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Michael Addition Initiated Carbocyclization Sequences with Nitroolefins for the Stereoselective Synthesis of Functionalized Heterocyclic and Carbocyclic Systems

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Abstract: The synthesis of various heterocycles and carbocycles (tetrahydrofurans, pyrrolidines, cyclopentanes) has been achieved by using new and efficient ionic addition/cyclization sequences. Nitroolefins play an important role in the Michael addition induced ring-closing reactions (MIRC) reported in the present article, with various substituted alcohols, amines, Grignard reactants, or malonate derivatives acting as the nucleophile partner. The optimized cascade reactions were high yielding in most cases and highly stereoselective, creating up to three stereogenic centers starting from achiral substrates.

Keywords: cyclization · cycloaddition · domino reactions · Michael addition · nitroolefins

Introduction

Heterocycles and carbocycles are key structural features in many biologically significant compounds. For example, tetrahydrofuran and -pyran skeletons are found in several intermediates for the synthesis of numerous polyethers and ionophore natural products.[1] Interesting biological activities are exhibited by several polysubstituted pyrrolidines.[2] Among carbocycles, five-membered rings are particularly important building blocks for the synthesis of natural products, for example, the prostaglandins.[3] Therefore, the development of highly stereoselective reactions for the synthesis of functionalized cyclopentane derivatives remains an important goal in organic synthesis.[3e]

Moreover, the presence of an unsaturated bond available for further elaboration has stimulated interest in a plethora of synthetic routes to 3-methylene tetrahydrofurans,[4] as well as methylene cyclopentanes.[5] For the construction of these motifs, two major five-membered ring-forming processes have been developed in recent years. Although the transition-metal-catalyzed cycloisomerization of 1,6-dienes represents an extremely powerful method for the rapid assembly of carbo- and heterocyclic compounds,[6] considerable attention has recently focused on [3+2] annulations,[3a,7] due to the advantage of creating two carbon–carbon or heteroatom–carbon bonds under the same reaction conditions.

Alternatively, regio- and stereoselective cyclizations can be achieved by intramolecular 1,3-dipolar cycloadditions,[8] usually for the construction of five-membered heterocycles. Indeed, two rings are generated during these cycloadditions, one of which is a five-membered heterocycle that can be cleaved, thereby leading to the formation of either a carbo- or a heterocycle, stereospecifically substituted by two new functional groups.[9]

As part of our sustained interest in one-pot diastereoselective cyclizations, we reported some years ago straightforward entries to functionalized carbocycles and heterocycles, provided by the Michael addition–intramolecular carbocyclization reaction between unsaturated nucleophiles and α,β-disubstituted nitroalkenes.[10] Very recently, we reported an asymmetric version of this efficient sequence that allows the

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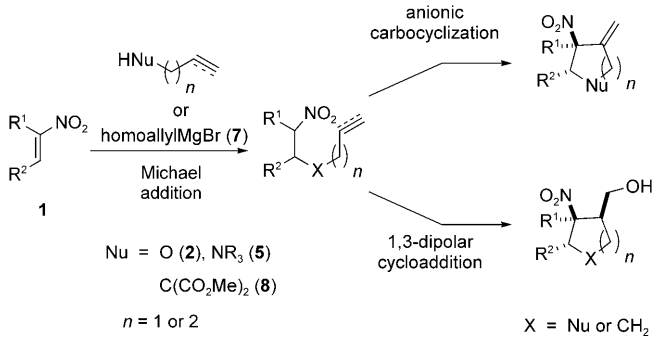
synthesis of fused isoxazoline precursors of enantiopure cyclopentanoids.[11]

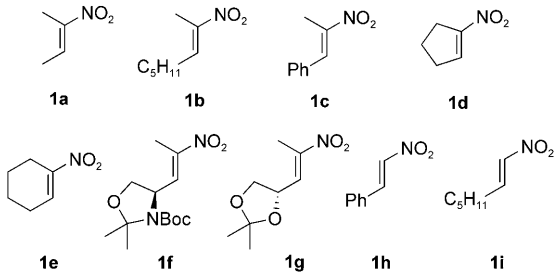
Inspired by the design of new domino reactions, which have become an attractive area of organic synthesis,[12] we tried to develop new and improved combinations of cascades, bearing in mind that when cyclizations are involved in these sequences, the ring closure generally proceeds in a highly stereoselective fashion. Michael addition induced ring-closing reactions (MIRC)[13] play a dominant role in this field. Herein, we report our studies on transformations initiated by a Michael addition to nitroalkenes **1** coupled with intramolecular additions to an unactivated double or triple bond, involving either simple anionic carbocyclization or 1,3-dipolar cycloaddition (Scheme 1). Unsaturated alcohols **2** and amines **5** were chosen to initiate hetero-Michael additions, and unsaturated Grignard reagents **7** and malonate derivatives **8** provided 1,4-additions of carbon-centered nucleophiles.



Scheme 1. The Michael addition–carbocyclization sequence.

The purpose of this article is to present the extension of these methodologies, including scope and limitations with full experimental data.

Michael addition to nitroalkenes:[4] Nitroalkenes constitute substrates of particular interest in synthesis, either in terms of their reactivity or their applications as key intermediates in the construction of complex and/or biologically active molecules.[15] The powerful electron-withdrawing effect of the nitro function is the main feature of nitroalkenes, which are hard electrophiles and therefore good acceptors in Michael additions.[16] The synthetic utility of these derivatives also arises from the easy transformation of the nitro group into many other functionalities.[17] Nitroalkenes are also precursors of very reactive 1,3-dipolar reagents, such as nitrile oxides, nitrones, and nitronates.[18] Chiral nitroalkenes are versatile precursors for 1,2-asymmetric induction. Hence, reactions of several nucleophiles in the cyclopropanation with the appropriate facial diastereoselectivities have been reported.[19] For this purpose, two nitroolefins **1f** and **1g** were elaborated from aldehydes with a stereogenic center in the alpha position.



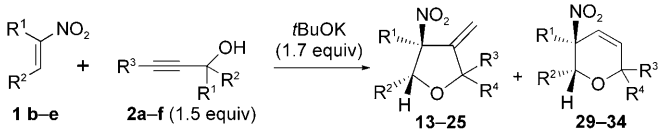
Results and Discussion

A range of nitroalkenes was prepared by adaptation of known procedures, that is, by the Henry reaction followed by dehydration of the resulting nitroaldols.[20] Nitroalcohols, prepared by the reaction of an aldehyde with nitroethane or -methane and aqueous NaOH in methanol, were dehydrated to provide *E*-nitroalkenes **1a–b** and **1i**.[21] Nitroalkenes **1f** and **1g** were obtained[22] starting from Garner's aldehyde[23] and (*R*)-isopropylidene glyceraldehyde, respectively.[24] Heating a solution of benzaldehyde and ammonium acetate at reflux in nitroethane for 12 h afforded **1c** in 97% yield,[25] and nitromercuration of cyclopentene and subsequent β-elimination provided **1d** in 80% yield.[26] 1-Nitrocyclohexene **1e** and β-nitrostyrene **1h** are commercially available.

Anionic domino Michael/carbocyclizations onto unactivated alkynes: Although the oxa-Michael addition of prop-2-ynyl alcohols to β-monosubstituted α-nitroalkenes in the presence of sodium or potassium hydride led to β-nitroprop-2-ynyl ethers,[27] only few recent preparations of five- or six-membered heterocycles involve a subsequent intramolecular addition to the triple bond.[28] Among them, *t*BuOK-promoted double Michael addition[29] and oxa-Michael/S_N2' substitution[30] with α,β-disubstituted nitroalkenes generate a stabilized nitronate anion, which subsequently adds to the activated alkyne moiety to provide the heterocycles. The two-step synthesis of α-methylene γ-lactams from 1-nitrocyclohexene, involving the formation of β-nitroamides, which undergo benzyltrimethylammonium hydroxide (Triton B)-promoted carbanion addition to an unactivated terminal alkyne is also of interest,[31] because it constitutes an unusual report of the addition of a carbon nucleophile to an unactivated alkyne moiety. These results underline the crucial effect of both the nitroalkene substitution pattern and the nature of the base on the reaction process. Therefore, we propose that an anionic domino oxa-Michael cyclization sequence with propargylic alcohols leading to methylenetetrahydrofurans should be possible by combining an appropriate set of experimental conditions. Indeed, we were pleased to find that when nitroalkenes **1b–e** were added to a solution of prop-2-ynyl alcohols **2a–d** containing *t*BuOK, a fast transformation occurred, leading to 3-methylenetetrahydrofurans **13–25** in moderate to good yields, which in some cases were accompanied by the corresponding dihydropyrans **29–34** (Scheme 2 and Table 1).

The best results were obtained when nitroalkenes were added slowly to a solution of **2** and *t*BuOK in a mixture of benzene and *t*BuOH at −5 °C; the reaction proceeded with total diastereoselectivity due to allylic 1,3-strain.[30,32] Unexpected regioselectivity was observed when the reactions were performed on nitroalkenes **1b** and **1e**: 5-*exo* adducts **13–15** (Table 1, entries 1–3) and **22–24** (Table 1, entries 10–12) were isolated along with 3,4-dihydropyrans **29–31** and **32–34**, which arise from a disfavored 6-*endo* cyclization (ratio 5-*exo*/6-*endo* = 1.7–20:1). We noticed a drastic effect of the nature of the unsaturated alcohol nucleophile on the course of the cyclization. Heterocycles obtained by reaction with secondary alcohol **2b** (Table 1, entries 2, 5, 8, 11) were obtained as a 0.7–0.9:1 mixture of separable diastereomers and the observed low facial selectivity with 2-methyl-substituted alcohols was increased up to 0.25:1 in **25** when alcohol **2d** (bearing the large benzyloxymethyl group) was involved in the Michael addition (Table 1, entry 13). Generally, a significant Thorpe–Ingold effect[33] was observed, accounting for the increased rate of the process in the case of **2c** (Table 1, entries 3, 6, 9, 12). On the other hand, addition of **2f** to nitroalkenes **1b** or **1d** resulted in a stabilization of the butadienyl anion, which underwent further cyclization into butadienyl tetrahydrofurans **26** and **27** (Table 1, entries 14–16) along with the formation of the opened keto adduct **28a**, which arises from a Nef transformation, when starting from **1b**. While **27** was isolated in the ratio *E*/*Z* = 17:83 (Table 1, entry 16), total selectivity for the *Z* isomer was observed in the formation of **26** (confirmed by a NOESY experiment). Finally, running the reaction with β-nitrostyrene (**1h**) resulted in the decomposition of the starting material (Table 1, entry 17), highlighting the crucial effect of the absence of substitution alpha to the nitro function. Indeed, the stability of the resulting nitronate intermediate is probably enhanced, which disfavors the carbocyclization step.

