**a**	80	Et_3N	82	60:40	—
3	**a**	**a**	5	Et_3N	43	65:35	—
4	**a**	**a**	-20	*n*-BuLi	14	67:33	
5	**b**	**a**	25	Et_3N	74	37:33	15:15
6	**c**	**a**	25	Et_3N	15	60:40	—
7	**a**	**b**	25	Et_3N	68	67:33	—
8	**a**	**c**	25	Et_3N	71	61:39	—

The cycloaddition between diphenylnitrilimine and levoglucosenone (**8**) gave a mixture of regioisomeric pyrazoles resulting from dehydrogenation *in situ* of the initially formed 4,5-dihydropyrazole cycloadducts[11] (Scheme 2).

Scheme 2



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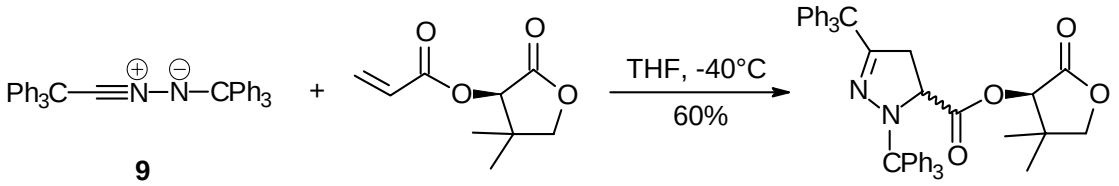
II.1.2 Enantiopure α,β-unsaturated esters

Cycloaddition of the stable bis(trityl)nitrilimine (**9**) to (*R*)-α-acryloxy-β,β-dimethyl-γ-butyrolactone gave diastereoisomeric cycloadducts (**10**) with 60% overall yield and 75:25 ratio as deduced from integration of ^{1}H NMR spectra[12] (Scheme 3). As far as regioselectivity is concerned, the exclusive formation of 5-substituted 4,5-dihydropyrazoles agrees with the HOMO-dipole (LUMO-dipolarophile) control which is typical for nitrilimine cycloadditions onto monosubstituted ethylenes bearing an electron-withdrawing group.[13,14]

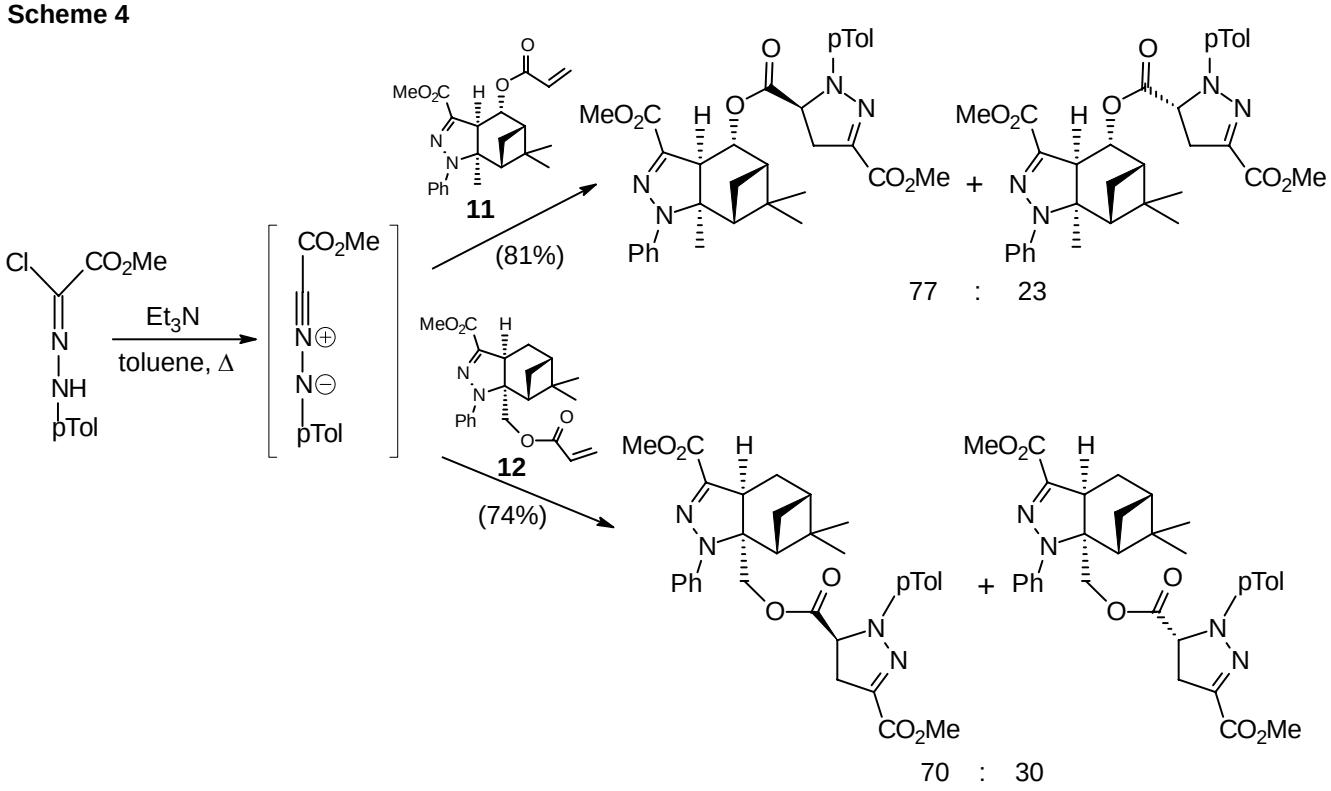
Scheme 3



9 **10** (75 : 25)

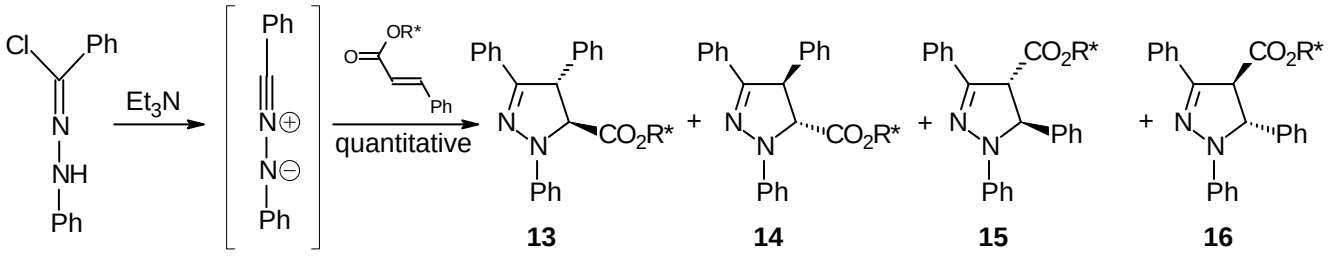
The same behaviour towards regio- and stereoselectivity is displayed by acrylates (**11**) and (**12**) which are derived from the monoterpenols verbenol and myrtenol, respectively.[15]

Scheme 4



In contrast, a complex mixture of regio- and stereoisomeric cycloadducts is obtained by nitrilimine attack onto β-substituted α,β-unsaturated esters[16] (Scheme 5).

Scheme 5



(**13**+**14**)/(**15**+**16**) = 38 : 62 **13**/**14** = 32 : 68

R* = (-)-8-phenylmenthyl **15**/**16** = 71 : 29

In order to implement both regio- and stereoselectivity outcome of the latter cycloaddition, α,β-unsaturated esters masked as Fischer alkenylcarbenes (**17**) were used as dipolarophiles. First, a two step procedure was envisaged, which allowed the isolation of metalated species (**18**) and (**19**) in moderate

yields and diastereoselectivity[17] (Scheme 6, Table 2). However, the latter compounds were found to be fairly unstable and, moreover, purification from their oxidation products was difficult.

Scheme 6

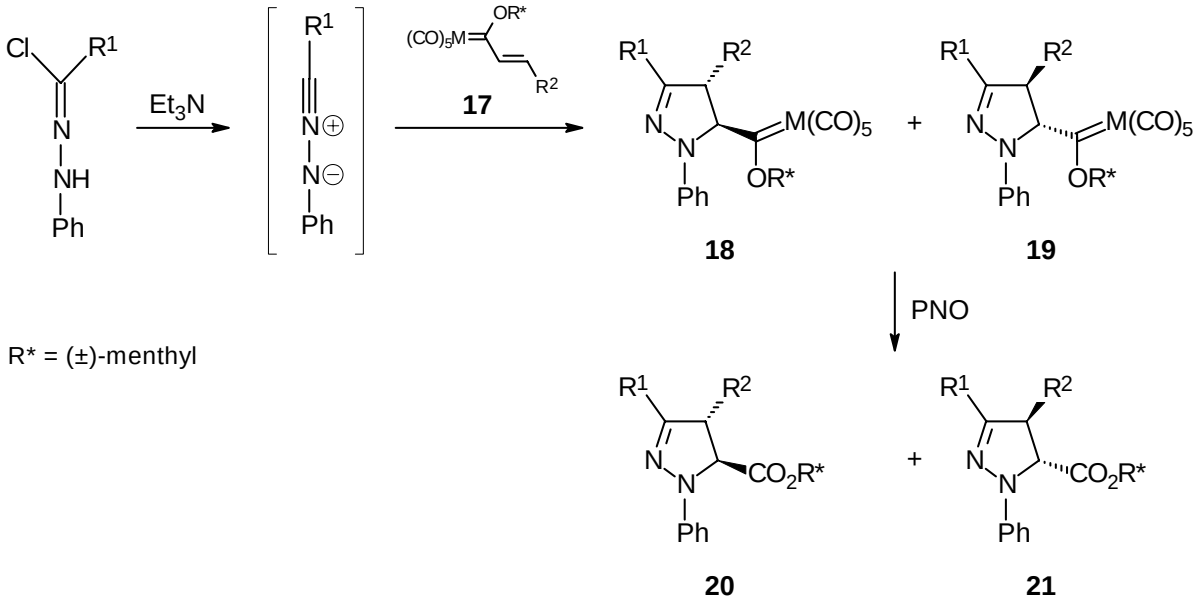


Table 2. "Stepwise sequence" nitrilimine cycloaddition to Fischer alkenylcarbenes (**17**).

Entry	R^1	R^2	M	Overall yield (%)	Stereoselective ratio **18**:**19**
1	Ph	Ph	Cr	67	63:37
2	Ph	2-furyl	Cr	80	60:40
3	COOEt	Ph	Cr	31	50:50
4	COOEt	2-furyl	W	10	52:48

Better yields of the 4,5-dihydropyrazoles (**20**) and (**21**) were achieved when the cycloaddition-oxidation stepwise sequence was performed one-pot without isolation of metalated species[16,17] (Scheme 7, Table 3).

