Conjugate Additions of Nitroalkanes to Electron-Poor Alkenes: Recent Results

Roberto Ballini,* Giovanna Bosica, Dennis Fiorini, Alessandro Palmieri, and Marino Petrini*

Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino, 1, I-62032 Camerino, Italy

Received September 30, 2004

Contents

1. Introduction

Conjugate addition of carbon nucleophiles to electron-poor alkenes is of paramount importance among the large body of synthetic processes devoted to carbon−carbon bond formation.[1] The first nucleophilic systems used for this purpose, more than a century ago, were stabilized carbanions that can be prepared in polar solvents from malonates and β-dicarbonyl derivatives in relatively mild conditions using bases of moderate strength.[2] This process is usually referred to as Michael addition, and ever since the number of carbanionic species that have been used for conjugate additions has considerably increased to include various enolate systems and strong nucleophilic species such as organometallic reagents. The utilization of these carbon nucleophiles has allowed the accomplishment of many synthetic processes with an outstanding degree of selectivity even though the related experimental procedures are often elaborated and not amenable to scale-up at the industrial level.

* To whom correspondence should be addressed. Phone: +39 0737 402270. Fax: +39 0737 402297. E-mail: roberto.ballini@unicam.it; marino.petrini@unicam.it.

Conjugate additions using highly stabilized carbanions are still of interest since a growing number of these procedures can be carried out in environmentally benign solvents such as water and using catalytic amounts of the basic promoter. In addition, the achievement of diastereo- and enantioselective processes is no longer an exclusive domain of highly reactive carbanionic systems working in carefully controlled conditions[3] but can be nowadays conducted even at room temperature using easily available substrates and suitable base/solvent combinations.

Nitroalkanes are a valuable source of stabilized carbanions since the high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α-position (cf. pk_a $MeNO_2$ = 10).[4−8] Nitronate anions **2** that can be generated from nitroalkanes **1** using a wide range of bases act as carbon nucleophiles with common electrophiles including haloalkanes,[9] aldehydes,[10,11] and Michael acceptors,[1] leading to carbon−carbon bond formation (Scheme 1).

The obtained adducts **3**−**5** still retain the nitro function, and therefore, a suitable transformation of the nitro group very often follows the main addition process. Reduction of the nitro group to a primary amine **7** can be easily carried out providing a modification of the oxidation state of the nitrogen atom (Scheme 2).

Alternatively, the nitro group can be removed from the molecule using two distinct synthetic strategies. Replacement of the nitro group with hydrogen gives the corresponding denitrated product **8** so that the whole process (nucleophilic addition−denitration) closely resembles the addition of an organometallic reagent to an electrophilic substrate.[5,12] The presence at the β-position of an electron-withdrawing group allows a base-assisted elimination of nitrous acid with consequent introduction of a double bond in the molecular framework **9**. A further option is represented by conversion of the nitro group into a carbonyl group **10**, a transformation widely known as the Nef reaction, which ultimately leads to a reversal in the polarity of the neighboring carbon atom from nucleophilic to electrophilic.[13,14] This review is focused on the utilization of nitroalkanes as nucleophiles in conjugate additions with electron-poor alkenes and covers the new procedures and related applications appearing in the literature after 1990. Emphasis will be given to asymmetric additions carried out using optically active alkenes or with the aid of chiral catalysts.

10.1021/cr040602r CCC: $53.50
Published on Web 02/03/2005

Roberto Ballini obtained his Laurea degree in Chemistry from the University of Camerino-Italy. After experience at the ENI-ANIC (Petrolchemical Industry) in Ravenna, he began his academic career in 1975 as a Research Fellow at the University of Camerino. Then he became Assistant Professor in Organic Chemistry (1978), was promoted to Associate Professor (Organic Chemistry), and then was promoted to Full Professor of Organic Chemistry in 2000. His research interests include a huge area of the chemistry of aliphatic nitro compounds, with particular interest in a new generation of both carbon–carbon single bond and carbon–carbon double bond, cleavage of the carbon–carbon bond, and use of nitroalkanes as the key building blocks in the synthesis of important targets such as natural products featuring enhanced biologically activity. Other special fields of extensive interest also concern (i) different aspects of heterogeneous catalysis applied to fine chemicals and pharmaceuticals production, (ii) exploitation of solvent-free and multicomponent reactions, and (iii) use of aqueous medium in the organic reactions.

Giovanna Bosica was born in Atri, Italy, in 1967. She has been a researcher at the Department of Chemical Sciences of the University of Camerino, Faculty of Sciences and Technologies, since 1999. She received her Laurea in Chemistry *cum laude* in 1993 from the University of Camerino and 4 years later from the same institution her doctoral degree in Chemical Sciences working under the supervision of Professor R. Ballini. She spent a research period from April to September 1995 in the laboratories of Professor B. Zwanenburg (Department of Organic Chemistry, University of Nijmegen, The Netherlands) as an Erasmus Fellow. Her research interests concern the use of nitro compounds in new synthetic methodologies, synthesis of heterocycle compounds and biologically active natural products, heterogeneous catalysis, and green chemistry.

2. General Aspects of the Conjugate Addition of Nitroalkanes

Regioselectivity is an important feature that makes nitroalkanes particularly efficient in conjugate additions with α,β-unsaturated carbonyl derivatives. Indeed, while other activating groups such as phenylsulfonyl give variable amounts of 1,2-addition when

Dennis Fiorini was born in 1975 and received her degree in Chemistry from the University of Camerino, Italy, in 2000. During the same year she had a grant for research on the chemical reactivity of nitro compounds and worked under the supervision of Professor Roberto Ballini. She is currently a third-year Ph.D. student in the same research group and is involved in the study of nitroalkanes ability to form single and double carbon carbon bonds and their application in the synthesis of natural target products showing biological activity. Some aspects of her recent research concern heterogeneous catalysis, solventless reactions, and other procedures related to green chemistry.

Alessandro Palmieri, born in Jesi, Italy, began his studies in Chemistry in 1997 at the University of Camerino-Italy, where he received his Laurea degree *cum laude* in 2002 under the guidance of Professor E. Marcantoni. After a scholarship in the laboratory of Professor R. Ballini on the synthesis of natural products with important biological activities, in March 2004 he started his Ph.D. studies in the same lab. His research interests include natural products synthesis and application of aliphatic nitro compounds in the formation of new C–C and C═C bond.

reacted with enones or enals,[15] nitroalkanes afford exclusively 1,4-addition using α,β-unsaturated ketones and propenal as reactive acceptors.[16] Conversely, 3-substituted α,β-unsaturated aldehydes give predominantly 1,2-addition with secondary nitroalkanes and β-nitro alcohols.[17,18]

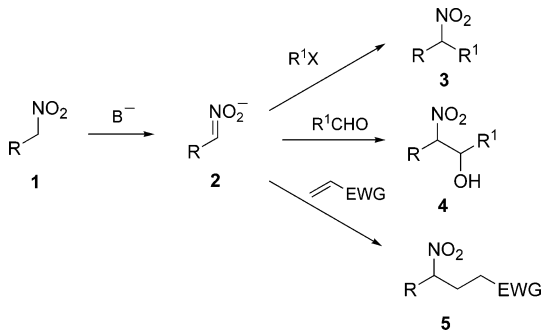
2.1. Multiple Additions

Undesired multiple additions on electron-poor alkenes are sometime possible on the initially formed products of conjugate addition. The amount of 1:2 adduct may be affected by the base/solvent combination used for the reaction (Scheme 3, Table 1).