Another interesting observation concerns the presence of a methyl group on the alkyne moiety in **2e**. Compound **2e** gives rise exclusively to oxa-Michael adduct **12** as a 4:1 mixture of diastereomers (Table 2, en-



2a: $R^1 = R^2 = R^3 = H$
2b: $R^1 = R^3 = H$; $R^2 = Me$
2c: $R^1 = R^2 = Me$; $R^3 = H$
2d: $R^1 = R^3 = H$; $R^2 = CH_2OBn$
2e: $R^1 = R^2 = H$; $R^3 = Me$
2f: $R^1 = R^2 = H$; $R^3 =$ vinyl

Scheme 2.

Table 1. Formation of 3-methylenetetrahydrofurans **13–27** and 3,4-dihydropyrans **29–34**.[a]

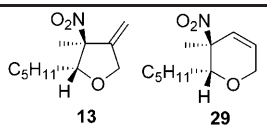
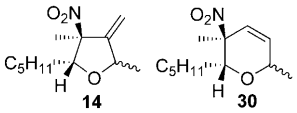
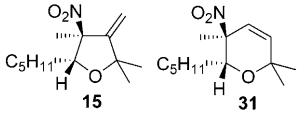
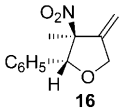
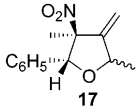
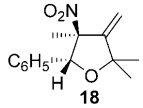
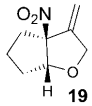
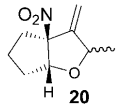
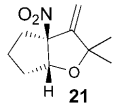
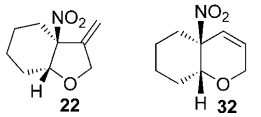
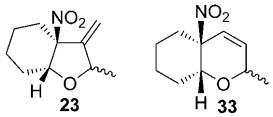
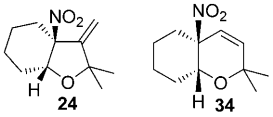
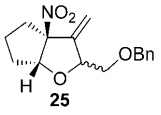
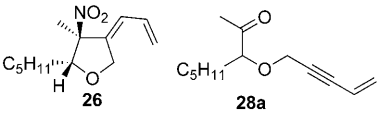
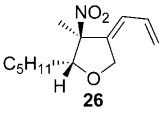
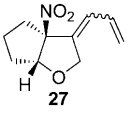
	1	2	*t*	Products	Yield [%]	*exo*/*endo*	dr[c]
1	**1b**	**2a**	12 h	 **13** **29**	57	20:1	
2	**1b**	**2b**	1 h	 **14** **30**	48	10:1	0.6:1
3	**1b**	**2c**	10 min	 **15** **31**	32	16:1	
4	**1c**	**2a**	12 h	 **16**	73		
5	**1c**	**2b**	2 h	 **17**	31		0.8:1
6	**1c**	**2c**	10 min	 **18**	58		
7	**1d**	**2a**	24 h	 **19**	84		
8	**1d**	**2b**	1 h	 **20**	80		0.6:1
9	**1d**	**2c**	0.5 h	 **21**	78		
10	**1e**	**2a**	21 h	 **22** **32**	78	1.7:1	

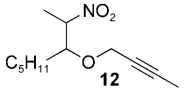
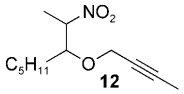
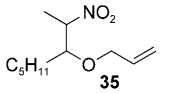
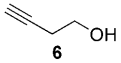
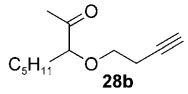
Table 1. (Continued)

	1	2	*t*	Products	Yield [%]	*exo*/*endo*	dr[c]
11	**1e**	**2b**	6 h	 **23** **33**	47	3:1	
12	**1e**	**2c**	10 min	 **24** **34**	37	3:1	
13	**1e**	**2d**	3 h	 **25**	85		0.25:1
14	**1b**	**2f**	2 h	 **26** **28a**	66 (3.7:1)		
15	**1b**	**2f**	12 h	 **26**	62		
16	**1d**	**2f**	2 h	 **27**	37	(17:83)[b]	
17	**1h**	**2a**	1 h	decomposition			

[a] All reactions were run in the presence of *t*BuOK (1.7 equiv) with **2** (1.5 equiv) in benzene/*t*BuOH (2:1, 0.4 M) at −5 °C. [b] *E*/*Z* ratio. [c] Determined by ^{1}H NMR spectroscopy of the crude product.

tries 1 and 2). Indeed, in these cases, cyclization would require the transient formation of a secondary vinyl anion, which would result in destabilization. Finally, as expected, the anionic cyclization did not occur on an unactivated double bond and only Michael adduct **35** was isolated when allylic alcohol **4a** was involved (Table 2, entry 3). Similarly,

Table 2. Michael addition to **1b**: Effect of the nature of the unsaturated alcohol.

	Alcohol	Conditions[a]	Products	Yield [%][b]
1	**2e**	25 °C, 1 h	 **12**	75 (4:1)[c]
2	**2e**	40 °C, 2 h	 **12**	70 (4:1)[c]
3	 **4a**	25 °C, 1 h	 **35**	87 (4:1)[c]
4	 **6**	25 °C, 5 h	 **28b**	68

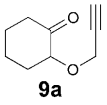
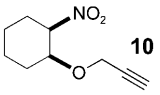
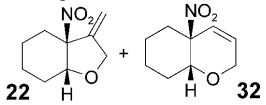
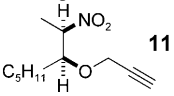
[a] All reactions were run in the presence of *t*BuOK (1.7 equiv) with 1.5 equiv of **2** in benzene/*t*BuOH (2:1, 0.4 M) at −5 °C. [b] Isolated yield. [c] *cis*/*trans* diastereomeric ratio; the assignment was done based on comparison of *J* values of protons α and β to NO_2 function.

the reaction of homoallylic alcohol **6** with nitroalkene **1b** was unsuccessful, resulting in the Nef oxidation of Michael adduct to form **28b** exclusively (Table 2, entry 4).

After these encouraging results, and to optimize this new one-pot anionic heterocyclization, we first decided to study the effect of the nature of the base on the yield and selectivity. The results of reactions between nitroalkenes **1b** and **1e**, propyn-1-ol **2a** and different bases under various reaction conditions are collected in Table 3.

When nitrocyclohexene (**1e**) was treated with an excess of the lithium alkoxide obtained by reaction of *n*-butyllithium (1.5 M) with propargyl alcohol (**2a**), a complex mixture was obtained and keto compound **9a**,[34] resulting from the Nef oxidation of the Michael adduct intermediate, was the sole product isolated (Table 3, entry 1). Michael adduct **10** was isolated in 27% yield when NaH was used as the base (Table 3, entry 2). Surprisingly, K_2CO_3 only resulted in the decomposition of the starting material and no product could be isolated (Table 3, entries 3 and 7). The hard base Cs_2CO_3 displayed approximately the same features as *t*BuOK, both in terms of products distribution and reaction times (Table 3, entries 4–6). Although yields were lower, the regioselectivity in favor of the 5-*exo* isomer **22** was increased up to 5:1 when three equivalents of propargyl alcohol **2a** were employed (Table 3, entry 5). Conducting the reaction with potassium hydride without the addition of *t*BuOH for 1 h from −40 to 0 °C afforded the Michael adduct **11** in good yield, according to previously reported results by the groups of Kurth[27] and Yao[35] (Table 3, entry 8). Lengthening the reaction time to 48 h, starting from −40 to 25 °C in the absence of *t*BuOH had a significant effect, leading to the formation of the expected cyclized derivatives (**13** and **29**) as minor products (Table 3, entry 9) together with the Michael adduct **11**. Finally, running the reaction under the same reaction conditions in the presence of the additive *t*BuOH resulted in the exclusive recovery of cyclized adducts **13** and **29** in the ratio 7:1 and 90% yield (Table 3, entry 10). This clearly shows the beneficial effect of the *t*BuOH as the proton source on the kinetic of the overall process. The carbocyclization step should be a thermodynamically unfavorable process because it converts a stabilized nitronate anion into a nonstabilized vinylic anion. However, when *t*BuOH is used

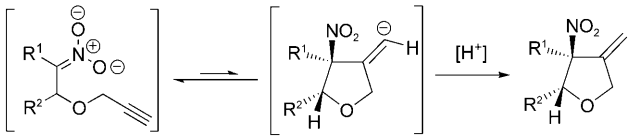
Table 3. Effect of base, solvent, and temperature on the oxa-Michael addition of propargyl alcohol **2a** on nitroalkene **1b** and **1e**.

	1	Base ([equiv])	**2a** [equiv]	Conditions[a]	Products	Yield [%]	5-*exo*/ 6-*endo*
1	**1e**	*n*BuLi (3)	3	25°C, 1 h	 **9a**	20	
2	**1e**	NaH (2)	2	−40°C, 1 h	 **10**	27[c]	
3	**1e**	K_2CO_3 (1.7)	1.5	18-C-6 25°C, 24 h	decomposition	–	
4	**1e**	Cs_2CO_3 (1.7)	1.5	−5°C, 22 h	 **22** + **32**	34	4:1
5	**1e**	Cs_2CO_3 (1.5)	3	−5°C, 22 h		24	5:1
6	**1e**	Cs_2CO_3 (1.5)	1	−5°C, 22 h		19	4:1
7	**1b**	K_2CO_3 (1.7)	1.5	25°C, 24 h	decomposition	–	
8	**1b**	KH (2)	2	−40 to 0°C, 1 h[b]	 **11**	71[c]	
9	**1b**	KH (2)	2	−40 to RT, 48 h[b]	(**11**[c]/**13**+**29**) (1.6:1)	81	2.5:1
10	**1b**	KH (2)	2	−40 to RT, 40 h	**13**+**29**	90	7:1

[a] Unless otherwise stated THF/*t*BuOH (30:1) was used as solvent. [b] THF was used as solvent. [c] Only one diastereomers (*cis*) was detected by analysis of the ^{1}H NMR of the crude product (see Experimental Section).

metal enolates to unactivated triple bonds to give methylenecyclopentanes. Such a transformation usually requires the assistance of a transition metal catalyst or the use of catalytic amount of base. In 1953, Eglinton and Whiting reported[39] that 1,1-dicarboethoxy-2-methylenecyclopentane was isolated from the cyclization of diethyl 5-hexyne-1,1-dicarboxylate in the presence of EtONa at reflux. This constituted the first anionic intramolecular cyclization onto a nonactivated alkyne to give the methylenecyclopentane skeleton, and similar results were disclosed a few years later.[40] Since these pioneering studies, the most common procedures for the synthesis of methylenecyclopentanes involve intramolecular addition of organometallic,[41] radical,[42] or anionic[43] centers to a triple bond and cycloisomerization of enynes,[44] dienes,[45] alkynones,[46] or ε-acetylenic β-ketoesters.[47] Whereas these approaches are concerned with a one-bond formation, considerable attention has also been focused on [3+2] annula-

as an additive, the vinylic anion is irreversibly protonated, which may drive the process to completion (Scheme 3).