Scheme 7

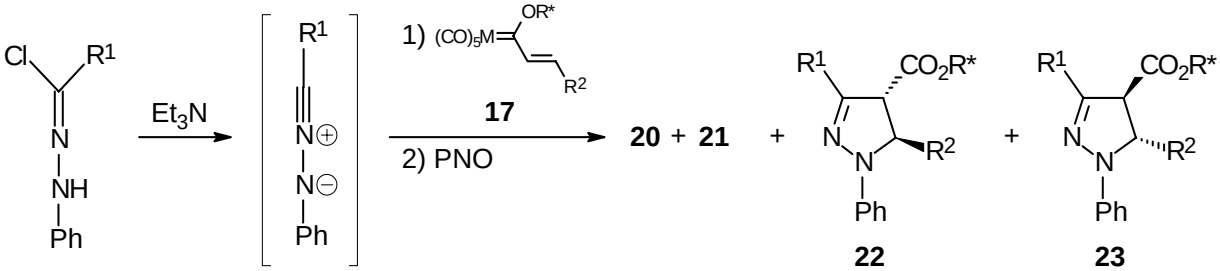


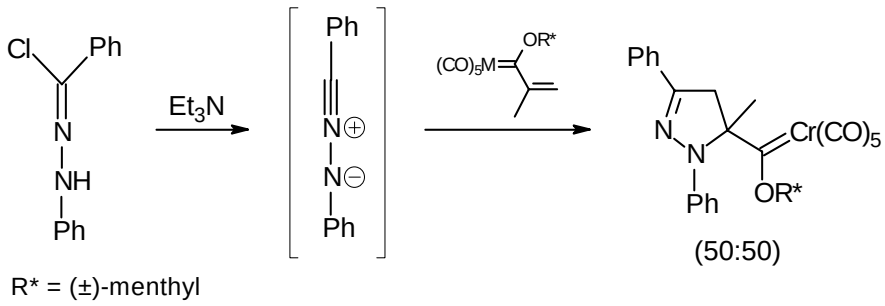
Table 3. One-pot nitrilimine cycloaddition to Fischer alkenylcarbenes (**17**).

Entry	R^1	R^2	M	R*	Overall Yield (%)	Stereoselective ratio	
						20:**21**	(**20**+**21**)/(**22**+**23**)
1	Ph	Ph	Cr	(±)-menthyl	72	63:37	100:0
2	Ph	2-furyl	Cr	(±)-menthyl	99	60:40	100:0
3	Ph	2-furyl	W	(±)-menthyl	92	55:45	94:6
4	Ph	p-anisyl	Cr	(±)-menthyl	82	60:40	100:0
5	p-anisyl	Ph	Cr	(±)-menthyl	80	50:50	100:0
6	p-anisyl	2-furyl	Cr	(±)-menthyl	87	50:50	85:15
7	p-anisyl	p-anisyl	Cr	(±)-menthyl	82	50:50	100:0
8	COOEt	Ph	Cr	(±)-menthyl	40	50:50	100:0
9	COOEt	Ph	Cr	(±)-menthyl	55	50:50	100:0
10	COOEt	Ph	Cr	(±)-menthyl	46	50:50	100:0
11	COOEt	Ph	Cr	(±)-menthyl	42	50:50	100:0
12	COOEt	Ph	W	(±)-menthyl	27	50:50	100:0
13	Ph	Ph	Cr	(-)-8-phenylmenthyl	55	92:8	>95:5
14	Ph	2-furyl	Cr	(-)-8-phenylmenthyl	35	>95:5	>95:5
15	p-anisyl	Ph	Cr	(-)-8-phenylmenthyl	40	>95:5	>95:5
16	p-anisyl	2-furyl	Cr	(-)-8-phenylmenthyl	73	>95:5	>95:5
17	p-anisyl	p-anisyl	Cr	(-)-8-phenylmenthyl	69	>95:5	>95:5

It can be inferred from Table 3 that: (*i*) reactions carried out in the presence of tungsten carbene complexes provided the corresponding cycloadducts in lower yields (Entries 3, 12) or with worse diastereoselectivity and regioselectivity (Entry 3 vs. 2), (*ii*) diastereoselectivity to **20** is strongly implemented in the presence of the (-)-8-phenylmenthyl pendant as the chiral auxiliary (Entries 13, 17).

The cycloaddition to methacrylates masked as pentacarbonylchromium derivatives was not stereoselective.[16]

Scheme 8



R* = (±)-menthyl

II.1.3 Enantiopure acrylamides

The behaviour of *N*-4-methylphenyl-*C*-methoxycarbonyl nitrilimine towards a series of enantiopure acrylamides (**24**) was investigated[18] (Scheme 9, Table 4). It can be seen from Table 4 that the diastereoisomeric ratio ranges between 58:42 and 83:17 depending upon the chiral auxiliary connected to

the α,β-unsaturated dipolarophile. The best results, obtained with acrylamides (**24c**) and (**24e**), possibly reflect the lower conformational flexibillity of the latter two substrates compared to **24a**, **24b** and **24d**. The base (chiral or achiral) and the presence of salts as LiCl and $(AcO)_2Mg$, which were investigated as potential complexating agents, exerted little or no influence on cycloaddition diastereoselectivity.

Scheme 9

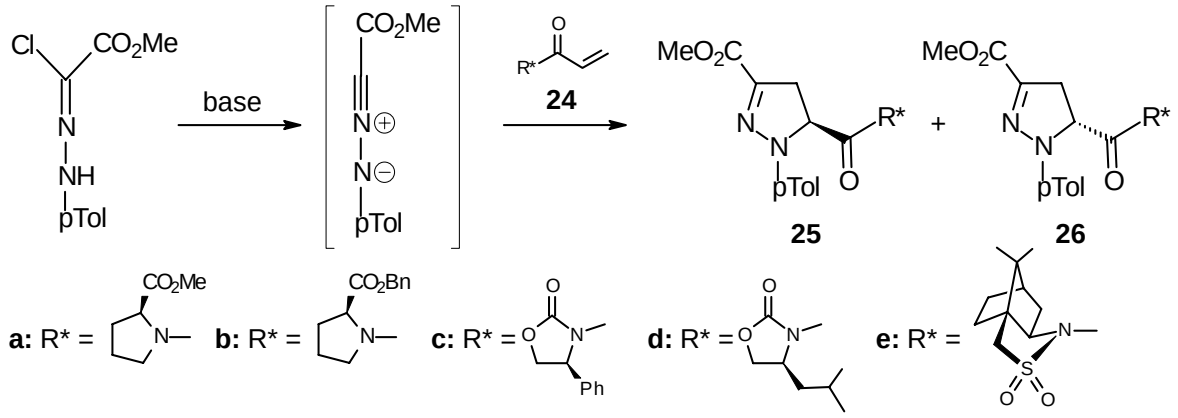
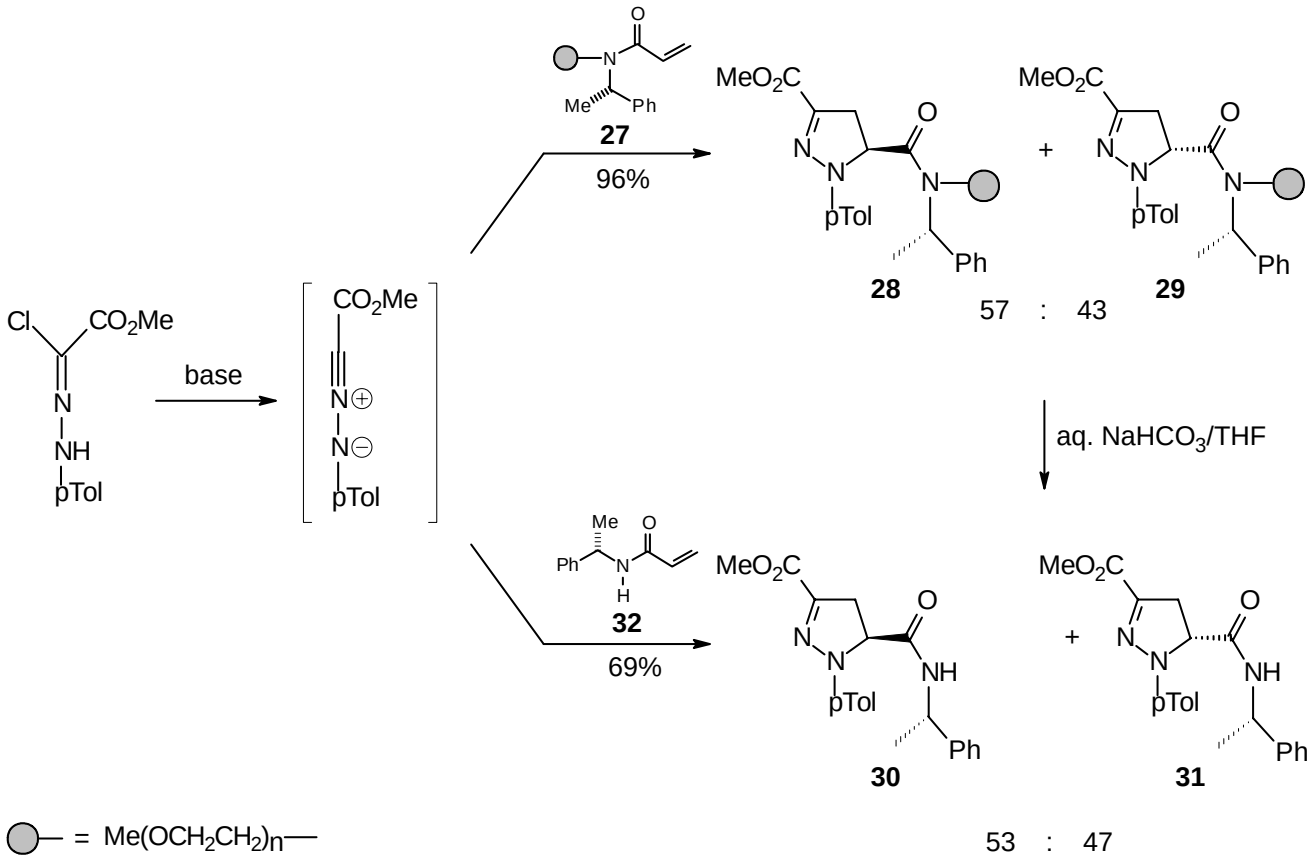


Table 4. Nitrilimine cycloadditions to enantiopure acrylamides (**24**).