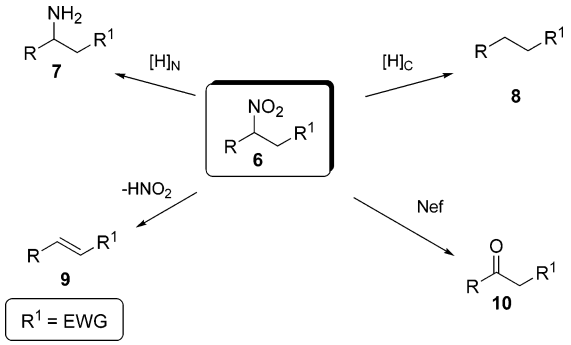
Reaction of nitro alcohol **1a** with phenylvinyl sulfone leads to an equimolar amount of mono and bis adducts, and this ratio is almost independent of the relative amounts of starting materials (Table 1,

Marino Petrini received his Laurea degree in Chemistry in 1980 (University of Camerino). In 1983 he became Research Associate in organic chemistry at the University of Camerino, and during the period 1987–88 he was a visiting scientist at the University of Montreal (Professor S. Hanessian). In 1992 he was appointed Associate Professor and then (2004) Full Professor in Organic Chemistry at the University of Camerino. His research interests mainly deal with the following topics: synthesis and reactivity of aliphatic and aromatic nitro compounds; reactivity of organometallic reagents toward carbon and nitrogen electrophiles; synthesis of natural products featuring enhanced biological activity; synthesis and reactivity of imino derivatives.

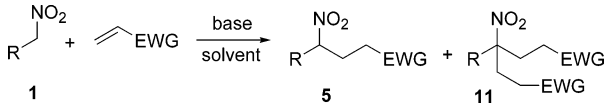
Scheme 1



Scheme 2



Scheme 3



entry 1).[19] The anion-solvating tendency exerted by the solvent and the electrophilicity of the alkene play a fundamental role in controlling the relative amounts of adducts obtained. Best results in the formation of 1:1 addition products are obtained exploiting moderate reaction rates, which for less reactive alkenes such as methylvinyl ketone (MVK)

Table 1. Multiple Additions in the Reaction of Nitroalkanes with Electron-Poor Alkenes

entry	1[a] R^1	EWG	base/solvent	yield (%) 5:11	ref.
1	 **1a**	SO_2Ph	TMG/CH_3CN	30:30	19
2	 **1b**	$COCH_3$	TMG/THF	68:5	20
			TMG/CH_3CN	43:20	
3	 **1b**	CN	TMG/THF	47:14	20
			TMG/CH_3CN	67:3	

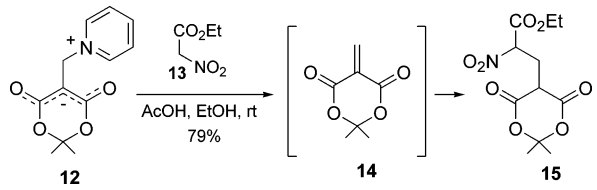
[a] R^1 = *tert*-butyldimethylsilyl.

involve utilization of low-solvating media such as THF (Table 1, entry 2). With more reactive acceptors such as acrylonitrile it is advisable to use a good solvating agent such as acetonitrile in order to lower the reactivity of the carbanionic species involved in the process (Table 1, entry 3).[20] Highly polar solvents such as DMSO, methanol, and water are able to facilitate the addition of nitroalkanes to MVK in neutral conditions.[21] Of these solvents, water is the one that minimizes formation of the 1:2 adduct using nitromethane and avoids any 1:2 adduct with nitroethane as reagent. A consistent rate acceleration is experienced adding glucose or saccharose to water in order to enhance the relative hydrophobic effect. Ruthenium complex $[Ru(O_2CH)(CO)_2(PPh)_3]_2$ is an effective catalyst for the conjugate addition of active methylene derivatives to enones.[22] However, utilization of ethyl nitroacetate as nucleophile only allows isolation of multiple addition products in the reaction with butenone. Finally, multiple additions are often experienced using nitromethane as nucleophile since the primary nitroalkane formed in the monoaddition process is still sterically unhindered enough to give a second attack on the electron-poor alkene.[23]

2.2. Basic Catalysts

A suitable choice of base/solvent combination is mandatory for successful conjugate addition of a nitroalkane to an electron-poor alkene. Weak bases such as trialkylamines and triphenylphosphine are able to promote the conjugate addition using α-nitro ketones as nucleophiles or when very reactive electron-deficient alkenes are employed as electrophilic substrates.[24,25] Other basic systems such as fluoride salts,[26] ammonium hydroxides,[27] alkaline metal hydroxides, and alkoxides[28,29] have also found some utilization in these additions. When poorly electrophilic alkenes such as vinyl sulfoxides or *β*-substituted enones and enoates are used as substrates, stronger bases such as DBU and TMG are needed in order to ensure an efficient reaction.[30–32] On the other hand, some Michael acceptors are so reactive that they do not require basic catalysis for the conjugate addition of activated nitroalkanes. Methylene Meldrum's acid **14** is generated in situ from zwitterionic compound **12** in the presence of AcOH and reacts with nitroester **13** in the same conditions to give the corresponding adduct **15** (Scheme 4).[33]

Scheme 4



Besides the procedures that work in homogeneous conditions, a number of methods using basic catalysts that operate in heterogeneous systems can be profitably employed to carry out a conjugate addition. Basic alumina is a formidable promoter of such nucleophilic additions that can be accomplished even in solventless conditions.[34] Alternatively, basic alumina can be doped with potassium fluoride to enhance the catalytic properties of the solid support.[35] Amberlyst A-21, a macroreticular ion-exchange resin, assists the conjugate addition of functionalized nitroalkanes to α,β-unsaturated derivatives; a simple filtration of the resin allows easy work up of the reaction mixture and rapid recovery of the crude products.[36] Fluorinated nitroalkanes such as 2,2,2-trifluoronitroethane and 3,3,3-trifluoro-2-nitropropane can eliminate HF in the presence of basic systems. However, using KF in 2-propanol or basic alumina in solventless conditions makes possible the use of these nitro derivatives in conjugate additions with several electron-deficient alkenes.[37,38]

3. New Basic Catalysts for the Conjugate Addition

During the past decade a number of different basic systems has been introduced to carry out the conjugate addition of nitroalkanes to electron-poor alkenes. Some of them are just a slight modification of previously known catalysts that are currently used for such additions; others are conceptually new reagents that improve the selectivity and efficiency of the reaction (Table 2).