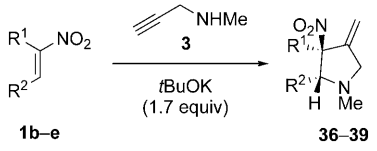


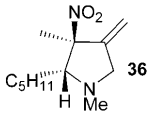
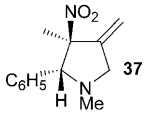
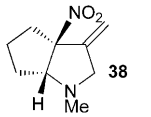
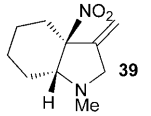
Scheme 3. Proposed mechanism for the carbocyclization process.

Interestingly, aza-Michael addition of *N*-methylprop-2-ynylamine (**3**) to nitroalkenes **1b–e** also proceeded with intramolecular nucleophilic carbocyclization to provide regio- and diastereoselectively the corresponding 3-methylenepyrrolidines **36–39** (Table 4). Similarly to the formation of the *O*-heterocycles described above, cyclization into 3-methylenepyrrolidines proceeded under total 1,3-allylic strain. Moreover, the intramolecular nucleophilic addition exclusively affords products arising from 5-*exo* cyclization. Indeed, the same regioselectivity was reported by Rosenberg and Rapoport[36] and Coldham et al.[37] in a study of anionic cyclization of (2-aza)- and (3-aza)-5-heptenyl systems.

To extend the overall heterocyclization to the synthesis of the corresponding valuable methylene carbocycles, we envisioned the reactivity of propargyl malonates as Michael donors. This will provide a Michael adduct intermediate with a geminal diester group in the hope of utilizing the Thorpe–Ingold effect[38] to promote the cyclization. In the literature there are few reports of the addition of stabilized

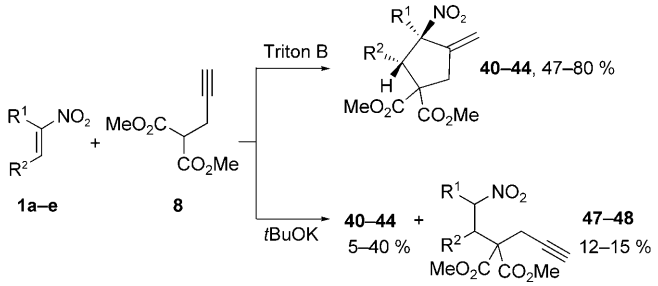
Table 4. Formation of 3-methylenepyrrolidines **36–39**.[a]



	1	*t* [h]	Product	Yield[b]
1	**1b**	1	 **36**	84
2	**1c**	2	 **37**	29
3	**1d**	1.5	 **38**	63
4	**1e**	2	 **39**	70

[a] All reactions were run in the presence of *t*BuOK (1.7 equiv) with 3.0 equiv of **3** in benzene/*t*BuOH (2:1, 0.4 M) at 0°C. [b] Isolated yield.

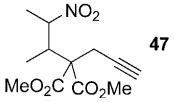
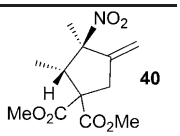
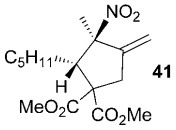
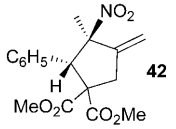
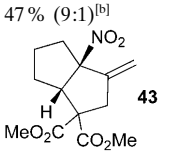
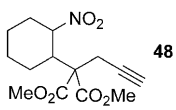
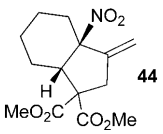
tions.[48] More particularly, encouraged by the interesting features of anionic [3+2] heterocyclizations that we developed above, we decided to examine the base-promoted Michael addition of dimethylpropargyl malonate **8** to nitroalkenes **1a–e** (Scheme 4 and Table 5). The benzene/*t*BuOH solvent system used previously (Tables 1 and 2) was replaced by THF/*t*BuOH for a better solubility of the nitronate intermediates. When nitroalkenes **1a–e** were reacted at 0°C in THF/*t*BuOH (30:1) with **8** in the presence of one equivalent of *t*BuOK, methylenecyclopentanes **41**, **43**, and **44** were isolated but in relatively modest yields, not exceeding 40% after a long reaction time, whereas **40** and **42** could only be detected in the crude reaction mixture (Table 5, entries 1, 3, 5, 7, and 9). Moreover, although total diastereoselectivity was observed with nitroalkenes **1c** and **1e** for derivatives **41** and **43** (which were also the only product formed, Table 5, entries 3 and 7), product **42** was obtained as a 1.4:1 *trans*/*cis* diastereomeric mixture (Table 5, entry 5) and methylenecyclopentanes **40** and **44** were formed along with the inseparable Michael adducts **47** and **48** in 12 and 15% yield, respectively (Table 5, entries 1 and 9). To optimize experimental conditions, a variety of bases were tested with nitrocyclohexene **1e**. K_2CO_3, Cs_2CO_3, KH, NaH, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and their solvent systems proved to be unsuccessful, but revealed once again the crucial effect of a proton source such as *t*BuOH.



Scheme 4. Synthesis of 3-methylenecylopentanes.

Gratifyingly, in the case of nitroalkene **1e**, the use of Triton B as the base provided the expected domino [3+2] annulation into methylenecyclopentane **44** (Table 5, entry 10) and a substantially improved yield (up to 80%) was attained when Triton B (1 equiv) was added at 0°C to a solution of nitroalkene **1e** (1.3 equiv) and **8** (1 equiv). The use of a catalytic amount of base resulted in the recovery of starting materials. With the optimal conditions in hand, we therefore examined this new domino reaction with nitroalkenes **1a–d**. The overall transformation was completed after a few minutes and the [3+2] annulation afforded methylene cyclopentanes **40–43** in 47–65% yields after purification by flash chromatography on silica gel. It should be noted that methylenecyclopentanes **40–44** are the sole products isolated when using Triton B, whereas Michael adducts **47** and **48** were obtained in 12–15% yield when *t*BuOK was employed as the base. The reaction proceeded with total diastereoselectivity for monocyclic compounds **40** and **41** (Table 5, entries 2 and 4), due to allylic 1,3-strain as previously reported in related systems.[30] The higher diastereoselectivity (9:1) observed in the formation of **42** (Table 5, entry 6) with respect to the reaction with *t*BuOK (1.4:1) can be accounted for by an interplay between stereo-

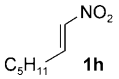
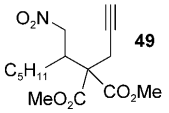
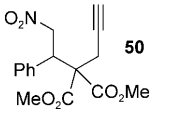
Table 5. Formation of methylenecylopentanes **40–44**.

	1	Conditions[a]	*t* [h]	Michael adduct	Cyclization product
				 **47**	 **40**
1	**1a**	*t*BuOK	12	12% (1:9)[b]	<5%
2	**1a**	Triton B	24	–	56%
					 **41**
3	**1b**	*t*BuOK	21	–	33%
4	**1b**	Triton B	5	–	51%
					 **42**
5	**1c**	*t*BuOK	24	–	<5% (1.4:1)[b]
6	**1c**	Triton B	16	–	47% (9:1)[b]
					 **43**
7	**1d**	*t*BuOK	13	–	35%
8	**1d**	Triton B	1	–	65%
				 **48**	 **44**
9	**1e**	*t*BuOK	18	15% (1:2)[b]	40%
10	**1e**	Triton B	0.5	–	80%

[a] All reactions were run in the presence of *t*BuOK or Triton B (1.0 to 1.3 equiv) with **8** (1.0 equiv) in THF/*t*BuOH (30:1) at 0°C. [b] *trans*/*cis* diastereomeric ratio.

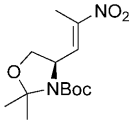
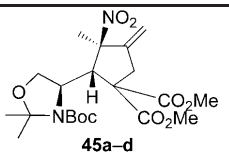
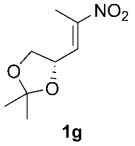
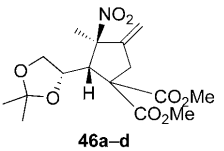
chemistry and ion pair formation. Indeed, the presence of the large benzyltrimethylammonium cation instead of potassium may affect ion pair formation[49] and therefore the allylic 1,3-strain effect. The relative stereochemistry of compounds **40**–**44** was deduced from their spectral data (^{1}H NMR NOESY experiments) and firmly assigned by X-ray structures for **40**, **42**, and **44**.[50] Finally, the nature of the substitution pattern on the nitroalkene proved to be crucial (Table 6). Indeed, when 1-nitroheptene (**1h**) and nitrostyrene (**1i**) were treated with **8** in the presence of NaH or Triton B, Michael adducts **49** and **50** were isolated respectively in 32–52% and 63–87% yields, respectively (*t*BuOK was unproductive). It was instructive to note that the reaction did not proceed with sequential intramolecular nucleophilic addition. These results indicate once again that the absence of a substituent at the α position of the nitroalkene has an unfavorable effect on ring closure, certainly due to a greater stability of the nitronate anion.

Table 6. Reaction of 1,2-disubstituted nitroalkenes.[a]

	Base	Nitroalkene	*t* [h]	Product	Yield [%]
1	Triton B		24		32
2	NaH		16		52
3	Triton B		5		63
4	NaH		3		87

[a] All reactions were run in the presence of NaH or Triton B (1.0 equiv) with **8** (1.0 equiv) in THF/*t*BuOH (30:1) at 0 °C.

Table 7. Functionalization of γ-chiral nitroalkenes **1f** and **1g**.[a]

	1	*T*	Products	Yield [%]
1		0 °C to RT		57
2		−90 °C to RT		65
3		0 °C to RT		63
4		−90 °C to RT		75

[a] All reactions were run in the presence of Triton B (1.0 equiv) with **8** (1.0 equiv) in THF/*t*BuOH (30:1).