Entry	Acrylamide	Base	Additive	Overall yield (%)	Stereoselective ratio **25**:**26**
1	**24a**	Et_3N	—	50	67:33
2	**24a**	Et_3N	LiCl	55	65:35
3	**24a**	Et_3N	$(AcO)_2Mg$	49	67:33
4	**24a**	AcOAg	—	70	67:33
6	**24b**	Et_3N	—	82	68:32
7	**24b**	Et_3N	LiCl	71	64:36
8	**24b**	Et_3N	$(AcO)_2Mg$	62	63:37
9	**24b**	AcOAg	—	85	67:33
10	**24b**	(-)-sparteine	—	32	63:37
11	**24c**	Et_3N	—	58	80:20
12	**24c**	Et_3N	LiCl	54	80:20
13	**24c**	Et_3N	$(AcO)_2Mg$	57	75:25
14	**24c**	AcOAg	—	64	80:20
15	**24c**	(-)-sparteine	—	45	80:20
16	**24d**	Et_3N	—	66	61:39
17	**24d**	Et_3N	LiCl	36	62.38
18	**24d**	Et_3N	$(AcO)_2Mg$	31	60:40
19	**24d**	AcOAg	—	60	58:42
20	**24d**	(-)-sparteine	—	28	58:42
21	**24e**	Et_3N	—	80	80:20
22	**24e**	Et_3N	LiCl	72	68:32
23	**24e**	Et_3N	$(AcO)_2Mg$	54	75:25
24	**24e**	AcOAg	—	62	83:17
25	**24e**	(-)-sparteine	—	41	78:22

Scheme 10 illustrates an example of clean nitrilimine cycloaddition to the enantiopure polyethylene glycol-supported acrylamide (**27**). A mixture of the inseparable 5-MeOPEG-supported 4,5-dihydro-pyrazoles (**28**) and (**29**) was obtained, in which the former cycloadduct was recognised as the major one on the basis of ^{1}H NMR spectra.[19] Although the 5-MeOPEG supported cycloadducts were obtained with satisfactory overall yield (96%), cycloaddition stereoselectivity was disappointing, being the ratio **28**:**29** = 57:43. Due to the good hydrolysis yield (87%), however, it was possible to perform the **27** → **30** + **31** "MeOPEG-supported" sequence with an overall yield of 84%. The complementary homogeneous phase synthesis starting from (*S*)-phenylethylacrylamide (**32**) occurred with 69% yield and a stereoselectivity outcome was **30**:**31** = 53:47.

Scheme 10



II.1.4 Enantiopure imines

The C=N bond of imines is capable of 1,3-dipolar cycloadditions with nitrilimines giving rise to a variety of 5-substituted 4,5-dihydro-1,2,4-triazoles.[20] The behaviour of enantiopure *N*-(1-phenylethyl)-1-aryl-methanimines (**33**) towards *C*-methoxycarbonyl-*N*-arylnitrilimines have been studied in order to establish the degree of stereoselectivity of the cycloaddition.[21] From the examples summarised in Scheme 11 and Table 5 it can be noted that stereoselectivity is generally low, ranging from 56:44 to 68:32 in favour of 1,2,4-triazole (**34**). The absolute (*S*) configuration to the newly-formed stereocentre of major **34** was

assigned upon NOE enhancements and conformational analysis calculations carried out at the B3LYP/cc-pVDZ level of theory.

Scheme 11

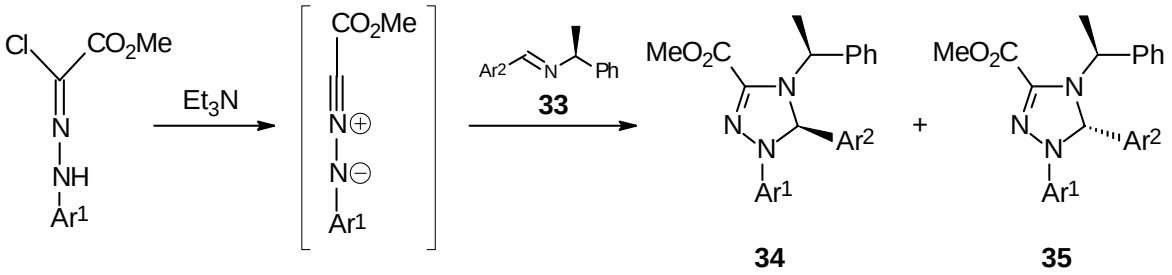


Table 5. Nitrilimine cycloaddition to enantiopure imines (**33**).

Entry	Ar^1	Ar^2	Overall yield (%)	Stereoselective ratio **34**:**35**
1	Ph	Ph	40	60:40
2	4-Me-C_6H_4	Ph	66	59:41
3	4-Me-C_6H_4	4-MeO-C_6H_4	34	56:44
4	4-Me-C_6H_4	4-NO_2-C_6H_4	40	63:37
5	4-Cl-C_6H_4	Ph	70	66:34
6	4-Cl-C_6H_4	4-MeO-C_6H_4	50	64:36
7	4-Cl-C_6H_4	4-NO_2-C_6H_4	57	68:32

The behaviour of cyclic imines has also been investigated. Stereoselective cycloaddition between nitrilimines and the C=N bond of enantiopure 1,4-benzodiazepin-4-ones (**36**) and 1,4-benzodiazepin-6-ones (**37**) gave interesting diastereoisomeric [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines (**38**-**41**) in the enantiopure forms,[22] (Scheme 12, Table 6) which were easily separated by chromatography. Cycloaddition stereoselectivity varies from nil to good depending upon: (*i*) the dipolarophile environment and (*ii*) the steric bulk of chiral auxiliary. The non-stereoselective cycloaddition outcomes of Entries 1-3 were ascribed to the planarity of the imino-amide moiety of **36**, which force the 1-(*S*)-phenylethyl group away from the reaction site. Thus, the incoming nitrilimine can hardly discriminate between the two diastereofaces of the C=N fragment. On the other hand, the seven-membered ring of **37** can assume a boat-like conformation which enables the chiral auxiliary to hide preferentially one of the C=N diastereofaces from dipolar attack. Finally, the diastereoselectivity of the cycloaddition was scarcely influenced by the base (chiral or not).

Scheme 12

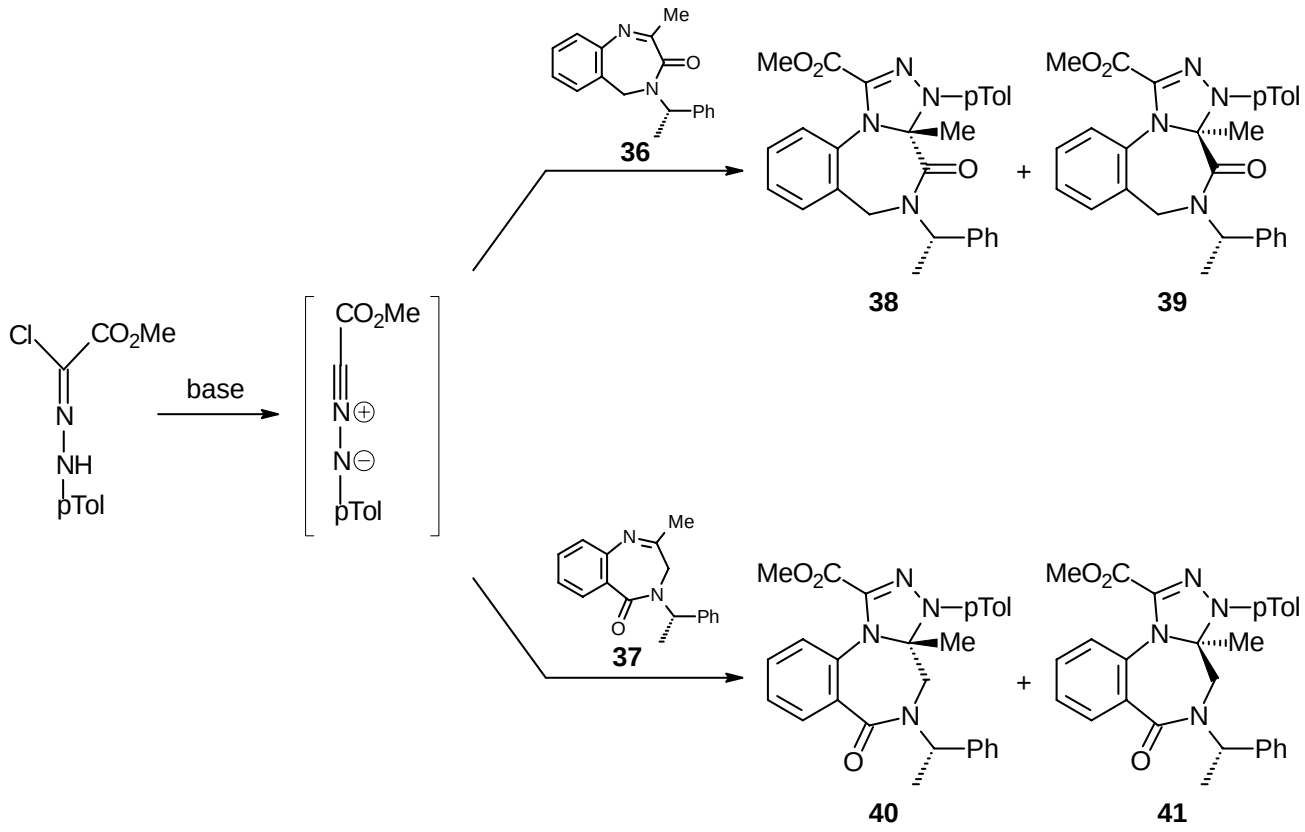


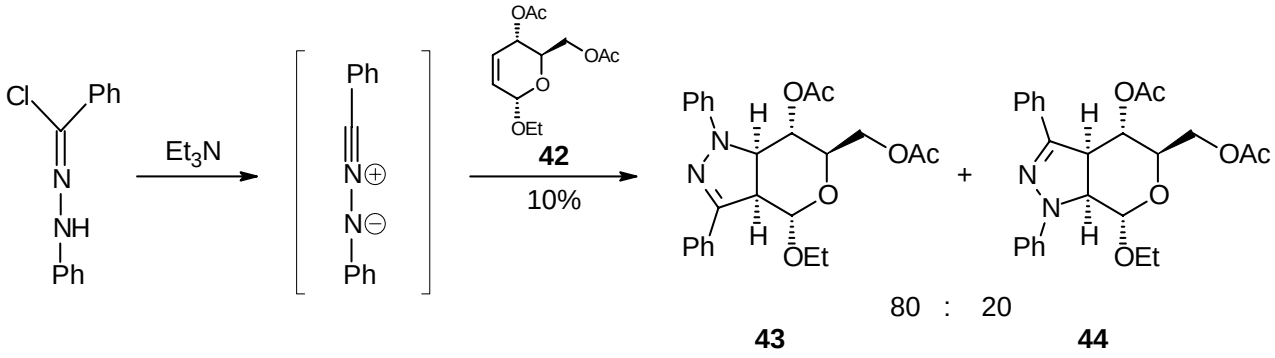
Table 6. Nitrilimine cycloadditions to enantiopure 1,4-benzodiazepinones (**36**) and (**37**).