However, it should be pointed out that the choice of a suitable basic catalyst for such conjugate additions is often strongly conditioned by the ready availability of the reagent. In fact, nonionic bases such as $P(RNCH_2CH_2)_3N$ (Verkade's bases)[50] work quite efficiently in a number of examples but their widespread utilization has been hampered by the fact that some of these reagents have become commercially available only recently. Activating techniques such as microwave or ultrasound irradiation may improve the efficiency of known catalysts, especially those working in heterogeneous and solventless conditions.[41,45,53,54] In this context, it is interesting to observe that almost all the newly introduced catalysts belong to the class of solid supports that in many instances present consistent advantages over soluble bases. For particularly reactive nitro derivatives, such as α-nitro ketones or esters, mild bases can be used and cyclic α-nitro ketones react even in water without the need of any added base.[59] The utilization of $Yb(OTf)_3$, a mild Lewis acid catalyst, represents one of the first examples of a conjugate addition of α-nitro ester in acidic conditions carried out in water.[57] In a related procedure a number of solid acidic catalysts has been checked for the solventless addition of α-nitro ketones to enones, revealing that silica gel 60 is the most effective promoter for this reaction.[58] A common feature of these acid-promoted additions is the long reaction times required (1−7 days). In principle, cathodic reduction of a nitroalkane by electrolysis would afford the corresponding nitronate anion that is amenable to conjugate addition with electrophilic alkenes; practically, this procedure often leads to decomposition of the nitro derivative employed. However, when the reaction is carried out in air-saturated acetonitrile, oxygen is reduced at the cathode, producing a superoxide anion that acts as an electrogenerated base toward the nitroalkane.[56] This procedure was formerly set up using ethyl nitroacetate but has been extended to the reaction of other nitroalkanes with levoglucosenone **16** (Scheme 5).[60,61]

Dienoic acid ester reacts with nitroalkanes giving the corresponding 1,6-adducts as a regioisomeric mixture of α,β- and β,γ-unsaturated compounds.[62] The yield of the adducts and the relative amount of regioisomers strongly depend from the nature of the base employed, as illustrated for the reaction of methyl 1,3-butadiene-1-carboxylate with nitroethane (Scheme 6, Table 3). The utilization of microwave irradiation allows a considerable shortening in the reaction time and improvement of the chemical yield of the process (Table 3, entry 5).

4. Diastereoselective Conjugate Additions

4.1. Intermolecular Additions

The newly formed carbon−carbon bond in a conjugate addition often involves the formation of stereogenic centers, and this has led to the development of stereoselective methods to prepare structurally defined compounds. The chiral information needed to obtain optically active derivatives can be contained in either the nucleophile or the alkene unit, but in any case, the best results in terms of diastereoselectivity are obtained using reagents bearing a chiral group in close proximity to the reaction center. In acyclic diastereoselection it is often advisable for cyclic frameworks containing heteroatoms linked to the alkene group to be present. The stereochemical bias offered by these heterocycles is extremely important for reactions that involve cyclic as well as open transition states. Enoate **21** bearing a chiral 1,3-dioxolane ring adds nitroalkanes in a diastereoselective fashion with enhanced preference for the *syn* stereoisomer **22** (Scheme 7, Table 4).[64,65]

The stereochemical outcome is little or not affected by the nature of the base employed (DBU or TBAF) but strongly depends on the stereochemistry of the double bond. Reaction of *Z*-**21** with most of nitroalkanes tested affords the corresponding adduct **22** with high diastereomeric excesses, while *E*-**21** gives poor results with the notable exception of nitromethane (Table 4, entry 1) and phenylnitromethane (Table 4, entries 11 and 12). Semiempirical calcula-

Table 2. Basic Catalysts for the Conjugate Addition of Nitroalkanes to Electron-Poor Alkenes

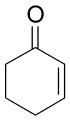
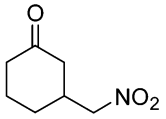
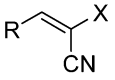
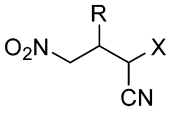
entry	nitro compound	alkene	conditions	product	yield %	ref
1	$MeNO_2$	CH_2=CHCOMe	HMS-R_3N, 4h, reflux	$O_2NCH_2CH_2CH_2COMe$	80	41
2			Al_2O_3-MW, 0.3h, 40°C		75	45
3			$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.15h, -63°C		78	50
4		Me_2C=CHCOMe	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.5h, rt	$O_2NCH_2Me_2CCH_2COMe$	99	50
5		PhCH=CHCOMe	0.1% NaOH, CTAB, 12h, rt	O_2NCH_2 (Ph)$CHCH_2COMe$	62	42
6			Al_2O_3-MW, 0.33h, 40°C		75	45
7			KF-natural phosphate, EtOH, 2h, rt		98	52
8		PhCH=CHCOPh	0.1% NaOH, CTAB, 8h, rt	O_2NCH_2 (Ph)$CHCH_2COPh$	62	42
9			Mg-Al-O-*t*-Bu hydrotalcite MeOH, 0.16h, rt		93	44
10			Al_2O_3-MW, 0.3h, 40°C		90	45
11		MeCH=$CHCO_2Et$	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.25h, -63°C	O_2NCH_2 (Me)$CHCH_2CO_2Et$	99	50
12			0.5M NaOH, 5h, rt		65	43
13			HMS-R_3N, 4h, reflux		90	41
14			$P(RNCH_2CH_2)_3N$, THF, 0.5h, rt		89	50
15		CH_2=$CHCO_2Et$	Mg-Al-O-*t*-Bu hydrotalcite MeOH, 0.75h, rt	$O_2NCH_2CH_2CH_2CO_2Et$	96	44
16			KF-natural phosphate, EtOH, 2h, rt		51	52
			Al_2O_3, microwave, 0.1h, 90°C			53 54
17		X = CO_2Me R = Ph			70	
18		X = CO_2Me R = 4-ClC_6H_4			72	
19		X = CO_2Me R = 2-BrC_6H_4			83	
20		X = CO_2Me R = 2-FC_6H_4			100	
21		X = CO_2Me R = 3-FC_6H_4			72	
22		X = CO_2Et R = *i*-Bu			70	
23		X = CN R = Ph			100	
24		X = $CONH_2$ R = Ph			68	
25	$EtNO_2$	CH_2=CHCOMe	Al_2O_3-MW, 0.25h, 40°C	$MeCH(NO_2)CH_2CH_2COMe$	72	45
26			Al_2O_3, 2h, 0°C		60	46