Facial diastereoselectivity: γ-Chiral-(*E*)-nitroalkenes **1f** and **1g** were involved in a project on the asymmetric synthesis of functionalized carbocycles. The most significant data among the addition of dimethylpropargylmalonate **8** to **1f** and **1g** are collected in Table 7.

Both reactions of **1f** and **1g** with **8** afforded methylenecyclopentanes **45a–d** and **46a–d**, respectively, as mixtures of four diastereomers (Table 8). Reactions were conducted for 12 h in the presence of Triton B, at a temperature range of 0 °C to room temperature or −90 °C to room temperature. Methylenecyclopentanes **45** and **46** were obtained in the best overall yields (57 and 75%, respectively) at lower temperature ranges. Diastereomers were detected by ^{1}H and ^{13}C NMR spectroscopy in a ratio deduced from the ^{1}H NMR spectrum of the crude product or by HPLC.

For **1f**, an insignificant effect on the diastereomeric ratio on varying the reaction temperature was observed. In contrast, this effect was drastic with **1g**, increasing the initial 48% ratio observed at 0 °C for **46a** up to 76% when the reaction was carried out at −90 °C (Table 8, entries 3 and 4).

The chromatograms (Figure 1) of products from the reaction between **1f** with propargyl malonate **8** display two major diastereomers **45a** and **45b**. When referring to the strongly favored stereochemistry related to methylenecyclopentanes **40**–**44**, we can reasonably assert that the nitro group and H-C_β are in a *cis* relationship in these major diastereomers **45a** and **45b**. This *cis* relative stereochemistry was firmly assigned by an X-ray structure in the case of **45a**

Table 8. Diastereomeric ratios for compounds **45a–d** and **46a–d**.

	1	*T* [°C]	Diastereomeric ratio [%]			
			45a	**45b**	**45c**	**45d**
1	**1f**	0	57	34	8	1
2		−90	60	32	6	2
			46a	**46b**	**46c**	**46d**
3	**1g**	0	48	36	13	3
4		−90	76	15	6	3

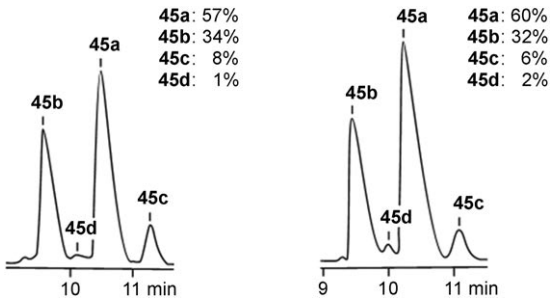


Figure 1. Chromatograms of HPLC analytical separations of stereoisomers **45a–d** (for conditions, see the Supporting Information).

(Figure 2), but unfortunately, crude **45b–d** could not be crystallized. Nevertheless, we should expect the same *cis* relationship for **45b**, whereas in **45c** and **45d**, the nitro group and H-C_β should have a *trans* relationship.

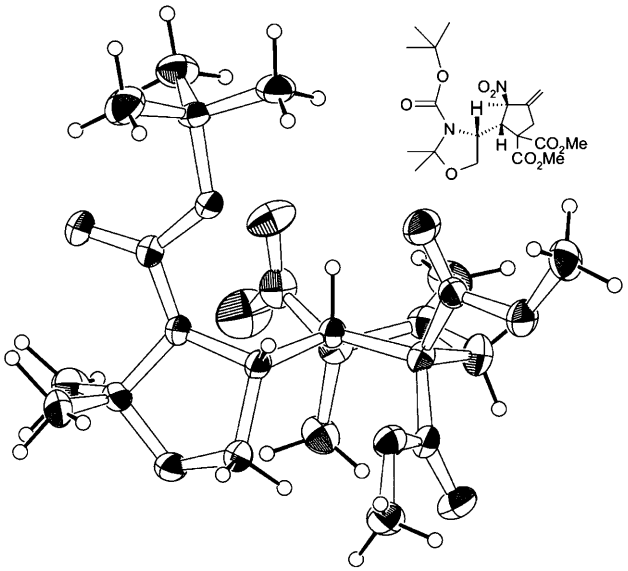
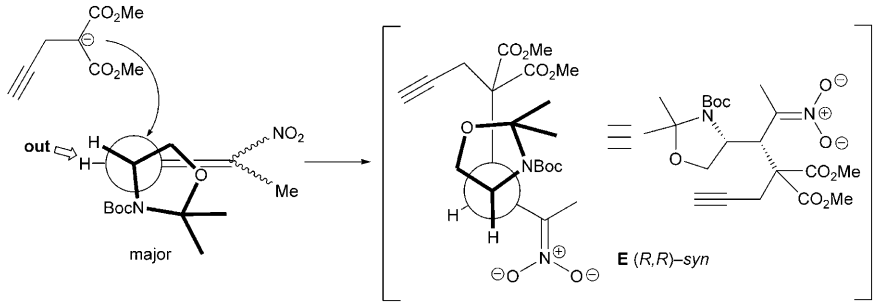


Figure 2. X-ray crystal structure of **45a**.

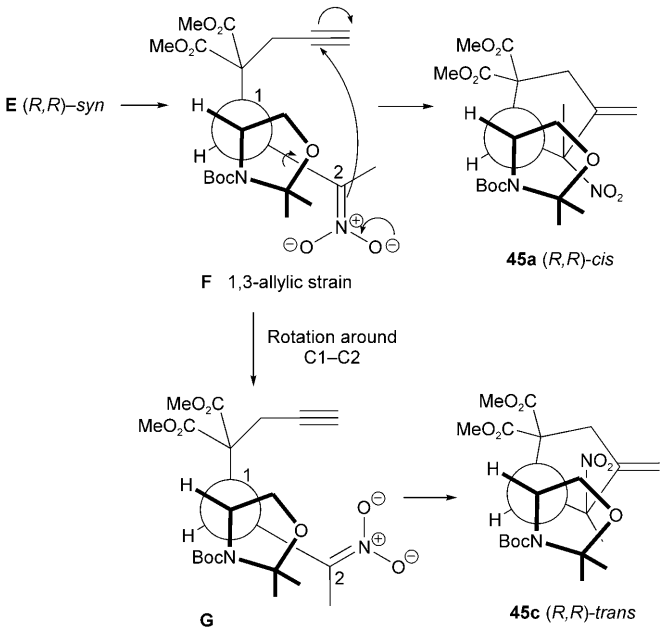
Moreover, the X-ray Ortep plot of **45a** (Figure 2) unambiguously indicates the favored stereofacial control leading to the *syn* stereochemistry with respect to the new C−C bond provided by the Michael addition.

This stereochemical outcome can be explained by Houk's outside-crowded model and periplanar effect.[22,51] Thus, the chiral substituent in **1f** is oriented mainly in such a way that the small hydrogen atom occupies the crowded outside position. The addition of the malonate anion to this conformation occurs antiperiplanar to the alkoxy group to afford the (*R,R*)-*syn* transient nitronate **E**, a precursor of **45a–b** (Scheme 5).

Conformation **F**, which is governed by 1,3-allylic strain, affords **45a**, whereas rotation around the C1−C2 bond provides **45c** through conformation **G** (Scheme 6).



Scheme 5.



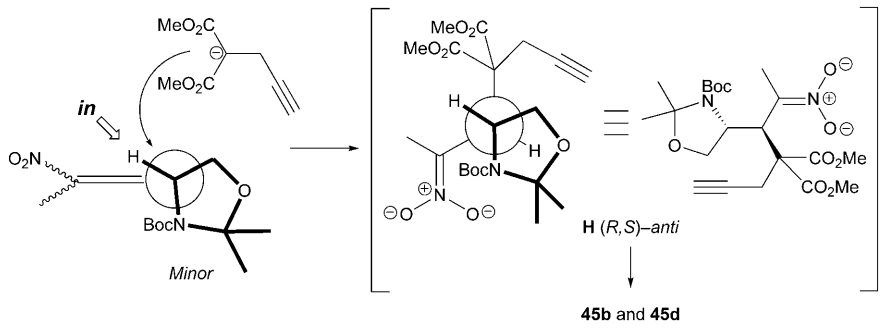
Scheme 6.

A conformation in which the hydrogen atom occupies the crowded inside position affords (*RS*)-*anti* transient nitronate **H** and subsequent cyclization provides (*RS*)-*cis* **45b** and (*RS*)-*trans* **45d** (Scheme 7).

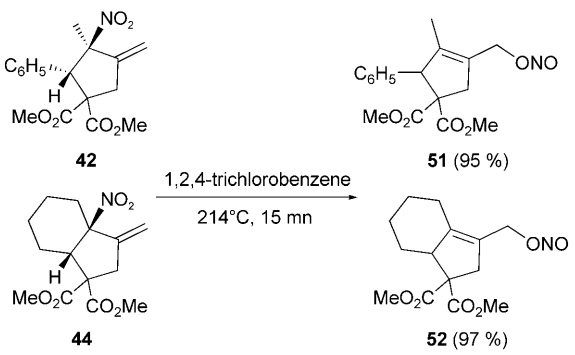
Structural modifications: To quantify the facial diastereoselectivity related to the Michael addition on substrates **1f** and **1g**, we decided to eliminate the stereogenic center with the functional nitro group. For this purpose, we decided to transpose allylic nitro compounds through [2,3]-sigmatropic rearrangement.[52] This rearrangement has received only little attention in the literature, despite its synthetic potential. Indeed, allylic alcohols are obtained through hydrolysis of an allylic nitrite intermediate and the yields are drastically improved when the thermolysis is performed in the presence of DABCO.[52a] Thermal reaction conditions[52c] were optimized on compounds **42** and **44**, which provided exceptionally stable nitrites **51** and **52** in high yields (Scheme 8).

Encouraged by the effectiveness of this transformation, the diastereomeric mixture **46a–d** was reacted under the same reaction conditions to undergo a [2,3]-sigmatropic rearrangement, providing a mixture of two diastereomers **53a** and **53b** in 96% yield (Table 9).

Compounds **53** were isolated as viscous oils that could not be crystallized and the relative stereochemistry remains undetermined at this time. Nevertheless, since *cis* stereochemistries have previously been assigned to **46a** and **46b**, whereas **46c**

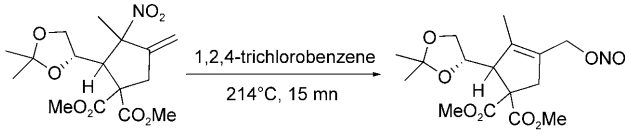


Scheme 7.