Entry	R	Base	Overall yield (%)		Stereoselective ratio	
			38 + **39**	**40** + **41**	**38** : **39**	**40** : **41**
1	—	Et_3N	44	—	50:50	—
2	—	(-)-sparteine	72	—	50:50	—
3	—	AcOAg	80	—	50:50	—
4	Ph	Et_3N	—	58	—	67:33
5	Ph	(-)-sparteine	—	75	—	70:30
6	Ph	AcOAg	—	78	—	75:25
7	t-Bu	Et_3N	—	55	—	75:25
8	t-Bu	(-)-sparteine	—	70	—	83:17
9	t-Bu	AcOAg	—	75	—	92:8

II.1.5 Miscellaneous enantiopure dipolarophiles

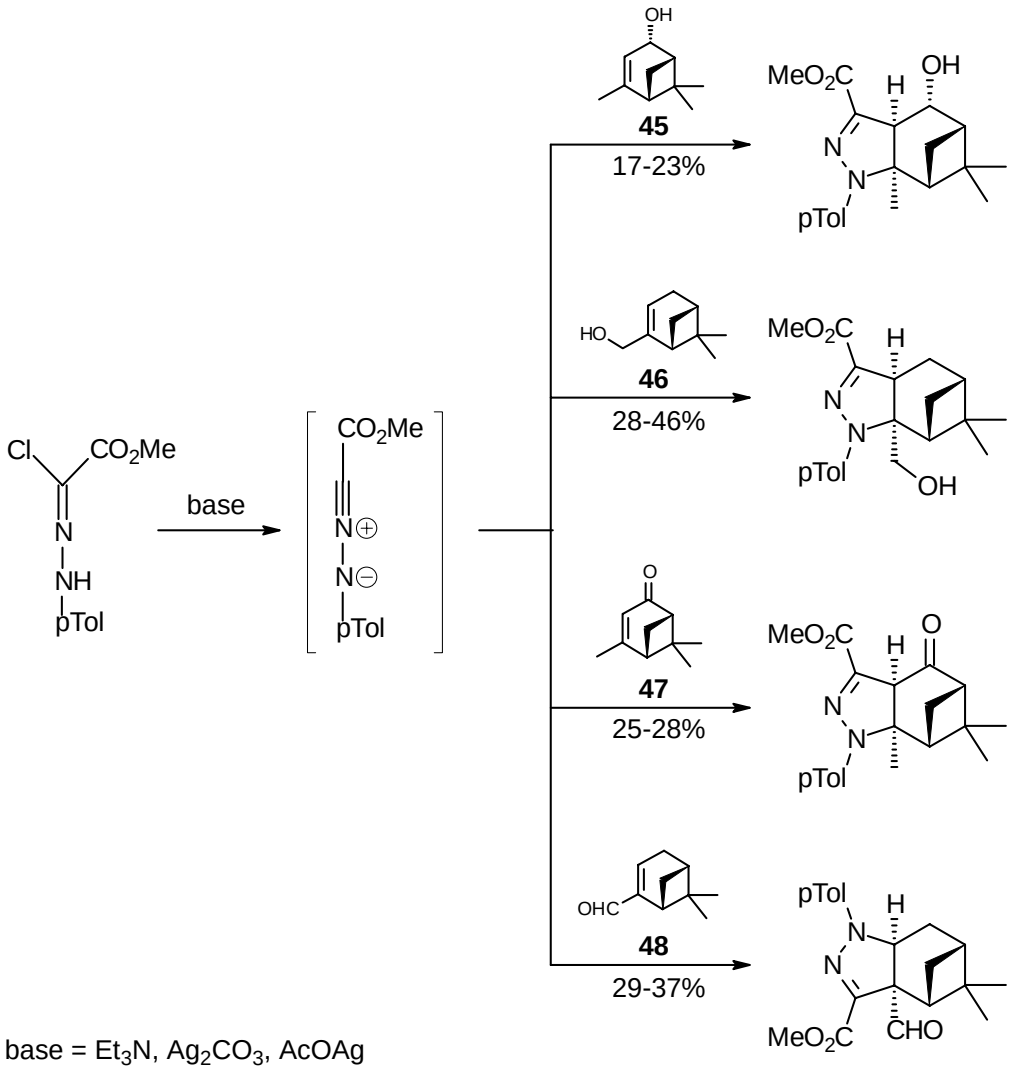
Sugar-derived dipolarophiles have been utilised in the synthesis of enantiopure pyrano[3,2-*c*]pyrazoles. In the following example, stereoselective cycloaddition of diphenylnitrilimine to ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**42**) gives rise to α-D-manno-hexopyranosido[3,2-*c*]pyrazole (**43**) and the [2,3-*c*] regioisomer (**44**).[23]

Scheme 13



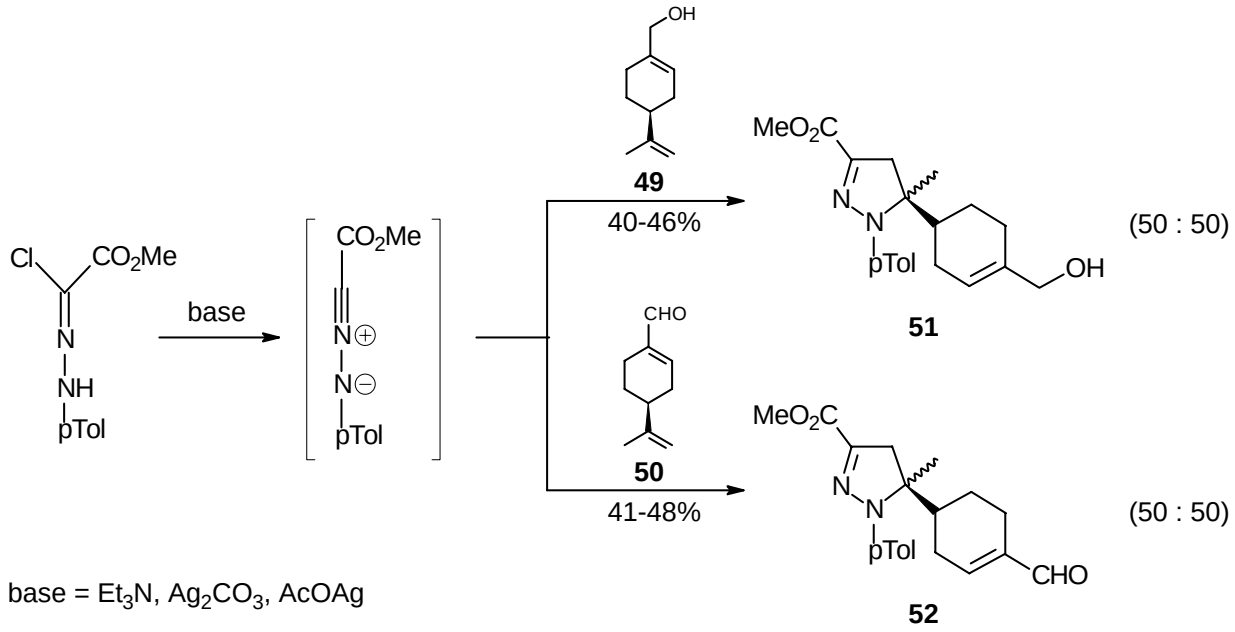
A variety of naturally-occurring pinane derivatives, namely (*S*)-*cis*-verbenol (**45**), (1*R*)-(-)-myrtenol (**46**), (1*S*)-(-)-verbenone (**47**) and (1*R*)-(-)-myrtenal (**48**) have been submitted to nitrilimine cycloaddition.[24] Due to the severe steric hindrance exerted by the two methyl groups placed onto the cyclobutyl ring of the dipolarophiles, these processes resulted fully stereoselective (Scheme 14). Cycloaddition yields were not improved by the change of the basic agent.

Scheme 14



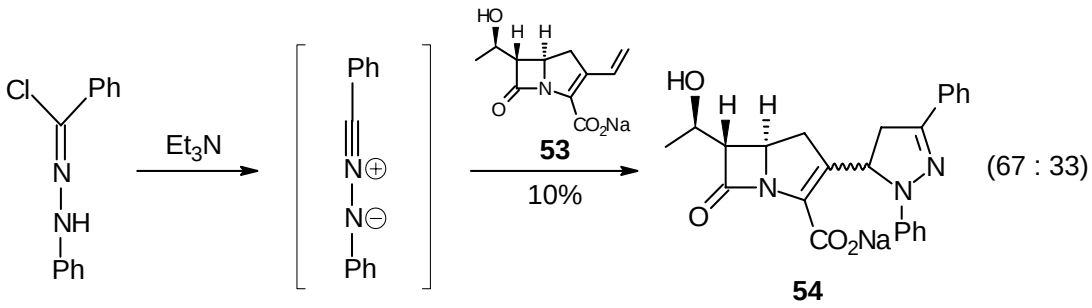
In contrast to the above examples, nitrilimine cycloadditions to limonene derivatives (1*S*)-(-)-perillyl alcohol (**49**) and (*S*)-(-)-perillaldehyde (**50**) resulted as site- and regioselective but not stereoselective processes.[24] Due to the unhindered environment of the 1,1-disubstituted ethylene moiety of both **49** and **50**, cycloadducts (**51**) and (**52**) were obtained as equimolecular mixtures of diastereoisomers.

Scheme 15



2-Vinylcarbapenem (**53**) was submitted to nitrilimine cycloadditions giving rise to diastereoisomers (**54**) in a 66:33 ratio.[25] The latter cycloadducts showed potent antibacterial activity.