Table 2 (Continued)

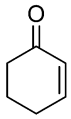
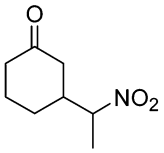
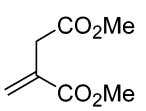
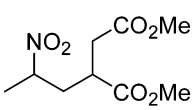
entry	nitro compound	alkene	conditions	product	yield %	ref
27			0.025M NaOH, CTACl,1h, rt		85	39
28			$Zr(KPO_4)_2$, 3h, rt		69	47
29			HMS-R_3N, 12h, reflux		94	41
30			3%[$RuH_2(PPh_3)_4$], CH_3CN, 10h, rt		83	48
31			KF-natural phosphate, EtOH, 2h, rt		55	52
32			Amberlyst A-27, 4h, rt		76	55
33			KG-60-NEt_2, 3h, rt		75	40
34		CH_2=CHCOEt	0.025M NaOH, CTACl, 2h, rt	MeCH(NO_2)CH_2CH_2COEt	76	39
35		MeCH=CHCOEt	Amberlyst A-27, 25h, rt	MeCH(NO_2)CH(Me)CH_2COEt	75	55
36		CH_2=CHCO*n*-Pr	0.025M NaOH, CTACl, 2h, rt	MeCH(NO_2)CH_2CH_2CO*n*-Pr	68	39
37		CH_2=CHCHO	Al_2O_3, 2h, -10°C	MeCH(NO_2)CH_2CH_2CHO	60	46
38			Mg-Al-O-*t*-Bu hydrotalcite MeOH, 0.5h, rt		98	44
39			0.025M NaOH, CTACl,2h, rt		72	39
40			Amberlyst A-27, 20h, rt		93	55
41		CH_2=CHCO$_2$Me	CTAOH, 1h, rt	MeCH(NO_2)$CH_2CH_2CO_2$Me	78	63
42		CH_2=CHCO$_2$Et	KF-natural phosphate, EtOH, 2h, rt	MeCH(NO_2)$CH_2CH_2CO_2$Et	98	52
43			HMS-R_3N, 1.5h, reflux		88	41
44		MeCH=CHCO$_2$Me	K_2CO_3, Aliquat® 336, ultrasound, 2h, rt	MeCH(NO_2)CH(Me)CH_2CO_2Me	90	51
45			0.025M NaOH, CTACl,15h, rt		60	39
46		MeCH=CHCO$_2$Bn	K_2CO_3, Aliquat® 336, ultrasound, 0.5h, rt	MeCH(NO_2)CH(Me)CH_2CO_2Bn	94	51
47		PhCH=CHCO$_2$Me	K_2CO_3, Aliquat® 336, ultrasound, 0.5h, rt	MeCH(NO_2)CH(Ph)CH_2CO_2Me	93	51
48			K_2CO_3, Aliquat® 336, ultrasound, 0.5h, rt		73	51
49		CH_2=CHCH=CHCO$_2$Et	Amberlyst A-27, microwave, 0.1h, 70°C	MeCH(NO_2)CH_2CH=CHCH_2CO_2Et	70	62

Table 2 (Continued)

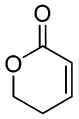
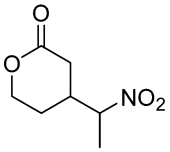
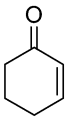
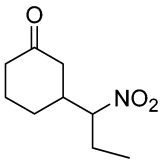
entry	nitro compound	alkene	conditions	product	yield %	ref
50			Amberlyst A-27, 20h, rt		55	55
51		$MeO_2CCH{=}CHCO_2Me$	K_2CO_3, Aliquat® 336, ultrasound, 0.3h, rt	$MeCH(NO_2)CH(CO_2Me)CH_2CO_2Me$	80	51
52		$CH_2{=}CHSO_2Ph$	KG-60-NEt_2, 25h, rt	$MeCH(NO_2)CH_2CH_2SO_2Ph$	81	40
53	*n*-$PrNO_2$	$CH_2{=}CHCOMe$	HMS-R_3N,1.5h, reflux	$CH_3CH_2CH(NO_2)CH_2CH_2COMe$	95	41
54			$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.15h, -63°C		81	50
55			0.025M NaOH, CTACl, 1h, rt		78	39
56			Amberlyst A-27, 7h, rt		90	55
57			KG-60-NEt_2, 25h, rt		80	40
58		$CH_2{=}CHCOEt$	0.025M NaOH, CTACl,1h, rt	$CH_3CH_2CH(NO_2)CH_2CH_2COEt$	64	39
59			Amberlyst A-27, 5h, rt		77	55
60			CTAOH, 1h, rt		83	63
61		$CH_2{=}CHCO$*n*-Pr	0.025M NaOH, CTACl,1h, rt	$CH_3CH_2CH(NO_2)CH_2CH_2CO$*n*-Pr	82	39
62			Amberlyst A-27, 4h, rt		85	55
63			CTAOH, 1h, rt		80	63
64		$CH_2{=}CHCO_2Me$	KG-60-NEt_2, 26h, rt	$CH_3CH_2CH(NO_2)CH_2CH_2CO_2Me$	61	40
65		$CH_2{=}CHCH{=}CHCO_2Et$	Amberlyst A-27, microwave, 0.1h, 70°C	$MeCH_2CH(NO_2)CH_2CH{=}CHCH_2CO_2Et$	62	62
66		$MeCH{=}CHCO_2Bn$	K_2CO_3, Aliquat® 336, ultrasound, 15h, rt	$CH_3CH_2CH(NO_2)CH(Me)CH_2CO_2Bn$	94	51
67			$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.25h, -63°C		71	50
68	9.5 equiv. nitro compound	$MeO_2CCH{=}CHCO_2Me$	K_2CO_3, Aliquat® 336, ultrasound, 0.05h, rt	$EtCH(NO_2)CH(CO_2Me)CH_2CO_2Me$	62	51
79	*i*-$PrNO_2$	$CH_2{=}CHCOMe$	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.25h, rt	$Me_2C(NO_2)CH_2CH_2COMe$	99	50
70			0.025M NaOH, CTACl, 1h, rt		75	39
71			Amberlyst A-27, 25h, rt		75	55
72			KG-60-NEt_2, 5h, rt		82	40

Table 2 (Continued)