Scheme 8.

Table 9. [2,3]-Sigmatropic rearrangement of **46** into **53**.

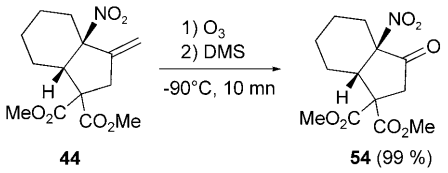


	46				53	
	46a	**46b**	**46c**	**46d**	**53a**	**53b**
1	48 %	36 %	13 %	3 %	61 %	39 %
2	76 %	16 %	5 %	3 %	81 %	19 %

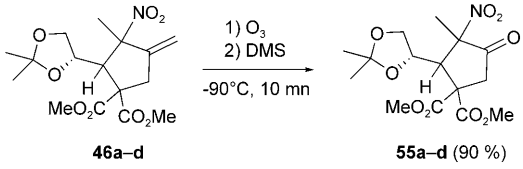
and **46d** were presumed to be *trans*, we could reasonably assume that **46a** and **46c** provide **53a**, whereas **46b** and **46d** are precursors of **53b**.

To obtain a crystallized derivative of **53**, we envisioned the formation of a hydrazone or an oxime, but failed to convert the nitrite group into aldehyde in the presence of BF_3•Et_2O and oxygen.[53] We therefore changed our strategy to the formation of a ketone, through ozonolysis of the *exo*-methylene group. The reaction was first optimized on substrate **44**, which was quantitatively transformed into keto derivative **54** (Scheme 9).

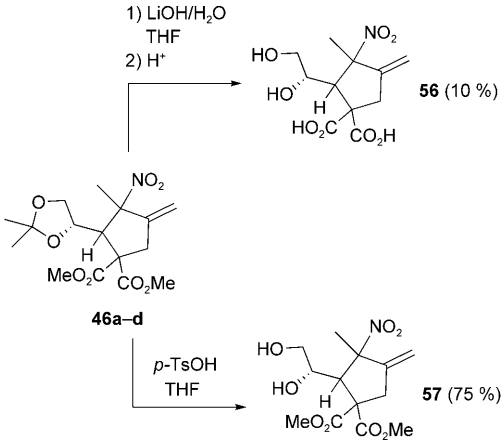
The mixture **46a–d**, consisting of four diastereomers (diastereomer ratio of 76:15:6:3; Table 8) was submitted to the same oxidation conditions to afford the corresponding ketones **55** in a few minutes in a similar ratio (determined by ^{1}H NMR spectroscopy) (Scheme 10).



Scheme 9.



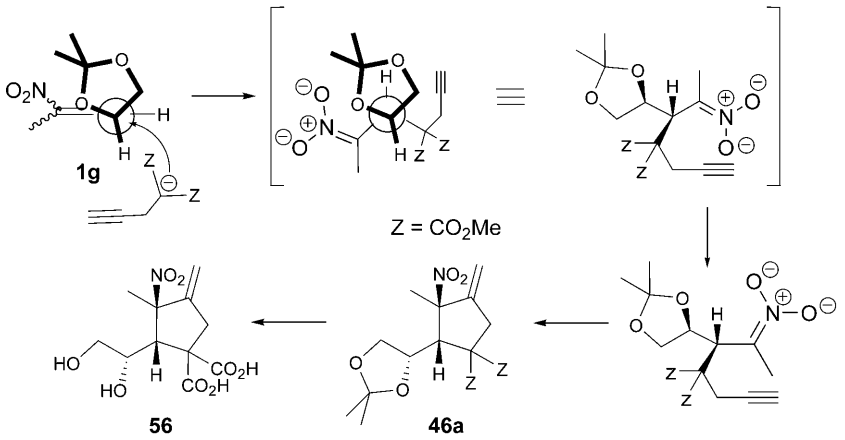
Scheme 10.



Scheme 11.

Unfortunately, attempts to separate the diastereomers resulted in degradation. We then embarked upon saponification of the ester groups. LiOH-promoted procedures[54] provided **56** by both saponification of the ester and deprotection of the dimethyldioxolane ring (Scheme 11).

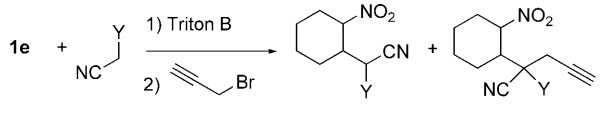
Formation of **56** most probably proceeds by deprotection during the acidification step, since the sensitive isopropylidene motif[55] still suffers the same transformation when treating **46** with *p*-TsOH to afford **57**. Although **56** was isolated in low yield as a colloidal white powder, it could not be recrystallized. Therefore, the relative stereochemistries of **46a–d** could not unambiguously be assigned. Nevertheless, a stereochemical preference, provided by the Felkin–Anh-like approach (Scheme 12) should be highly favored and would be expected to provide **46a**.



Scheme 12.

Multicomponent reactions: To extend the carbocyclization of α-nitroalkenes to other propargyl malonic-type nucleophiles, we envisioned that Michael adduct precursors could be available by a three-component reaction involving a malonic derivative, propargyl bromide and a nitroalkene. Experiments were carried out with Triton B as the base (Table 10).

Table 10. Three-component reactions.[a]

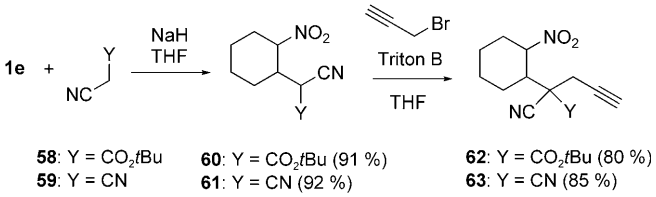


	Y	Triton B [equiv]	*t* [h]	Products (yields [%])			
1	CO_2tBu	1	6	**60**	(50)	**62**	(43)
2		2	12		(52)		(38)
3	CN	1	5	**61**	(32)	**63**	(47)
4		2	14		(47)		(46)

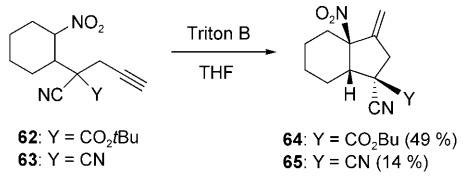
[a] All reactions were carried out at 0°C.

Starting with **1e** and cyanobutylmalonate (**58**) or malonitrile (**59**), Michael adducts **60** and **61** were isolated along with the expected δ-nitroalkynes **62** and **63** (obtained as mixtures of diastereomers) in an approximately 1:1 ratio and good overall yield. Unfortunately, even two equivalents of base did not promote the one-pot carbocyclization step. To optimize the formation of δ-nitroalkynes **62** and **63**, we decided first to prepare the Michael adducts **60** and **61** according to standard procedures. Subsequent alkylation with propargyl bromide should provide required δ-nitroalkynes. When nitroalkene **1e** was treated with malonate derivative **58** or **59** and a catalytic amount of NaH (1:1:0.1), Michael adducts were obtained in 91–92% yields as mixtures of diastereomers (Scheme 13). Note that the use of base in a catalytic amount provides adducts in good yields, suggesting that the nitronate anion acts as a base to deprotonate a new malonate molecule.

Alkylation of **60** and **61** with propargyl bromide promoted by Triton B in THF afforded adducts **62** and **63** in 80 and 85% yields, respectively. Subsequently, methylenecyclopentanes **64** and **65** were obtained in 49 and 14% yields, respectively as pure diastereomers (stereochemistries established by NOE experiments) by reaction of pure isolated Michael adduct **62** and **63** with Triton B in THF (Scheme 14).



Scheme 13.



Scheme 14.

Quenching the cyclization of **63** after 30 min resulted in the recovery of a large amount of nitroalkene along with propargyl malononitrile. This result confirms a favored retro-Michael reaction in the case of these malonate derivatives, which explains the low yield of **65**.

Indeed, the observed yields in cyclization products are in agreement with the observed pK_a (Table 11), since the greater difference of pK_a between malonate derivatives and nitronate anions results in the more favored retro-Michael process.

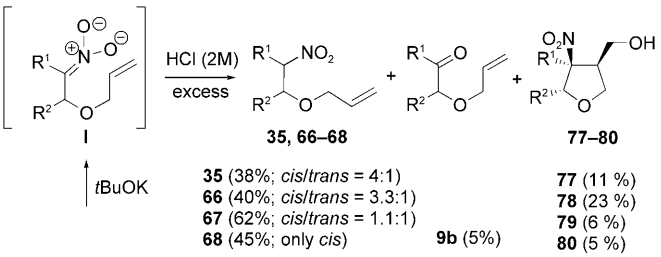
Carboxycyclopentannulation of a nonactivated alkene through 1,3-dipolar cycloadditions: Although reaction of propargyl alcohol **2a** with nitroalkenes in the presence of *t*BuOK/*t*BuOH provided methylenetetrahydrofurans by intramolecular cyclization of nitronates to the triple bond, we observed that addition of allylic alcohols **4a** and **6** to nitroalkene **1b** under the same reaction conditions failed to undergo carbocyclization (see Table 2). Similarly, addition of **4a–c** to nitroalkenes **1a–c**, **1e**, or **1g** also provided oxa-Michael adducts **35** and **66–71** after hydrolysis of the resulting nitro-

Table 11. pK_a values of various malonate derivatives.

Malonate derivative	pK_a in DMSO
propargylmalonitrile	12–13
2-propargyl-*t*Bu cyanoacetate	14–15
dimethylpropargylmalonate	16–17
nitronate anion	17–18

nates under mild acidic conditions in good to excellent yields (Table 12).

Surprisingly, we found that when *aci*-nitro anions **I** (obtained by oxa-Michael addition of allylic alcohol (**4a**) to nitroalkenes **1a–c** and **1e** with *t*BuOK in THF/*t*BuOH (30:1)) were hydrolyzed with excess 2 M HCl, an unprecedented transformation took place leading to the formation of *exo*-nitro alcohols **77–80** in 5–23% yields together with the Michael adducts **35**, **66–68** (Scheme 15).



Scheme 15.

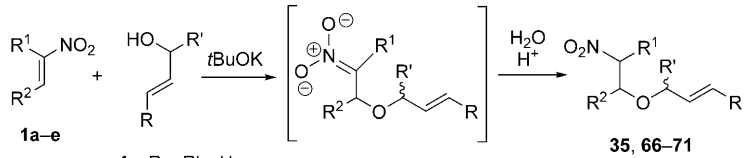
Starting from **68**, the corresponding α-alkoxy ketone **9b**[56] (which forms from an in situ Nef reaction) was also isolated in 5% yield.