Scheme 16

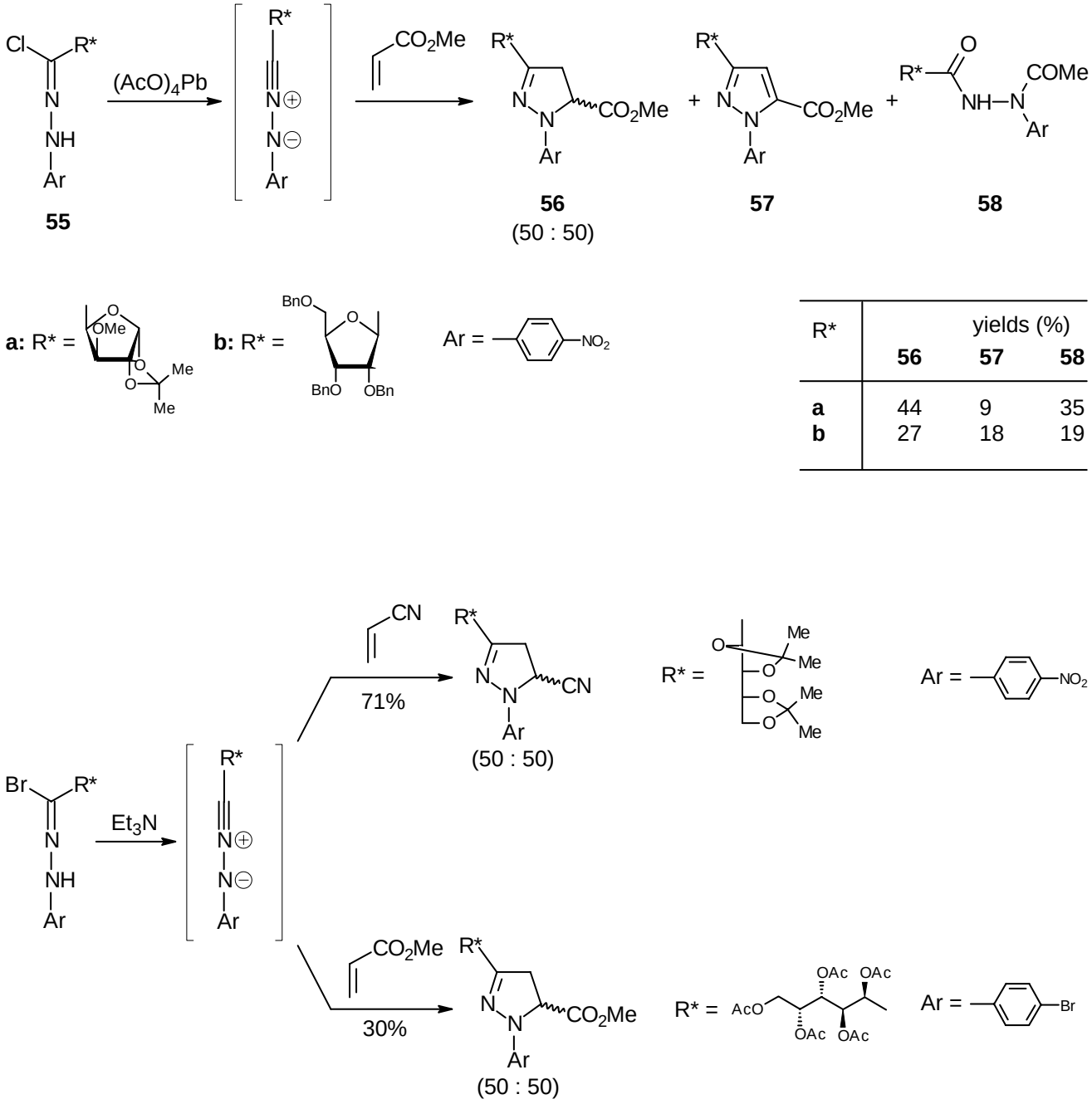


II.2. Cycloadditions of enantiopure nitrilimines to achiral dipolarophiles.

Sugar-derived nitrilimines have appeared in early works concerning their cycloadditions to simple ethylenic dipolarophiles.[26-29] From the examples listed in Scheme 17 it is apparent that non-stereoselective cycloadditions occurred, giving equimolecular mixtures of diastereoisomers. This lack of stereoselectivity have not been fully explained. Moreover, nitrilimine generation by oxidation of

the corresponding phenylhydrazones (**55**) implied the formation of sizeable amounts of pyrazoles (**57**) due to the overoxidation of the first-formed 4,5-dihydropyrazole cycloadducts (**56**) and by-product (**58**).[28]

Scheme 17

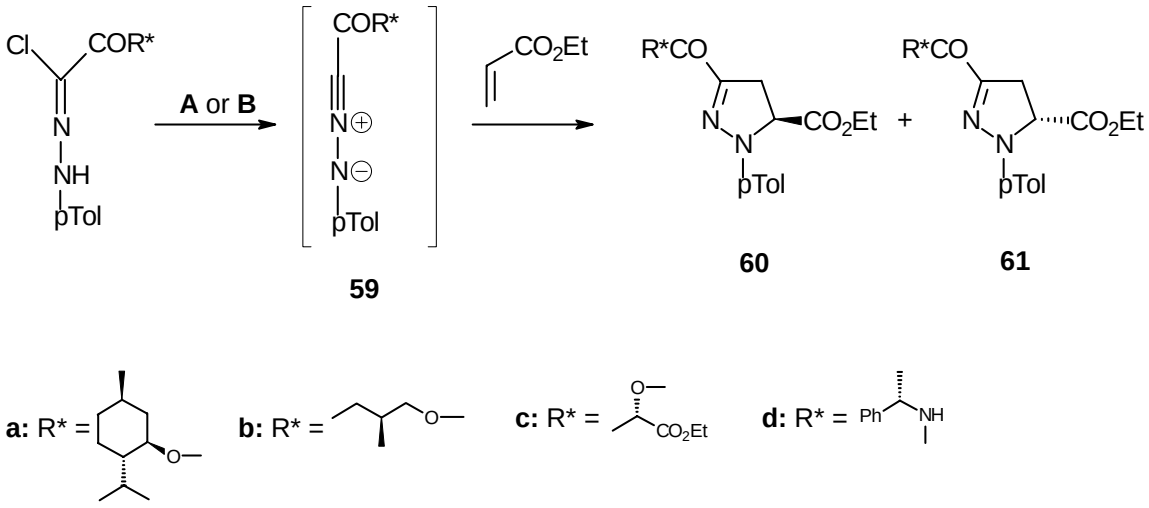


R*	yields (%)		
	56	**57**	**58**
a	44	9	35
b	27	18	19

Better results were obtained with nitrilimines containing non-sugar chiral auxiliaries. The diastereoselective cycloadditions of enantiopure nitrilimines (**59**) with ethyl acrylate gave 4,5-dihydropyrazoles (**60**) and (**61**) which were separed by differential crystallisation (Scheme 18). These cycloadditions were carried out through two different reaction conditions and media: (*i*) in dry toluene

and in the presence of triethylamine (homogeneous conditions), and (*ii*) in aqueous sodium hydrogencarbonate (heterogeneous conditions).[30] It was noted that rate acceleration and better diastereoselectivity were experienced in aqueous media (Table 7). Furthermore, reaction work-up was greatly simplified and an environmentally friendly 1,3-dipolar cycloadditive protocol can be elaborated upon.

Scheme 18



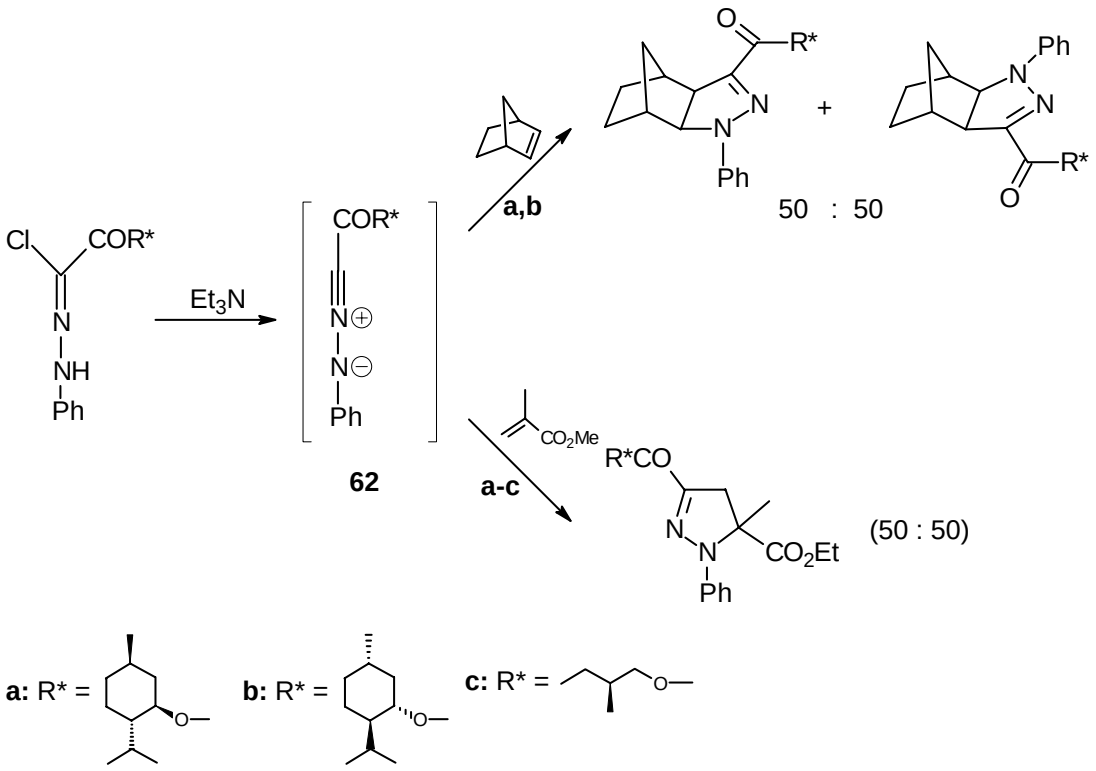
Method **A**: Et_3N, toluene, Δ; method **B**: aq. $NaHCO_3$, tetrahexylammonium chloride, rt

Table 7. Cycloadditions of nitrilimines (**59**) to ethyl acrylate.

Nitrilimine	Method	Overall yield (%)	Stereoselective ratio **60**:**61**
59a	**A**	80	60:40
59a	**B**	73	68:32
59b	**A**	81	65:35
59b	**B**	74	68:32
59c	**A**	43	57:43
59c	**B**	70	60:40
59d	**A**	40	65:35
59d	**B**	75	72:28

Cycloadditions of enantiopure nitrilimines (**62**) to norbornene resulted as fully diastereoselective but not regioselective processes[10] (Scheme 19), while an opposite behaviour was observed with methyl methacrylate. It is apparent that steric requirements of the dipolarophile are essential to dictate the stereoselectivity outcome of the cycloaddition.

Scheme 19



II.3. Cycloadditions of enantiopure nitrilimines to enantiopure dipolarophiles.

An early example of double stereoselection involved nitrilimines (**62**) which were reacted with enantiopure α,β-unsaturated ketone (**3a**). Despite the use of a pair of enantiopure reagents, the corresponding 4,5-dihydropyrazole cycloadducts (**63-66**) were obtained with low diastereoselectivity[10] (Scheme 20). As can be inferred from Table 8, the reaction was not fully regioselective (Entries 1 and 2).