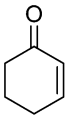
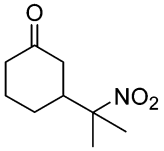
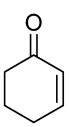
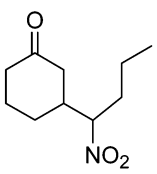
entry	nitro compound	alkene	conditions	product	yield %	ref
73		CH_2=CHCOEt	0.025M NaOH, CTACl, 1h, rt	$Me_2C(NO_2)CH_2CH_2COEt$	71	39
74			Amberlyst A-27, 15h, rt		70	55
75		CH_2=CHCO*n*-Pr	0.025M NaOH, CTACl, 2h, rt	$Me_2C(NO_2)CH_2CH_2CO$*n*-Pr	77	39
76			Amberlyst A-27, 13h, rt		85	55
77		PhCH=CHCOPh	KF-natural phosphate, EtOH, 4h, rt	$Me_2C(NO_2)$ CH(Ph)CH_2COPh	98	52
78		Me_2C=CHCOMe	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.33h, rt	$Me_2C(NO_2)CMe_2CH_2COMe$	99	50
79		CH_2=CHCO$_2$Me	Amberlyst A-27, 4h, rt	$Me_2C(NO_2)CH_2CH_2CO_2Me$	80	55
80		CH_2=CHCO$_2$Et	Ar_3P-polymer supported, heptane-MeOH, 24h, rt	$Me_2C(NO_2)CH_2CH_2CO_2Et$	71	49
81			KF-natural phosphate, EtOH, 4h, rt		91	52
82		MeO_2CCH=CHCO$_2$Me	K_2CO_3, Aliquat® 336, ultrasound, 0.3h, rt	$Me_2C(NO_2)CH(CO_2Me)CH_2CO_2Me$	80	51
83			$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.25h, rt		99	50
84		CH_2=CHSO$_2$Ph	Amberlyst A-27, 20h, rt	$Me_2C(NO_2)CH_2CH_2SO_2Ph$	80	55
85			KG-60-NEt_2, 25h, rt		90	40
86		CH_2=CHCN	Amberlyst A-27, 4h, rt	$Me_2C(NO_2)CH_2CH_2CN$	75	55
87	*n*-BuNO_2	CH_2=CHCOMe	0.025M NaOH, CTACl, 1h, rt	*n*-PrCH$(NO_2)CH_2CH_2$COMe	83	39
88			KG-60-NEt_2, 5h, rt		85	40
89		CH_2=CHCOEt	0.025M NaOH, CTACl, 1h, rt	*n*-PrCH$(NO_2)CH_2CH_2$COEt	70	39
90			CTAOH, 1h, rt		75	63
91			KG-60-NEt_2, 6h, rt		83	40
92		CH_2=CHCO*n*-Pr	0.025M NaOH, CTACl, 2h, rt	*n*-PrCH$(NO_2)CH_2CH_2CO$*n*-Pr	68	39
93			Amberlyst A-27, 7h, rt		86	55
94			0.025M NaOH, CTACl, 2h, rt		79	39

Table 2 (Continued)

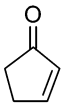
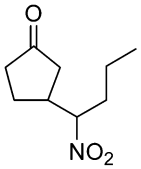
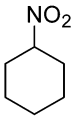
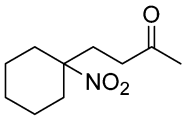
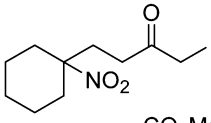
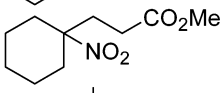
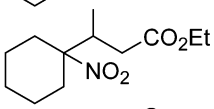
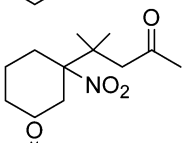
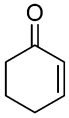
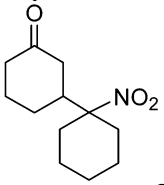
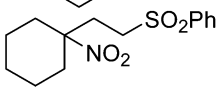
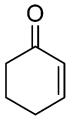
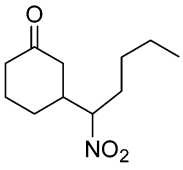
entry	nitro compound	alkene	conditions	product	yield %	ref
95			0.025M NaOH, CTACl, 2h, rt		93	39
96		CH_2=$CHCO_2Me$	KG-60-NEt_2, 30h, rt	*n*-$PrCH(NO_2)CH_2CH_2CO_2Me$	62	40
97			CTAOH, 1h, rt		77	63
98		CH_2=$CHCH$=$CHCO_2Et$	Amberlyst A-27, microwave, 0.1h, 70°C	*n*-$PrCH(NO_2)CH_2CH$=$CHCH_2CO_2Et$	55	62
99		CH_2=$CHSO_2Ph$	KG-60-NEt_2, 28h, rt	*n*-$PrCH(NO_2)CH_2CH_2SO_2Ph$	65	40
100		CH_2=CHCN	KG-60-NEt_2, 15h, rt	*n*-$PrCH(NO_2)CH_2CH_2CN$	58	40
101		CH_2=CHCOMe	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 0.25h, rt		93	50
102			0.025M NaOH, CTACl, 2h, rt		72	39
103		CH_2=CHCOEt	Amberlyst A-27, 8h, rt		65	55
104		CH_2=$CHCO_2Me$	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 4h, rt		100	50
105		MeCH=$CHCO_2Et$	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 4h, rt		100	50
106		Me_2C=CHCOMe	$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 1h, rt		95	50
107			$P(RNCH_2CH_2)_3N$, Et(Me)CHCN, 1h, rt		99	50
108		CH_2=$CHSO_2Ph$	Amberlyst A-27, 10h, rt		70	55
109	*n*-$C_5H_{11}NO_2$	CH_2=CHCOMe	CTAOH, 1h, rt	*n*-$C_4H_9CH(NO_2)CH_2CH_2COMe$	74	63
110		CH_2=CHCOEt	Amberlyst A-27, 5h, rt	*n*-$C_4H_9CH(NO_2)CH_2CH_2COEt$	84	55
111			CTAOH, 2h, rt		90	63
112		CH_2=$CHCO_2Me$	Amberlyst A-27, 9h, rt	*n*-$C_4H_9CH(NO_2)CH_2CH_2CO_2Me$	75	55
113		CH_2=$CHSO_2Ph$	Amberlyst A-27, 15h, rt	*n*-$C_4H_9CH(NO_2)CH_2CH_2SO_2Ph$	65	55

Table 2 (Continued)