To our delight, although yields were not optimized under these standard reaction conditions, we noticed that tetrahydrofuranylnitro alcohols **77–80**, which have three stereogenic centers, were isolated with total diastereoselectivity. This observation suggested that an intramolecular [3+2] cycloaddition of nitronic acids followed by an in situ oxidative ring cleavage of cycloadduct intermediate should account for the overall ionic transformation. Whereas alkyl or silyl nitronates have been successfully involved in intramolecular 1,3-dipolar cycloadditions with olefins to give useful isoxazoline and isoxazolidine intermediates,[18b,9a,c,57] it is of significant interest to notice that their nitronic acid precursors, easily obtained by protonation of nitronates, have never been reported to undergo similar behavior.[18c]

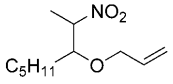
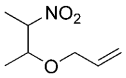
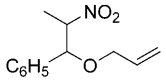
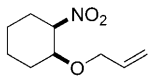
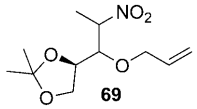
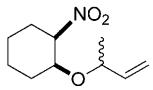
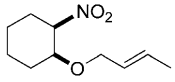
To confirm that nitro alcohols **77–80** undoubtedly result from 1,3-dipolar cycloaddition and therefore to enlarge the scope of this stereoselective carbocyclization that leads to functionalized tetrahydrofurans, we decided to study the reactivity of the corresponding silyl nitronates (Table 13).

β-Nitro allyl ethers **35**, **66–68**, **70** and **71** were first treated with Me_3SiCl (2 equiv) and DBU (1 equiv) in CH_2Cl_2 at 0 °C to smoothly afford *N*-(trimethylsilyloxy)isoxazolidines **84–87**, **89** and **90** in 62–86% yields (Table 13, entries 1, 2, 4, 6, 8, and 10). This [3+2] heter-

Table 12. Preparation of β-nitroallyl ethers **35**, **66–71**.[a]

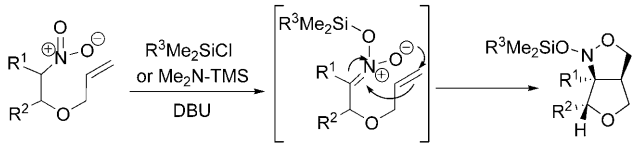


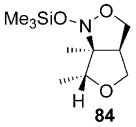
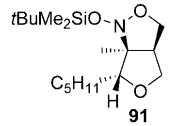
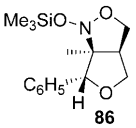
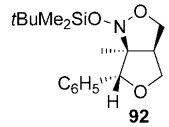
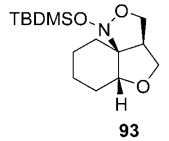
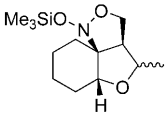
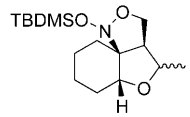
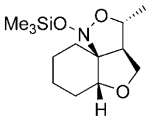
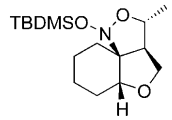
4a: R = R' = H
4b: R = H; R' = Me
4c: R = Me; R' = H

	1	Product	Yield [%] (*cis*/*trans* ratio)
1	**1b**	 **35**	66 (3:1)
2	**1a**	 **66**	85 (3.3:1)
3	**1c**	 **67**	67 (1:1)
4	**1e**	 **68**	100
5	**1g**	 **69**	81 (mixture of diastereomers)
6	**1e**	 **70**	67 (6:1)
7	**1e**	 **71**	100

[a] All reactions were run in the presence of *t*BuOK (1.0 equiv), 3 Å molecular sieves with 1.0 equiv of the corresponding alcohol in THF/*t*BuOH (30:1) at 0 °C for 4 h. The reactions were then quenched by adding 2 M HCl (1–1.5 equiv)

Table 13. Formation of isoxazolidines **84–95**.



Precursor	Entry	Isoxazolidine	Yield [%]	Entry	Isoxazolidine	Yield [%][c]
35	1	 **84**	72[a]	–	–	–
66	2 3	 **85**	62[a] 96[b]	12	 **91**	93
67	4 5	 **86**	82[a] 98[b]	13	 **92**	69
68	6 7	 **87**	84[a] 100[b]	14	 **93**	84
70	8 9	 **89**	77[a] 89[b]	15	 **94**	31
71	10 11	 **90**	86[a] 97[b]	16	 **95**	94

[a] TMSCl/DBU was employed as the silylating agent. [b] Me_2N-TMS/DBU. [c] TBDMSCl/DBU.

ocyclization is related to the well-documented intramolecular silylnitronate olefin cycloaddition (ISOC reaction).[9,18c,64] The tendency of silylnitronates to add smoothly in a 1,3 dipolar fashion to the alkene moiety was enhanced when DBU/Me_3SiNMe_2 was used as the silylating reagent, resulting in increased yields (89–100%) and purity obtained (Table 13, entries 3, 5, 7, 9, 11). Alternatively, the bi- and tricyclic analogues **91–95** could also be easily prepared in moderate to very good yields using the system TBDMSCl/DBU system (Table 13, entries 12–16).

Crude **84–87**, **89** and **90** were stable enough[58] to provide satisfactory spectroscopic data without purification, and **91–95** (Table 13, entries 12–16) could be easily purified by flash chromatography on silica gel.

Whereas isoxazolidines **89** and **94** were isolated as 1:1 epimeric mixtures (Table 13), compounds **84–87**, **90–93** and **95** were diastereomerically pure and their stereochemistries were assigned by NOESY experiments.

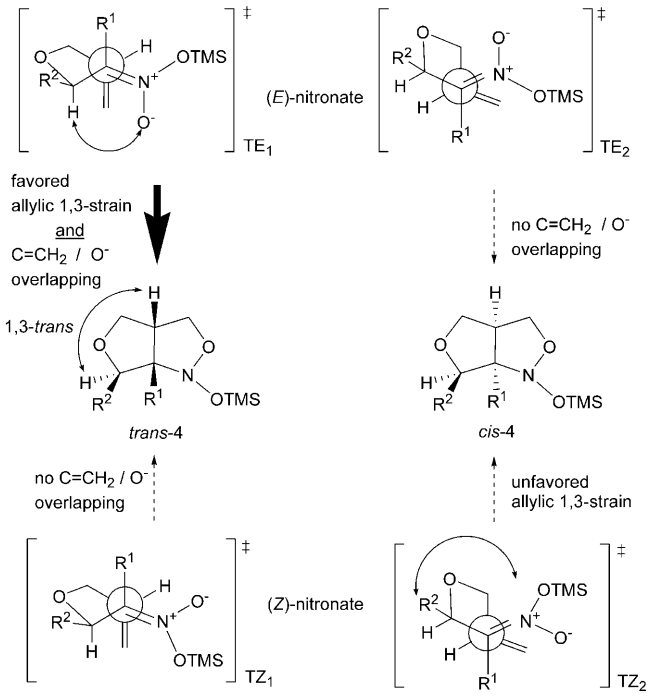
Both required stereochemistries of the intramolecular cycloaddition together with allylic 1,3-strain control account for the high selectivities observed. Isoxazolidines with 1,3-*trans* stereochemistries (related to hydrogen atoms) are formed through a proposed transition state TE_1 with minimum allylic strain and favored overlapping between $C{=}CH_2$ and O^- (Scheme 16).

TBAF-promoted desilylation of these oxazolidines led to a general and unprecedented oxidative cleavage, affording **77–82** (Table 14).

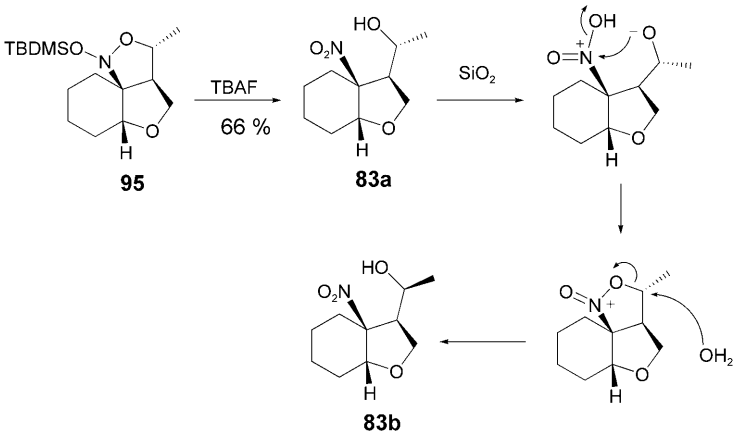
The transformation proved to be quite general regardless of the structure of the isoxazolidine, leading to acceptable isolated yields of the expected nitro alcohol. Note that bicyclic compound **83a** obtained in 66% yield from **1e** and crotonic alcohol **4c** can be totally epimerized at the carbon with the hydroxyl group to give **83b**, probably through an intramolecular transesterification during chromatography on silica gel (Scheme 17).

The crucial point in this unexpected transformation is the in situ oxidative ring cleavage of the isoxazolidine intermediate, which does not need the addition of any specific metallic or organometallic oxidant. From a mechanistic point of view, although oxidation of nitroso compounds into the corresponding nitro derivatives usually requires powerful oxidants,[59] nitroso compounds are likely to be intermediates in our transformation (Scheme 18). Indeed, we have been able to isolate and fully characterize nitroso intermediates **96–98** (10–23% yield). As complementary experimental evidence, we have shown that pure **96** underwent an uncatalyzed aerobic oxidation to furnish the expected hydroxymethyl tetrahydrofuran **80** in quantitative yield, the reaction being monitored by NMR.

Facial diastereoselectivity: To evaluate π-facial diastereoselection, we applied the overall sequence to nitroalkene **1g**, which has the chiral substituent attached to the β-carbon of the double bond. Michael adducts **69** were obtained in 81% yield by addition of allylic alcohol to chiral nitroalkene **1g**, and ^1H NMR spectroscopy indicated the presence of two major diastereomers in a ratio of 5:3 (Scheme 19). Indeed, due to the presence of the stereogenic center, the two faces of nitroalkene **1g** are diastereotopic, allowing the oxa-Mi-

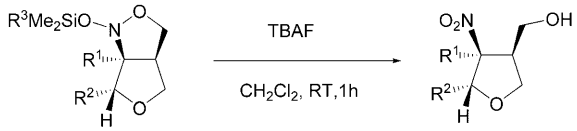


Scheme 16. Favored and unfavored (*E*) and (*Z*)-nitronate transition states leading to the observed *trans* stereochemistry of isoxazolidines.