Scheme 20

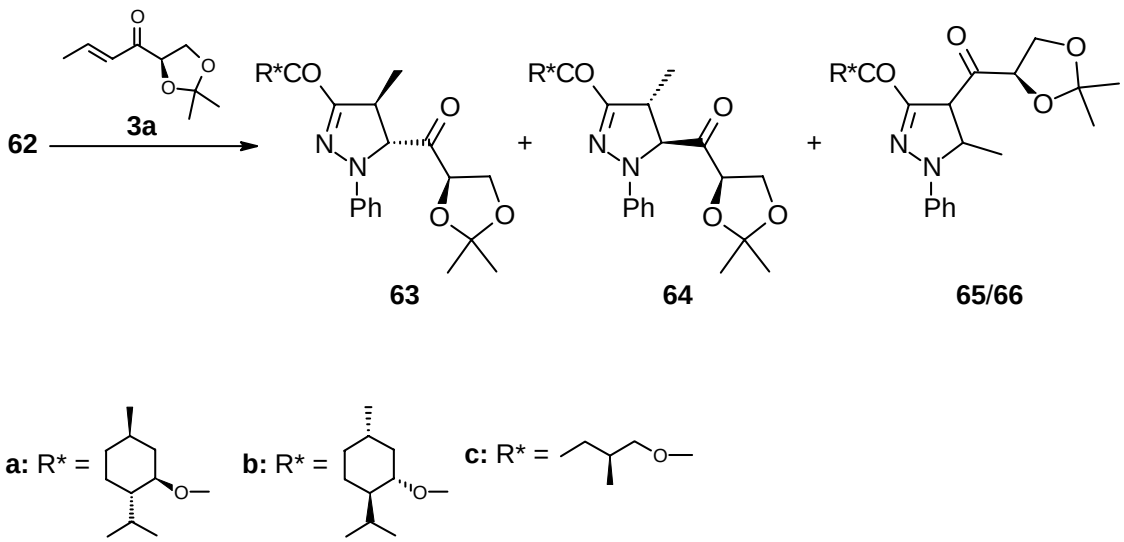


Table 8. Cycloaddition of nitrilimines (**62**) to α,β-unsaturated ketone (**3a**).

Entry	Nitrilimine	Overall yield (%)	Stereoselective ratio	
			63:**64**	**65**:**66**
1	**62a**	81	54:41	5:0
2	**62b**	77	55:41	4:0
3	**62c**	79	60:40	—

The use of enantiopure acrylic esters and amides as dipolarophiles towards homochiral nitrilimines is summarised in Scheme 21 and Table 9.[29]

Scheme 21

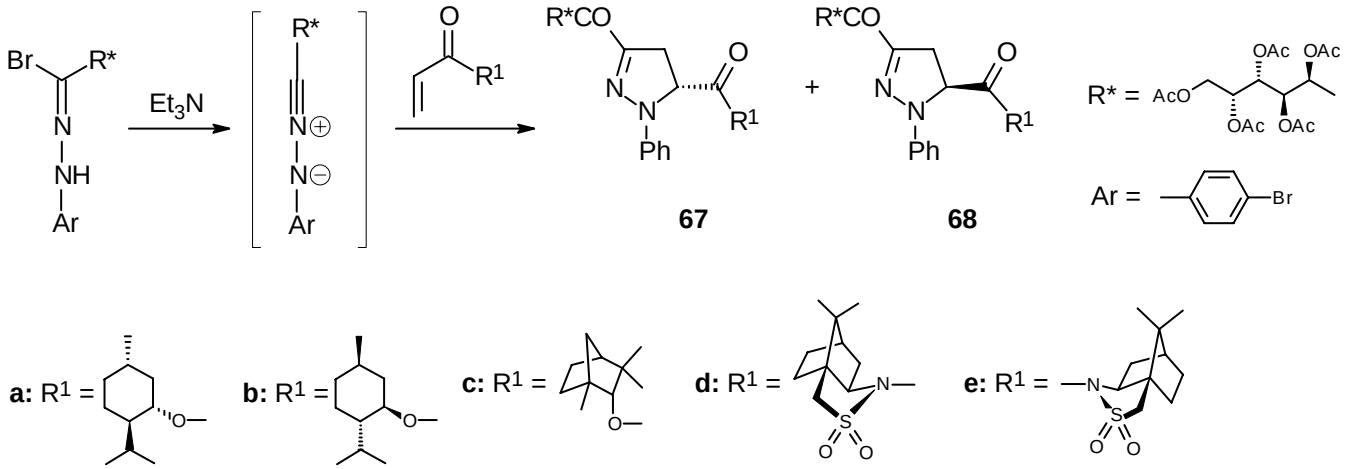


Table 9. Cycloadditions of homochiral nitrilimines to enantiopure acrylic esters and amides.

Entry	R^1	Overall yield (%)	Stereoselective ratio **67**:**68**
1	**a**	—[a]	54:46
2	**b**	—[a]	62:38
3	**c**	—[a]	60:40
4	**d**	31	100:0
5	**e**	—[a]	80:20

[a]Yields not given from ref. 29.

Reactions with (-)-menthyl acrylate gave isomeric mixture of cycloadducts (Entry 1) as the result of double stereoselection of a mismatching pair of reagents. Better stereoselectivitiy was observed with

(+)-menthyl acrylate (matching pair). The same trend of matching/mismatching pair of reagents illustrated by entries 4 and 5 is concerned with the use of Oppolzer's camphor sultam derivatives.

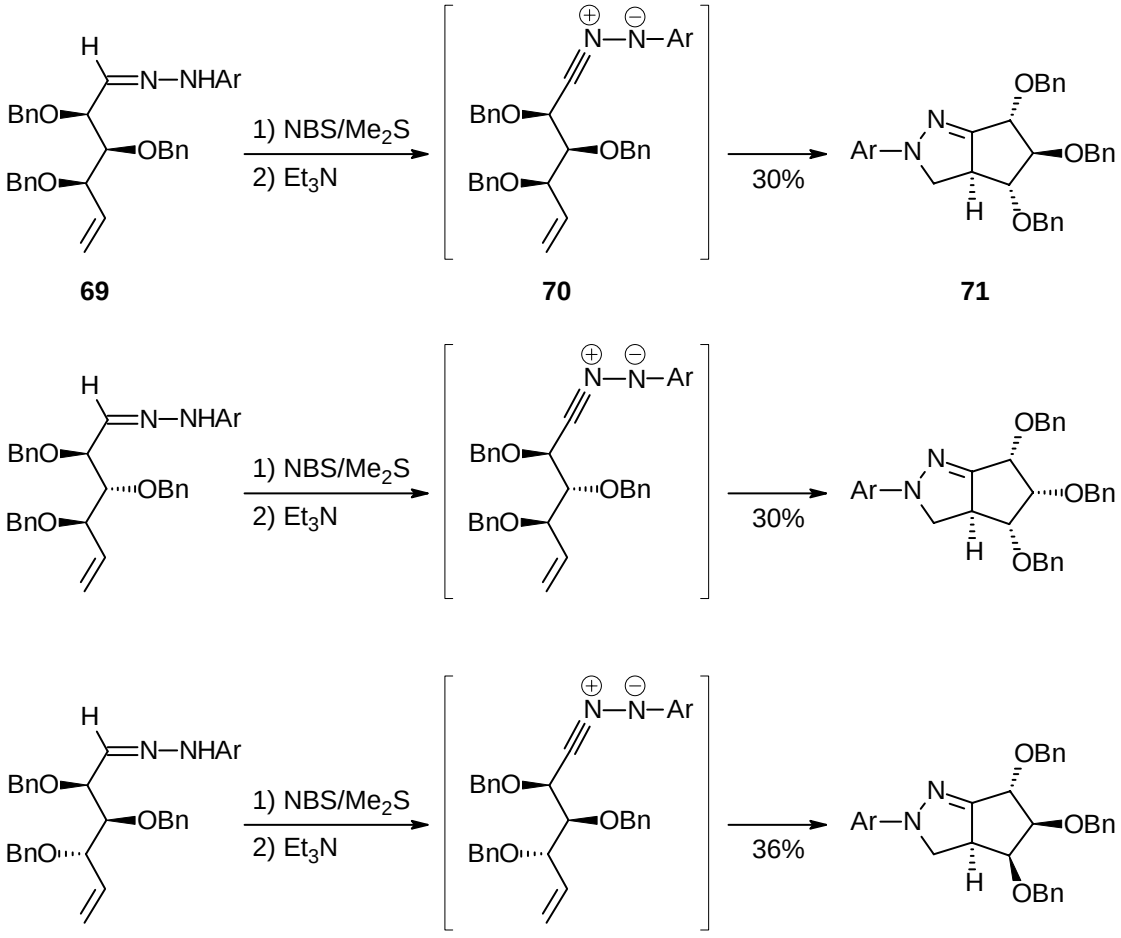
III. INTRAMOLECULAR CYCLOADDITIONS

The field of intramolecular nitrilimine cycloaddition have been explored from long time,[31] and a large body of literature is now available on this subject.[32] Since the reaction products are generally complex polycyclic, annulated, and fused ring heterocycles that are very difficult to prepare by any other method,[33] a way which allows their synthesis in the enantiopure form should be higly desirable. The first case of asymmetric induction in intramolecular nitrilimine cycloadditions was reported in 1999,[34] and a number of examples have appeared later. This section is aimed at offering a systematic survey on the stereoselective intramolecular cycloadditions of homochiral nitrilimines according to the size of the ring annulated to the pyrazole nucleus.

III.1. Formation of 4,5-dihydropyrazoles annulated to a five-membered ring.