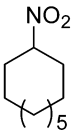
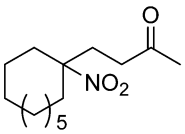
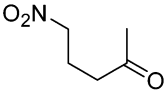
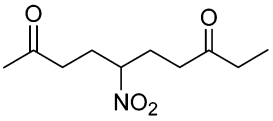
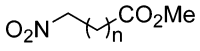
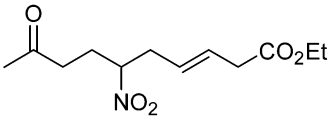
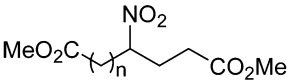
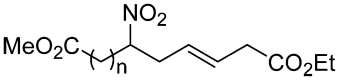
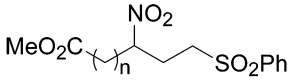
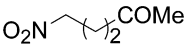
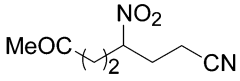
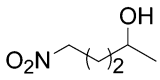
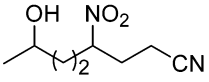
entry	nitro compound	alkene	conditions	product	yield %	ref
114		CH_2=CHCN	Amberlyst A-27, 10h, rt	*n*-$C_4H_9CH(NO_2)CH_2CH_2CN$	60	55
115	*n*-$C_6H_{13}NO_2$	CH_2=CHCOMe	CTAOH, 1h, rt	*n*-$C_5H_{11}CH(NO_2)CH_2CH_2COMe$	77	63
116		CH_2=$CHCO_2Me$	CTAOH, 1h, rt	*n*-$C_5H_{11}CH(NO_2)CH_2CH_2CO_2Me$	87	63
117		CH_2=CHCN	KG-60-NEt_2, 16h, rt	*n*-$C_5H_{11}CH(NO_2)CH_2CH_2CN$	56	40
118			CTAOH, 1h, rt		70	63
119		CH_2=$CHSO_2Ph$	CTAOH, 1h, rt	*n*-$C_5H_{11}CH(NO_2)CH_2CH_2SO_2Ph$	70	63
120		CH_2=CHCH=$CHCO_2Et$	Amberlyst A-27, microwave, 0.1h, 70°C	*n*$C_5H_{11}CH(NO_2)CH_2CH$=$CHCH_2CO_2Et$	68	62
121		CH_2=CHCOMe	0.025M NaOH, CTACl, 2h, rt		74	39
122	$PhCH_2CH_2NO_2$	CH_2=CHCH=$CHCO_2Et$	Amberlyst A-27, microwave, 0.1h, 70°C	$PhCH_2CH(NO_2)CH_2CH$=$CHCH_2CO_2Et$	60	62
123		CH_2=CHCOEt	Amberlyst A-27, 4h, rt		75	55
124		CH_2=CHCH=$CHCO_2Et$	Amberlyst A-27, microwave, 0.1h, 70°C		55	62
125	n=2	CH_2=$CHCO_2Me$	Amberlyst A-27, 7h, rt		85	55
126		CH_2=CHCH=$CHCO_2Et$	Amberlyst A-27, microwave, 0.1h, 70°C		75	62
127	n=4	CH_2=$CHSO_2Ph$	CTAOH, 2h, rt		73	63
128		CH$_2$=CHCN	CTAOH, 1h, rt		65	63
129		CH$_2$=CHCN	CTAOH, 1h, rt		72	63
	$RCOCH(R^1)NO_2$					
130	R = Ph R^1= H	CH_2=CHCOMe	Silica gel 60, 22h, rt	$PhCOCH(NO_2)CH_2CH_2COMe$	87	58
131		CH_2=CHCO*n*-Pr	Silica gel 60, 23h, rt	$PhCOCH(NO_2)CH_2CH_2CO$*n*-Pr	86	58
132	R = Me R^1= Et	CH_2=CHCOMe	Silica gel 60, 100h, rt	$MeCOC(Et)(NO_2)CH_2CH_2COMe$	74	58

Table 2 (Continued)

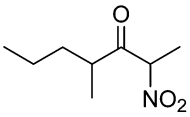
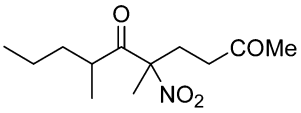
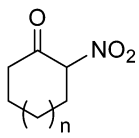
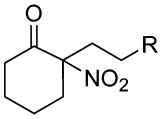
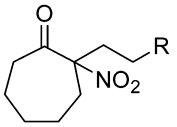
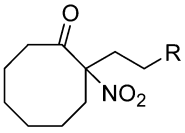
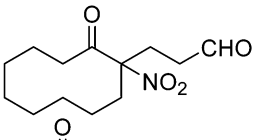
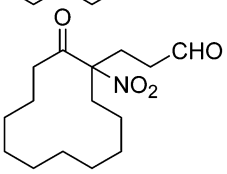
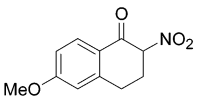
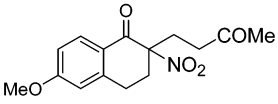
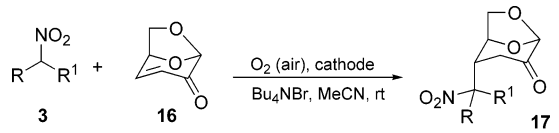
entry	nitro compound	alkene	conditions	product	yield %	ref
133		CH_2=CHCO*n*-Pr	Silica gel 60, 23h, rt	MeCOC(Et)$(NO_2)CH_2CH_2$CO*n*-Pr	65	58
134	R = *i*-Pr R^1= *n*-Pr	CH_2=CHCOEt	Silica gel 60, 20h, rt	*i*-PrCOC(*n*-Pr)$(NO_2)CH_2CH_2$COEt	72	58
135	R = *n*-C_5H_{11} R^1= Me	CH_2=CHCOEt	Silica gel 60, 50h, rt	*n*-C_5H_{11}COC(Me)$(NO_2)CH_2CH_2$COEt	77	58
136	R = $Ph(CH_2)_2$ R^1= Et	CH_2=CHCOEt	Silica gel 60, 120h, rt	$Ph(CH_2)_2$COC(Et)$(NO_2)CH_2CH_2$COEt	76	58
137	R = *c*-C_6H_{11} R^1= *n*-Bu	CH_2=CHCOMe	Silica gel 60, 100h, rt	*c*-C_6H_{11}COC(*n*-Bu)$NO_2CH_2CH_2$COMe	86	58
138		CH_2=CHCOMe	Silica gel 60, 35h, rt		88	58
	$MeO_2CCH(R)NO_2$					
139	R = H	CH_2=CHCOMe	Yb$(OTf)_3$, H_2O, rt	$MeO_2CCH(NO_2)CH_2CH_2$COMe	98	57
140	R = CH_2=$CHCH_2$	CH_2=CHCOMe	Yb$(OTf)_3$, H_2O, rt	$MeO_2CC(R)(NO_2)CH_2CH_2$COMe	96	57
	$EtO_2CCH(R)NO_2$					
141	R = H	CH_2=$CHCO_2$Et	Bu_4NClO_4, THF, electrolysis, rt	$EtO_2CCH(NO_2)CH_2CH_2CO_2$Et	82	56
142		CH_2=CHCN	Bu_4NBr, MeCN, electrolysis, rt	$EtO_2CCH(NO_2)CH_2CH_2$CN	85	56
143	R = Me	CH_2=$CHCO_2$Et	Bu_4NBr, MeCN, electrolysis, rt	$EtO_2CC(Me)(NO_2)CH_2CH_2CO_2$Et	85	56
144		CH_2=CHCHO	Yb$(OTf)_3$, H_2O, 3d, rt	$EtO_2CC(Me)(NO_2)CH_2CH_2$CHO	98	57
145		CH_2=CHCOMe	Yb$(OTf)_3$, H_2O, 3d, rt	$EtO_2CC(Me)(NO_2)CH_2CH_2$COMe	99	57
146		CH_2=CHCOEt	Yb$(OTf)_3$, H_2O, 3d, rt	$EtO_2CC(Me)(NO_2)CH_2CH_2$COEt	98	57
147		CH_2=CHCOPh	Yb$(OTf)_3$, H_2O, 3d, rt	$EtO_2CC(Me)(NO_2)CH_2CH_2$COPh	98	57
148		CH_2=C(Me)CHO	Yb$(OTf)_3$, H_2O, 7d, rt	$EtO_2CC(Me)(NO_2)CH_2CH(Me)$CHO	72	57
149	R = Et	CH_2=CHCOMe	Yb$(OTf)_3$, H_2O, rt	$EtO_2CC(Et)(NO_2)CH_2CH_2$COMe	99	57
150	R = CH_2=$CHCH_2$	CH_2=CHCOMe	Yb$(OTf)_3$, H_2O, rt	$EtO_2CC(R)(NO_2)CH_2CH_2$COMe	99	57
151	R = $CH_2CH_2CO_2$Et	CH_2=$CHCO_2$Et	Bu_4NBr, MeCN, electrolysis, rt	$EtO_2CC(R)(NO_2)CH_2CH_2CO_2$Et	84	56
152	R = CH_2CH_2CN	CH_2=CHCN	Bu_4NBr, MeCN, electrolysis, rt	$EtO_2CC(R)(NO_2)CH_2CH_2$CN	82	56
	 n = 1					
153		CH_2=CHCOMe	Silica gel 60, 44h, rt	R = COMe	75	58