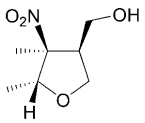
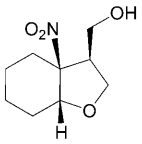
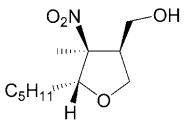
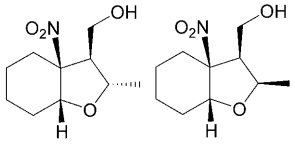
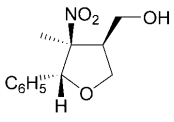
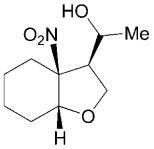
Scheme 17. Epimerization of **83a**.

Table 14. Oxidative cleavage of isoxazolidines.



84–87, **89**, **90**: R = Me
91–95: R = *t*Bu

77–82

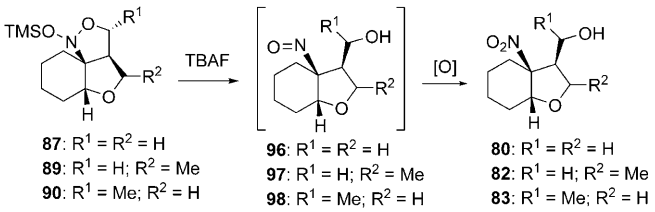
Entry	Isoxazolidine	Yield [%]	Entry	Isoxazolidine	Yield [%]
1	**84**	 **77** (50 %)	4	**87**, **93**	 **80** (61 %)
2	**85**, **91**	 **78** (48 %)	5	**89**, **94**	 **81** (32 %) **82** (13 %)
3	**86**, **92**	 **79** (40 %)	6	**90**, **95**	 **83a** (66 %)

chael addition to proceed either on the *si* or on the *re* face, leading to *anti* **69a** or *syn* **69b**. The *anti* stereochemistry of the major diastereomer has been assigned on the basis of Hassner's results, which are based on a correlation between the stereochemistry and ^{1}H NMR *J* values in a series of oxa-Michael adducts of allylic alcohol on nitroalkenes.[60] The observed *J* values between H4 and H7 are in the range of 8–10 Hz for an *anti* stereochemistry, whereas this value falls to 2–4 Hz for a *syn* stereochemistry.

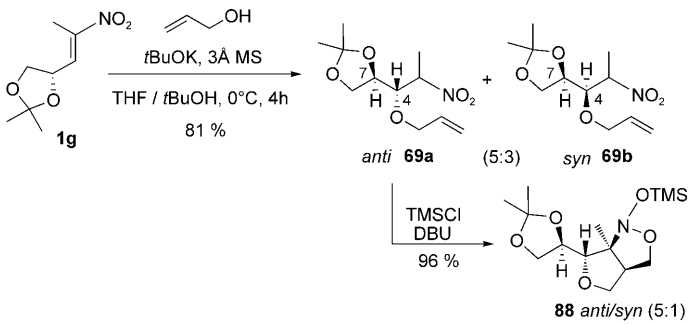
An enriched mixture of **69a**/**69b** (5:1) was isolated by chromatography and was converted into silyl nitronate. which spontaneously cyclized in situ to afford **88** as two diastereomers in the same ratio of 5:1. Although their configurations could not be assigned, the same hypothesis could indicate the relative stereochemistries of these diastereomers. Therefore, the 8.1 Hz *J* value observed for the major diastereomer **88** should be indicative of *anti* stereochemistry.

This observed stereochemical preference can be interpreted by invoking a Felkin—Anh-like approach[61] to provide an highly preferred conformation in which the γ-oxygen almost overlaps the "inside" position of the alkene bond. Then, the steric approach of alkoxide on nitroalkene **1g** affords the major *anti* Michael adduct, which upon reaction with TMSCl undergoes an ISOC reaction to provide *anti* isoxazolidine **88** (Scheme 20).

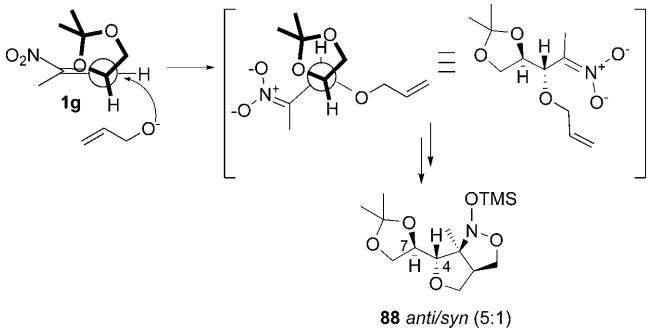
One-pot desilylation with tetrabutylammonium fluoride (TBAF) and concomitant N–O bond cleavage (which certainly proceeds through an alkoxynitroso intermediate) provides a diastereomeric mixture of tetrahydrofurans **99** in the



Scheme 18.

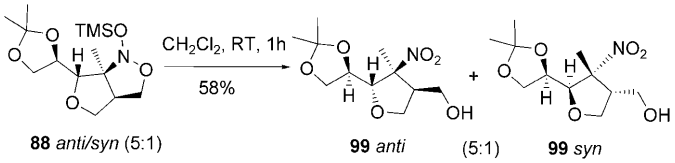


Scheme 19.



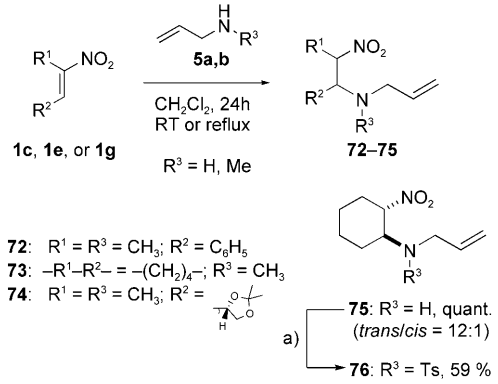
Scheme 20.

ratio of *anti*/*syn* 5:1 in 58% yield. Stereochemistries were assigned by ^{1}H NMR spectroscopy: coupling constants between Cβ-H and Cγ-H of 8.9 Hz for the *anti* isomer and of 1.5 Hz for the *syn* isomer were observed (Scheme 21).



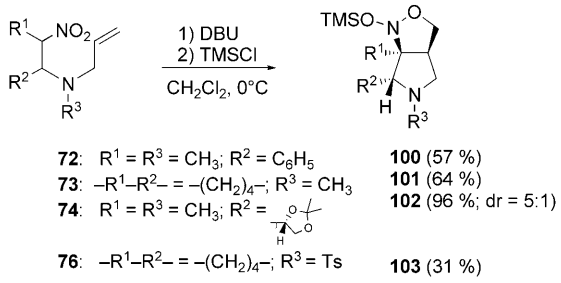
Scheme 21.

Stereoselective synthesis of functionalized pyrrolidines: The procedure developed for the preparation of functionalized tetrahydrofurans through an ISOC sequence was extended to the synthesis of pyrrolidines. Although the aza-Michael addition of a secondary amine to a conjugated nitroalkene suffers from a competitive retro-Michael reaction,[62] we prepared β-(allylamino)nitroalkanes **72–75** according to Sturgess' conditions,[63] by heating an excess of allylmethylamines **5a**,**b** at reflux in dichloromethane containing nitroalkene **1c**, **e**, or **g** (Scheme 22). Nitroalkene **1g** derived from (*R*)-2,3-isopropylidene glyceraldehyde was an efficient Michael acceptor, affording **74** in 53% yield as an inseparable mixture of diastereomers. β-Nitrotosylamine **76** was prepared in 59% yield by tosylation of adduct **75**.



Scheme 22. Preparation of β-nitrotosylamine **72–76.** **72**: 66% (*trans*/*cis* 4.2:1); **73**: 97%; **74**: 53% (mixture of isomers). Reaction conditions: a) TsCl, NEt_3, CH_2Cl_2, RT.

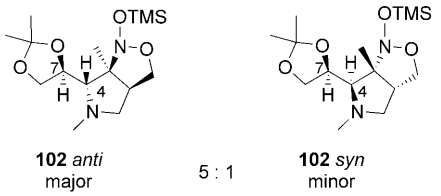
Unsaturated amino silyl nitronates have been shown to be efficient precursors to the highly selective ISOC sequence.[64] Indeed, the reaction of **72–74** and **76** in the presence of DBU/ trimethylsilyl chloride (TMSCl) in CH_2Cl_2 at 0°C afforded **100–103** in 31–96% yield (Scheme 23).



Scheme 23.

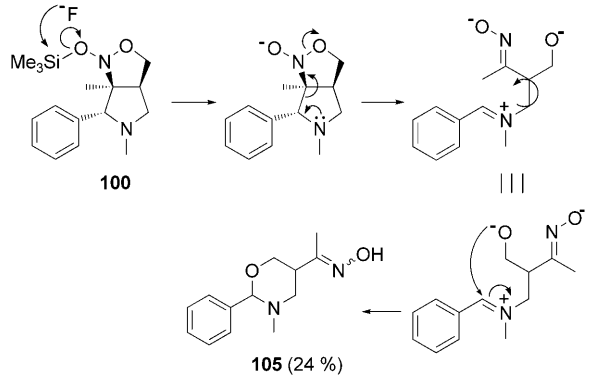
Trimethylsilyl isoxazolidine **102**, isolated in 96% yield, was obtained as a mixture of two diastereomers, in a ratio of 5:1 (determined by ^{1}H NMR spectroscopy). The coupling constant of 9.1 Hz between H7 and H4 suggests a facial differentiation in favor of the *anti* isomer (Scheme 24).

Surprisingly, TBAF-promoted desilylation of **100–102** was unproductive. Extensive degradation was observed, except in the case of compound **100**, which underwent an unexpected ring-opening/-closing rearrangement to give **105** in 24% yield. The donating effect of the *N*-methyl group combined with the presence of the phenyl substituent required for the



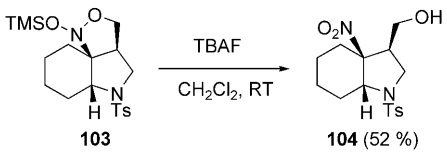
Scheme 24.

stabilization of an iminium intermediate seems to be crucial in this unexpected transformation (Scheme 25).



Scheme 25.