C-Functionalised nitrilimines are able to undergo intramolecular cycloaddition giving 4,5-dihydropyrazole annulated to a five-membered ring. The D-xylo-pentamonoaldose arylhydrazone (**69**)

Scheme 22

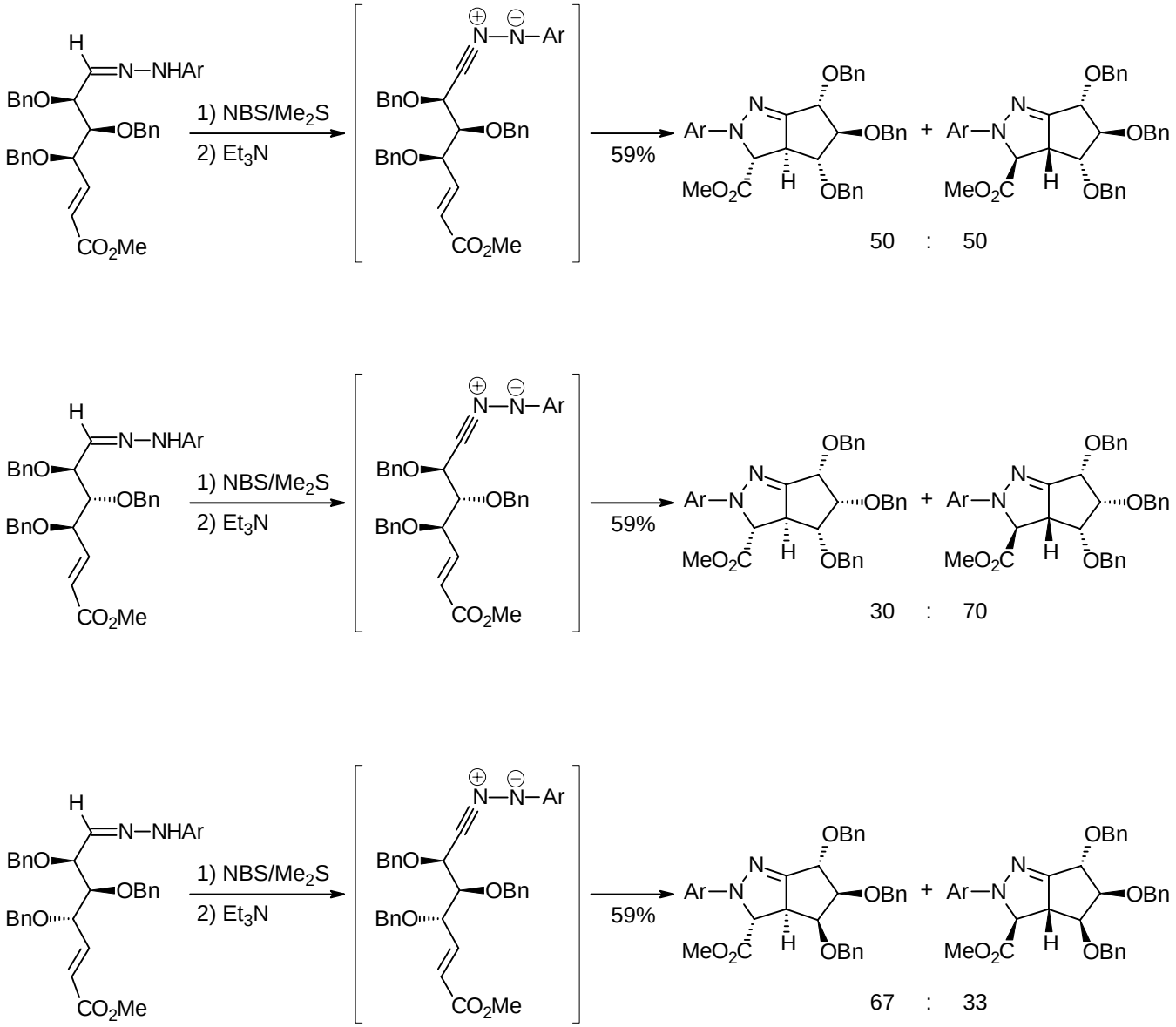


69 **70** **71**

have been prepared from 2,3,4-tri-*O*-benzyl-D-xylose in five steps. Its treatment with *N*-bromo succinimide/dimethyl sulfide and triethylamine led to the one-pot generation of nitrilimine intermediate (**70**) which underwent cycloaddition to product (**71**) as a single diastereoisomer.[35] Scheme 22 illustrates this example and that of similar arylhydrazones having D-ribo- and L-arabino- stereotriads in the tether chain joining the reacting moieties.

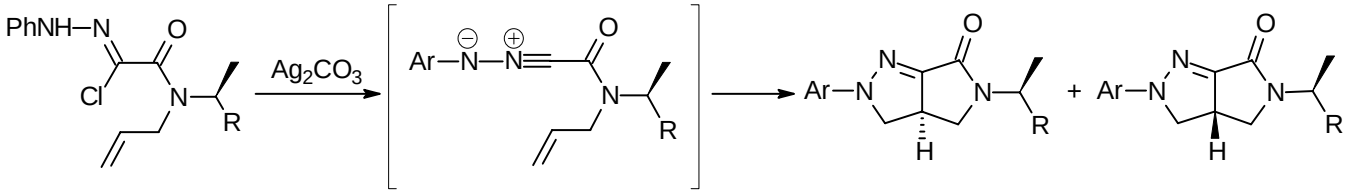
Sugar-derived nitrilimines which carry a methoxycarbonyl group linked to the terminal carbon of the alkene moiety gave mixtures of diastereoisomeric cycloadducts[35] (Scheme 23). A rationale of this different stereochemical output with respect to nitrilimine intermediate (**70**) has been found on computational grounds at the AM1 level of theory by comparing the relative energies of diastereoisomeric transition states leading to cycloadducts.

Scheme 23



Intramolecular cycloadditions of nitrilimines (**72**) occurred with a low degree of stereoselectivity, possibly due to the large distance between the pre-existing stereocentre in the chiral auxiliary and the reaction site[36] (Scheme 24, Table 10).

Scheme 24



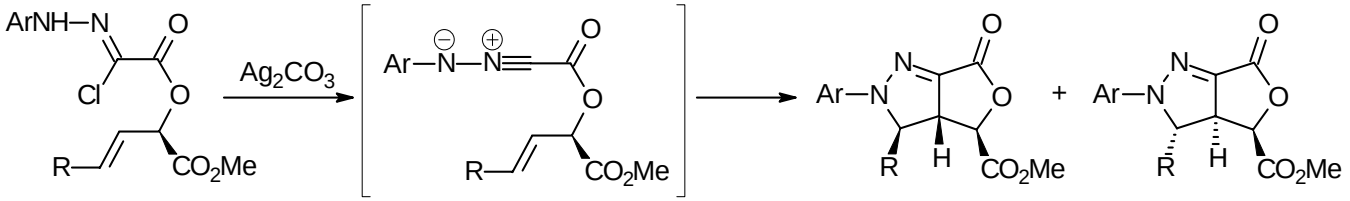
72 **73** **74**

Table 10. Intramolecular cycloadditions of nitrilimines (**72**).

Ar	R	Overall yield (%)	Stereoselective ratio **73**:**74**
4-Cl-C_6H_4	$COOCH_2Ph$	82	54:46
4-Cl-C_6H_4	Ph	61	56:44
4-NO_2-C_6H_4	$COOCH_2Ph$	49	57:43
4-NO_2-C_6H_4	Ph	65	57:43

From the examples selected in Scheme 25 and 26 and corresponding Tables 11 and 12 it is apparent that better diastereoselectivities are obtained if the pre-existing stereocentre is placed in the α- position to the ethylenic dipolarophile or the 1,3-dipole (closer to the reaction site).[34,37]

Scheme 25

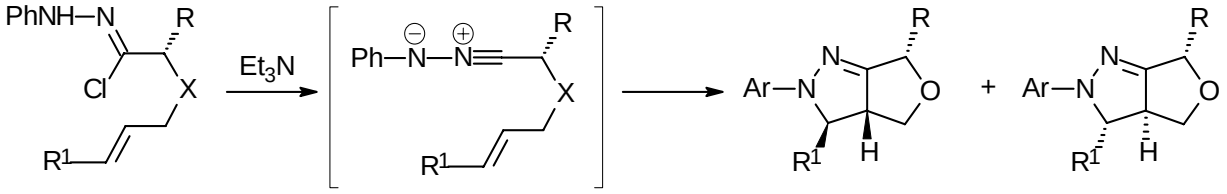


75 **76**

Table 11. Synthesis of diastereoisomeric furo[3,4-*c*]pyrazoles (**75**) and (**76**).

Ar	R	Overall yield (%)	Stereoselective ratio **75**:**76**
Ph	Me	66	67:33
4-Cl-C_6H_4	Ph	66	76:24

Scheme 26



77 **78**

Table 12. Synthesis of diastereoisomeric furo[3,4-*c*]pyrazoles (**77**) and (**78**).

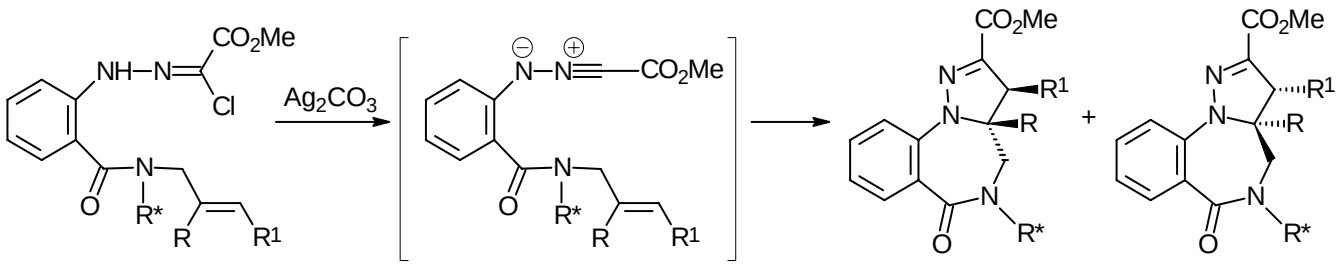
R	R^1	X	Overall yield (%)	Stereoselective ratio **77**:**78**
Me	H	O	74	86:14
Me	Me	O	65	70:30
Ph	H	O	39	100:0
Me	H	N-allyl	70	87:13
CH_2Ph	H	N-allyl	46	100:0

III.2. Formation of 4,5-dihydropyrazoles annulated to a seven-membered ring.

Annulated [1,4]benzodiazepines and their oxo- derivatives constitute valuable synthetic targets due to their well-known pharmacological activity as hypnotics and sedatives.[38,39] This has prompted a search for their synthesis in the enantiopure form by stereoselective nitrilimine cycloaddition.

Nitrilimines (**79**) undergo cycloaddition to diastereoisomeric pyrazolo[1,5-*a*][1,4]benzodiazepine-6(4*H*)-ones (**80**) and (**81**).[40] As can be inferred from Scheme 27 and Table 13, stereoselectivities ranges from fair to good; this is worth of noting because the distance between the pre-existing and the newly-formed stereocentres is rather large. A reversal of the stereochemical preference occurred switching the base from silver carbonate to triethylamine (Entries 1 vs. 5); however, the origin of such a reversal is not clear.

Scheme 27



79 **80** **81**

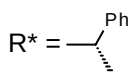
R* = 

Table 13. Intramolecular cycloadditions of nitrilimines (**79**).