Table 2 (Continued)

entry	nitro compound	alkene	conditions	product	yield %	ref
154		CH_2=CHCHO	H_2O, 14h, rt	R = CHO	98	59
	n = 2					
155		CH_2=CHCOEt	Silica gel 60, 90h, rt	R =COEt	82	58
156		CH_2=CHCHO	H_2O, 8h, rt	R = CHO	85	59
157			0.07 M K_2CO_3, 0.5h, rt		55	59
158		CH_2=CHCOMe	H_2O, 4d, rt	R =COMe	93	59
159			0.07 M K_2CO_3, 0.5h, rt		92	59
160		CH_2=CHCOEt	H_2O, 4d, rt	R =COEt	85	59
161			0.07 M K_2CO_3, 1h, rt		80	59
162		CH_2=CHCO$_2$Me	0.07 M K_2CO_3, 0.75h, rt	R =CO$_2$Me	30	59
163		CH_2=CHCN	0.07 M K_2CO_3, CTAB (10%), 3h, rt	R =CN	60	59
164		CH_2=CHSO$_2$Ph	0.07 M K_2CO_3, 0.75h, rt	R =SO$_2$Ph	77	59
	n = 3					
165		CH_2=CHCHO	H_2O, 14h, rt	R = CHO	99	59
166		CH_2=CHCOMe	H_2O, 4d, rt	R =COMe	98	59
167	n = 5	CH_2=CHCHO	H_2O, 37h, rt		99	59
168	n = 7	CH_2=CHCHO	H_2O, CTAB (10%), 5d, rt		99	59
169		CH_2=CHCOMe	Silica gel 60, 70h, rt		88	58

tions (AM1) demonstrate that **RZ** is the most stable rotamer for enoate *Z*-**21,** but two nearly isoenergetic rotamers **RE$_1$** and **RE$_2$** are possible for compound *E*-**21** (Scheme 7). Thus, attack from the *re* side of *Z*-**21** through rotamer **RZ** produces *syn*-**22** with high diastereoselectivity, while the same reaction of *E*-**21** can occur on the *re* (**RE$_1$**) or *si* (**RE$_2$**) side without a great difference in the energy of the corresponding transition states. The stereoselectivity at the carbon atom bearing the nitro group is usually rather poor, and this result is probably due to the low enantiofacial discrimination exerted by the enoate on the nitronate anion. A *syn*-selective reaction is also observed in the reaction of nitromethane with 2-sub-

Scheme 5



3	R	R^1	yield 17 %
a	H	CO_2Et	85
b	Me	CO_2Et	89
c	CO_2Et	$CH_2CH_2CO_2Et$	82
d	Me	Me	93
e	$-(CH_2)_5-$		96
f	CO_2Et	$CH_2{=}CHCH_2$	89
g	H	NO_2	88

Scheme 6

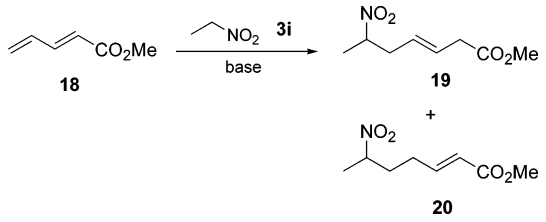
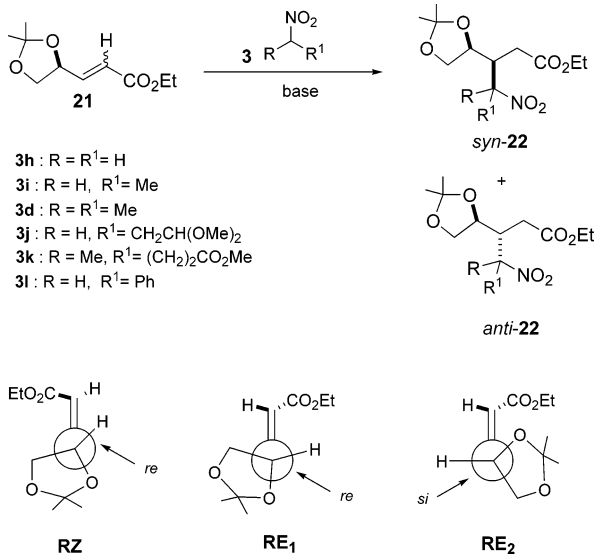


Table 3. Regioselective Addition of Nitroethane to Diene 18

entry	catalyst	solvent	reaction time	yield (%) **19:20**
1	DBU	MeCN	2 days	6:40
2	NaOH 0.1M	H_2O	2 days	40:6
3	TMG	THF	12 h	35:7
4	Amberlyst A-27	neat	2 days	38:4
5	Amberlyst A-27 microwave 500W	neat	7 min	85:10

Scheme 7



stituted analogues of enoate **22** and other related systems.[66]