In contrast, the presence of the *N*-tosyl function in **103** allowed the expected in situ diastereoselective N–O oxidative bond cleavage to form **104** in 52% yield (Scheme 26).

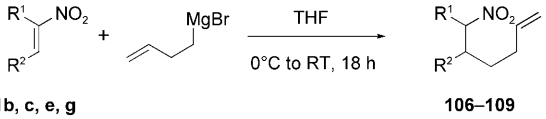


Scheme 26.

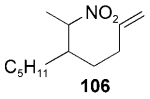
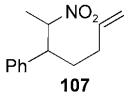
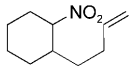
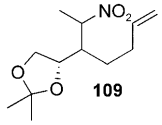
Synthesis of functionalized cyclopentanes: Our results obtained in the anionic [3+2] heterocyclization prompted us to investigate the addition of unsaturated carbon-centered nucleophiles to nitroolefins, to extend the overall methodology to the synthesis of carbocycles. The most widely used carbon nucleophiles in Michael additions are organometallics such as alkylstannanes,[65] organoaluminium etherates,[66] cuprates, or organolithiums,[67] organozincs,[68] or Grignard reagents.[18b,69] Grignard reagents are the most important of the Group IIA organometallics used as nucleophiles in conjugate additions, due to the high electron density on the carbon atom.

Provided the Michael adducts obtained incorporate a suitably located double bond, a predictable 1,3-dipolar cycloaddition with the nitronate moiety should generate a carbocycle. Indeed, recently, Dehaen and Hassner[58] and Yao et al.[69c,d] developed a highly stereoselective strategy for the construction of carbocycles based on Michael addition of Grignard reagents to aromatic α-unsubstituted nitroalkenes. Although initial reports of attempted Michael addition of Grignard reagents to monosubstituted aliphatic nitroalkenes were not encouraging,[69a,b,70] in our hands, addition of a 0.5 M solution of Grignard reagent (prepared from homoallylbromide) to nitroalkenes **1b**, **1c**, **1e**, or **1g** afforded Michael adducts **106–109** in 7–98% yields (Table 15). These products were always isolated as undetermined mixtures of diastereomers, which is not detrimental to the carbocyclization step.

Table 15. Condensation of homoallyl Grignard reagent to 1,2-disubstituted nitroalkenes.



1b, c, e, g — 106–109

Entry	Adducts	Yields [%][a]	dr[c]
1	 106	93	1.1:1
2	 107	71	1.8:1
3	 108	98	6:1
4	 109	7	
5		32[b]	n.d.[d]

[a] Grignard reagent (1,5 equiv) was added slowly to a solution of nitroalkene (1 equiv) in THF (0.2 M) under argon atmosphere at 0°C. [b] Addition of Grignard reagent (2.0 equiv) and $CeCl_3$ (2.0 equiv). [c] *cis* and *trans* isomers have not been assigned. [d] n.d. = not determined.

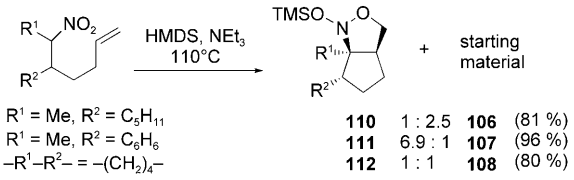
The low yield obtained in the case of **109** (Table 15, entry 4) was increased up to 32% by the addition of $CeCl_3$[71] to the reaction mixture (Table 15, entry 5).

In our case, α,β-disubstitution of nitroalkenes **1b**, **1c**, **1e**, and **1g** certainly accounts for the fair to good yields obtained in these Grignard Michael additions.

Unfortunately, neither the use of chlorotrimethylsilane nor *N*,*N*-dimethylsilylamine with DBU as the base gave isoxazolidine products and only starting materials were recovered. Addition of hexamethylphosphoramide (HMPA) as a stabilizing and solubilizing additive did not affect the course of the reaction. Heating the reaction at 60°C in toluene was also ineffective. Finally, the starting Michael adducts were recovered by treatment with Et_3N and TMSCl in the presence of HMPA as performed by Hassner et al.[7d] for the construction of isoxazolines from substrates unsubstituted at the α position of the nitro group. Undoubtedly, in our cases,

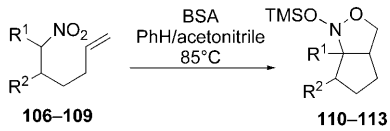
the α substitution of the nitro group prevents the [3+2] cycloaddition. Some years ago, Veselovsky and co-workers reported the synthesis of natural (+)-iridomyrmecin and its unnatural enantiomer according to an intramolecular [3+2]-dipolar cycloaddition of silylnitronate by using two different procedures.[72] In the first method, the reaction was conducted in hexamethyldisilazane (HMDS) and Et_3N at 110 °C, whereas in the second procedure *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and the unsaturated nitro compound were reacted at 85 °C in benzene/acetonitrile. Both procedures afforded the same ratio of *N*,*O*-silylated diastereomeric oxazolidines in 50 and 68 % yields, respectively.

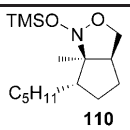
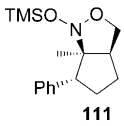
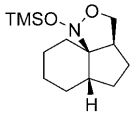
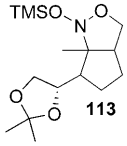
When Michael adducts **106–108** were treated with HMDS/Et_3N at 110 °C according to the first procedure, we observed the formation of **110–112** along with remaining starting materials (80–96 % overall yield; Scheme 27).



Scheme 27.

Table 16. Formation of bicyclic isoxazolidines.



Entry	Michael adduct	Isoxazolidine	Yield [%]
1	**106**	 **110**	69
2	**107**	 **111**	92
3	**108**	 **112**	99
4	**109**	 **113**	100 (1.2:1)[a]

[a] Diastereomeric ratio determined by ^1H NMR spectroscopy of the crude product.

The best yield was obtained for the transformation of **107**, but the conversion did not exceed 6.9:1. We therefore tested more drastic conditions, but heating **106** and **108** at reflux in HMDS resulted in degradation. The unsatisfactory yields obtained in these transformations prompted us to investigate the second procedure reported by Veselovsky et al.[72] and we were delighted to observe high yields for the conversion of Michael adducts **106–109** into the corresponding isoxazolidines **110–113** in 69–100 % yields (Table 16). Isoxazolidines **110–112** were isolated as pure diastereomers starting from a *cis*/*trans* isomer mixture of Michael adduct starting materials. Both the stereochemistry of intramolecular cycloaddition together with 1,3-allylic strain stereocontrol account for the total diastereoselectivity of the reaction, as we observed previously in the heterocyclic series. In the particular case of chiral nitroalkene **1g**, due to a low facial stereoselectivity, a 1.2:1 diastereomeric ratio was observed in the formation of **113** (Table 16, entry 4).

Desilylation of oxazolidines **110–113** was performed with TBAF in CH_2Cl_2 at room temperature and subsequent in situ oxidation allowed the formation of sensitive hydroxymethyl nitrocyclopentanes **114–117**, isolated as crude products in 69–100 % yield (Table 17). Purification of all of these compounds by flash chromatography on silica gel provided partial nitrous acid elimination and separable cyclopentenes **118–121** were always produced as minor components.

Compounds **114–116** were isolated as pure diastereomers, whereas **117** was obtained as a 1.2:1 diastereomeric mixture of *anti* and *syn* diastereomers, which were separable by chromatography on silica gel. Unfortunately, the spectroscopic data obtained for **117** were insufficient to assign the configuration of these diastereomers. However, according to an analogous pathway encountered in the oxygenated series, we can reasonably predict that the 1.2:1 facial diastereoselectivity of the Michael addition is in favor of the *anti* isomer (Scheme 28).

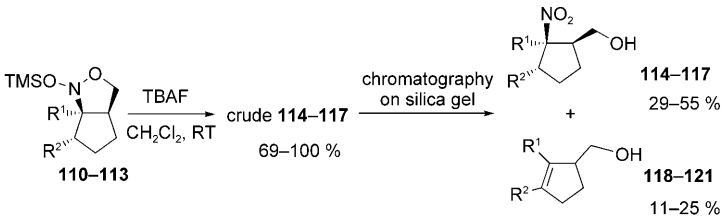
Conclusion

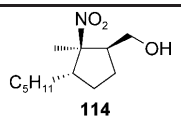
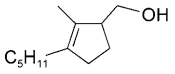
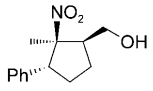
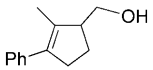
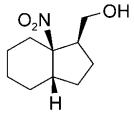
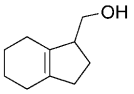
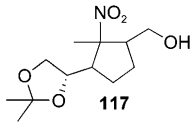
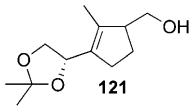
We have developed new Michael addition initiated anionic sequences that provide stereoselective preparations of a variety of highly functionalized carbo- and heterocyclic compounds starting from simple achiral nitroolefins.

Upon reaction with propargyl alcohols or amines, nitroalkenes acted as excellent Michael acceptors, with the option to undergo subsequent ring closure onto nonactivated alkynes, which lead to *exo*-methylene heterocycles for *t*BuOK-promoted domino reactions. According to a similar MIRC process, Triton B-promoted addition of propargyl malonate afforded methylene cyclopentanes.

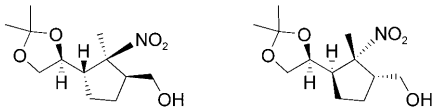
Finally, highly stereoselective intramolecular 1,3-dipolar cycloadditions to give isoxazolidines were initiated by conversion of unsaturated nitro compounds into silylnitronates. The unprecedented in situ oxidative ring cleavage of the isoxazolidines was the key step of this new sequential carbohydroxy cyclopentannulation, which resulted in the diastereoselective formation of five-membered-ring carbocycles and heterocycles with up to four consecutive stereogenic centers.

Table 17. Formation of hydroxymethyl five-membered rings.



Entry	Isoxazoline	Cyclopentane	Yield [%]	Cyclopentene	Yield [%]
1	**110**	 **114**	54	 **118**	15
2	**111**	 **115**	55	 **119**	11
3	**112**	 **116**	29	 **120**	15
4	**113**	 **117**	42 (1.2:1)[a]	 **121**	25

[a] Diastereomeric ratio determined by proton NMR of the crude product.



Scheme 28.

Experimental Section

Full experimental procedures and characterization data are given in the Supporting Information.

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[50] CCDC-161075, 161076, and 161077 contain the supporting crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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