Entry	R	R^1	Base	Overall yield (%)	Stereoselective ratio **80**:**81**
1	H	H	Ag_2CO_3	86	70:30
2	Me	H	Ag_2CO_3	71	60:40
3	H	Me	Ag_2CO_3	40	75:25
4	H	Ph	Ag_2CO_3	68	64:37
5	H	H	Et_3N	81	35:65

Furthermore, the diastereopreference of a closely related cycloaddition did not change with different basic agents[41,42] (Scheme 28, Table 14).

Scheme 28

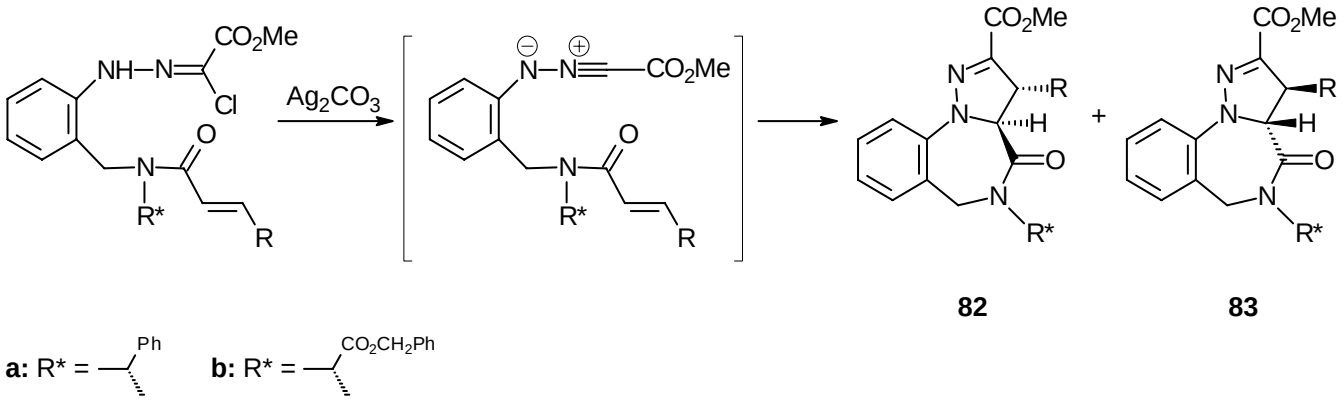
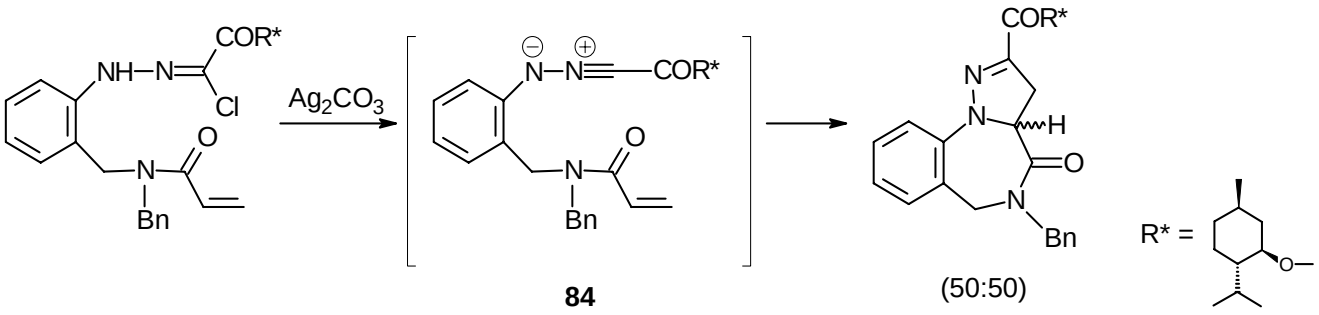


Table 14. Synthesis of diastereoisomeric pyrazolo[1,5-*a*][4,1]benzodiazepines (**82**) and (**83**).

Entry	R	Chiral auxiliary	Base	Overall yield (%)	Stereoselective ratio **82**:**83**
1	H	**a**	Ag_2CO_3	96	78:22
2	Me	**a**	Ag_2CO_3	94	65:35
3	Ph	**a**	Ag_2CO_3	96	72:28
4	H	**a**	Et_3N	72	72:28
5	H	**b**	Ag_2CO_3	70	80:20
6	Me	**b**	Ag_2CO_3	80	54:46
7	Ph	**b**	Ag_2CO_3	70	60:40

Finally, the presence of the (-)-menthyl chiral auxiliary of **84** does not promotes any diastereoselectivity in its intramolecular cycloaddition[43] (Scheme 29).

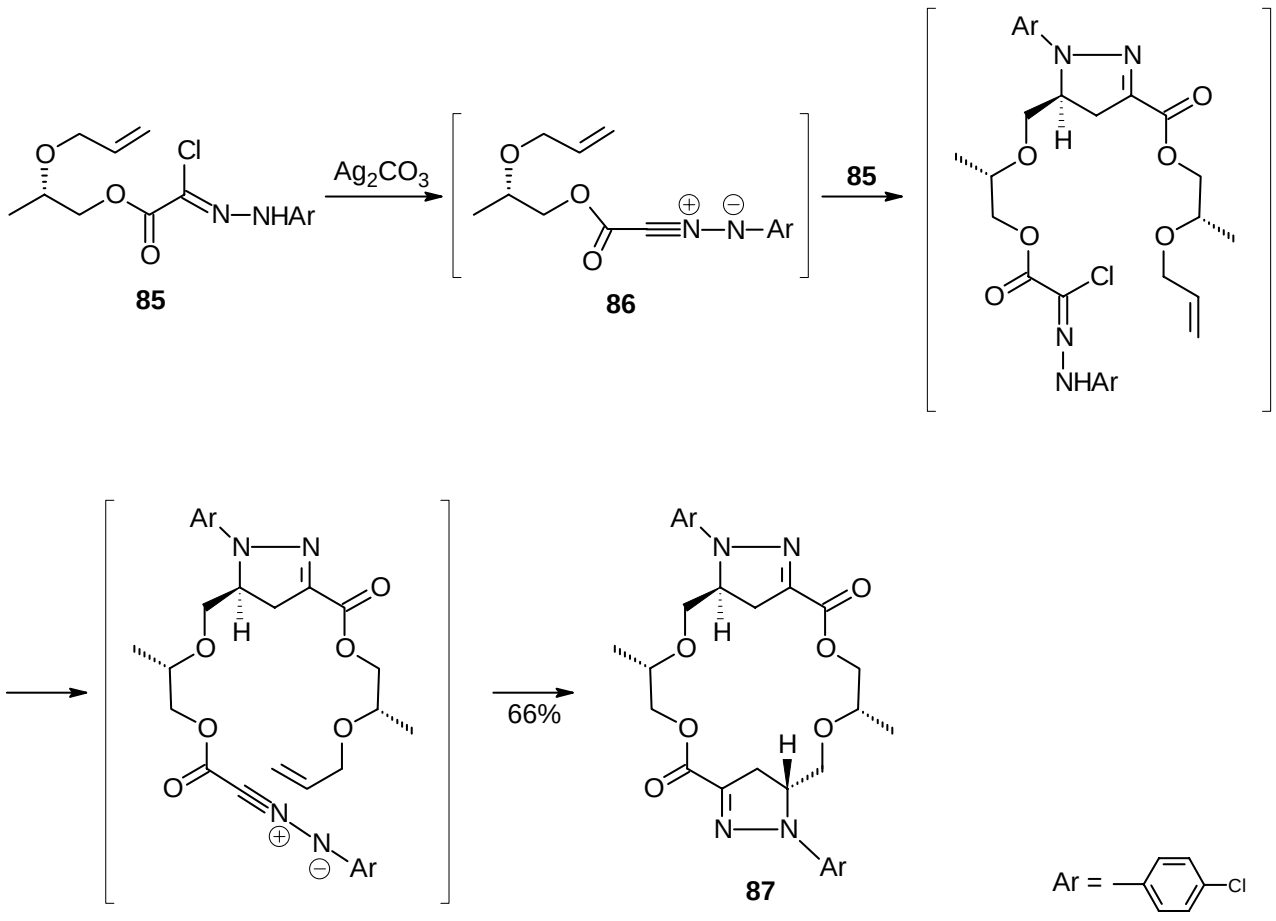
Scheme 29



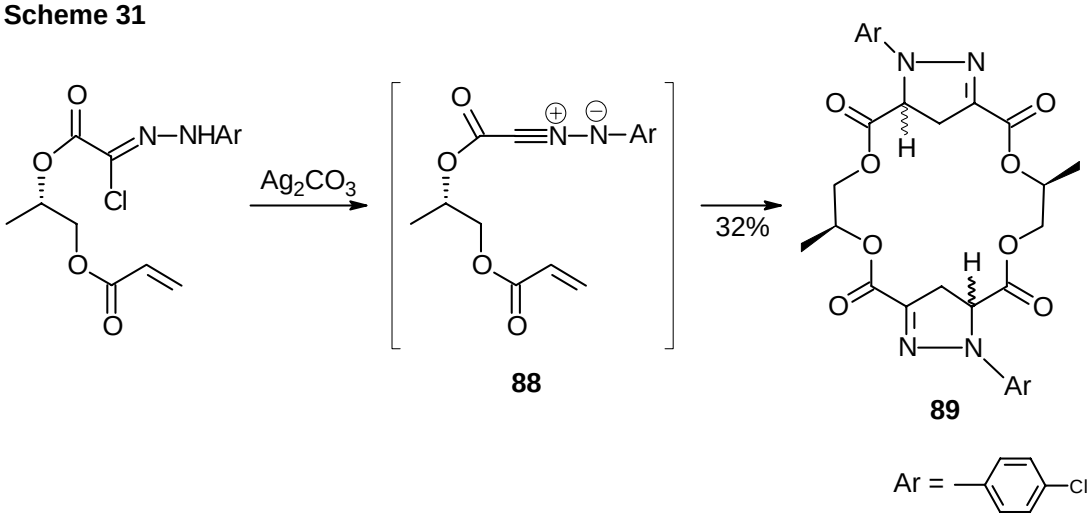
III.3. Formation of 4,5-dihydropyrazoles annulated to a large-sized ring.

The sequential inter- intramolecular cycloadditions of nitrilimines (**85**) and (**88**) outlined in Schemes 30 and 31 give rise to the enantiopure pyrazolophanes (**87**) and (**89**), respectively.[44] These macrocyclic compounds have been obtained as single diastereoisomers due to the asymmetric induction of the pre-existing stereocentre reinforced by some kind of coordination between the silver ion and the ethereal oxygens of the reactants. Although the absolute configurations of macrocycle **87** have been established by X-Ray diffractometric analysis, that of compound (**89**) remains undetermined.

Scheme 30



Scheme 31



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