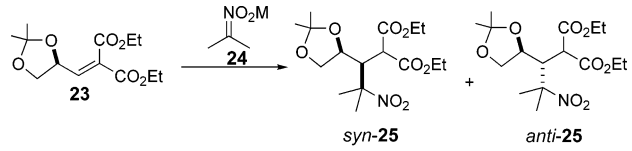
A diastereofacial preference for the *re* side of alkylidenemalonate **23** is also observed in the reaction with metal nitronate **24** (Scheme 8).[67] The addition is fully diastereoselective in THF at room temperature, but after 1 h in DMSO at room temperature the *syn*/*anti* ratio is much lower (77:23). After 48 h the diastereoselectivity in DMSO increases

Table 4. Diastereoselective Addidion of Nitro Compounds 3 to Chiral Enoate 21[a]

entry	**21**	**3**	base	product yield (%)	*syn*:*anti* d.e.(%)
1	Z/E	**3h**	TBAF	71	90
2	Z	**3h**	DBU	70	80
3	Z	**3i**	DBU	70	90
4	E	**3i**	DBU	65	50
5	Z	**3d**	TBAF	80	94
6	E	**3d**	DBU	68	0
7	Z	**3j**	TBAF	77	94
8	E	**3j**	TBAF	70	34
9	Z	**3k**	TBAF	80	100
10	E	**3k**	DBU	70	6
11	Z	**3l**	DBU	67	80
12	E	**3l**	DBU	65	80

[a] DBU/MeCN and TBAF/THF at room temperature are used.

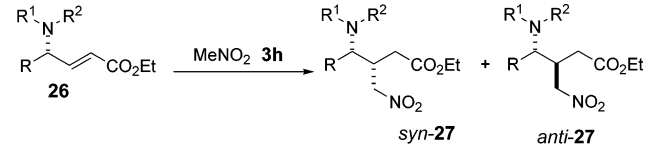
Scheme 8



M	solvent/T°C	time h	yield(%)	*syn*:*anti*
Li	THF, rt	0.5	71	100:0
Li	DMSO, rt	1	96	77:23
Li	DMSO, rt	48	-	98:2
K	DMSO, rt	1	77	90:10

to 98/2, and this definitely suggests thermodynamic control in the formation of the more stable *syn* diastereomer. This assumption is also corroborated by the diastereomeric ratio (*syn*/*anti* = 90:10) obtained using potassium nitronate **24** in DMSO at room temperature. Conjugate addition of nitromethane to optically active *N*-protected vinylogous amino esters affords the corresponding nitro derivatives in good yield and fair diastereoselectivity.[68] The *syn*/*anti* ratio of the resulting adducts is always around 80:20 regardless of the nature of the substituents at the nitrogen atom or in the alkenyl chain (Scheme 9). The basic system used to promote the

Scheme 9

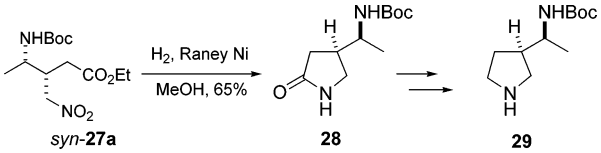


Entry	R	R^1	R^2	base	yield(%)	*syn*:*anti*
a	Me	H	Boc	DBN	95	84:16
b	Me	Bn	Bn	DBU	78	81:19
c	*i*-Pr	H	Boc	DBU	98	86:14
d	CH_2Ph	H	Boc	DBU	83	80:20

addition can affect the chemical yield of the process but has a narrow impact on the diastereoselection. Interestingly, the conjugate addition of cyanide ion on the same substrates occurs with no stereoselectivity under different reaction conditions.

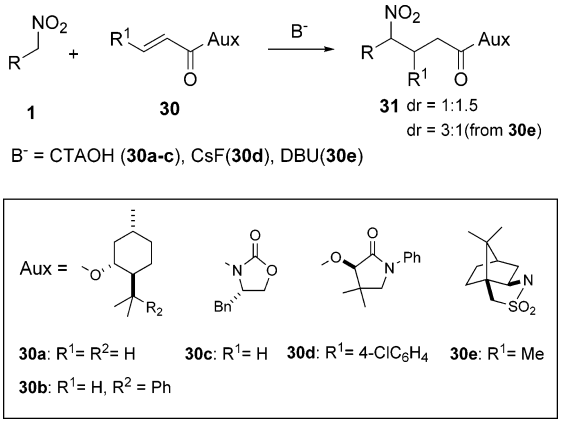
This study was originally designed as a synthetic approach to the preparation of chiral 3-aminoalkyl pyrrolidine residue in fluoroquinolone antibiotics (Scheme 10).

Scheme 10



The introduction of a chiral auxiliary in the acylic group of enoate systems does not usually produce a significant diastereoselection in the conjugate addition of nitroalkanes (Scheme 11). Nitromethane as

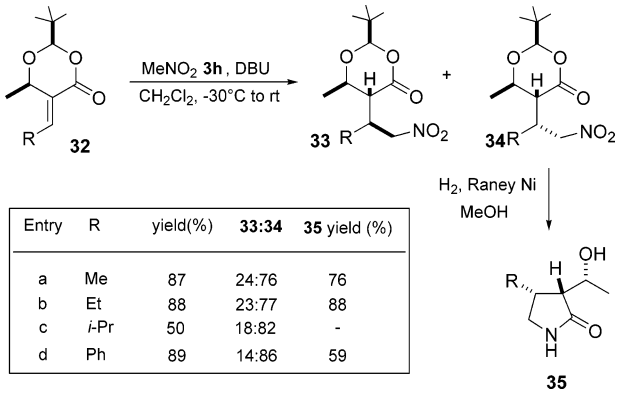
Scheme 11



well as functionalized secondary nitro derivatives add to enoates **30a**−**d** with a diastereomeric ratio of 1:1.5, a value that is not useful for whatever synthetic application.[69,70] Crotonylbornane sultam **30e** gives better results in the conjugate addition with nitromethane, affording a 3:1 diastereomeric couple of products in which stereoisomer 3*S* predominates.[195]

Chiral 5-alkenyl-1,3-dioxan-4-ones react with nitromethane at the exocyclic double bond in the presence of DBU with respectable diastereoselectivity. Attack of the nitronate anion occurs selectively at the *re* face, providing adduct **34** as the major stereoisomer (Scheme 12).[71]

Scheme 12

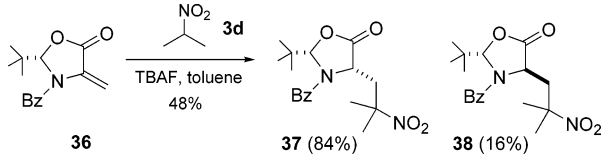


Entry	R	yield(%)	**33**:**34**	**35** yield (%)
a	Me	87	24:76	76
b	Et	88	23:77	88
c	*i*-Pr	50	18:82	-
d	Ph	89	14:86	59

After chromatographic separation, compounds **34** are reduced and the resulting amino derivatives spontaneously cyclize to afford optically active hydroxypyrrolidinones **35.**

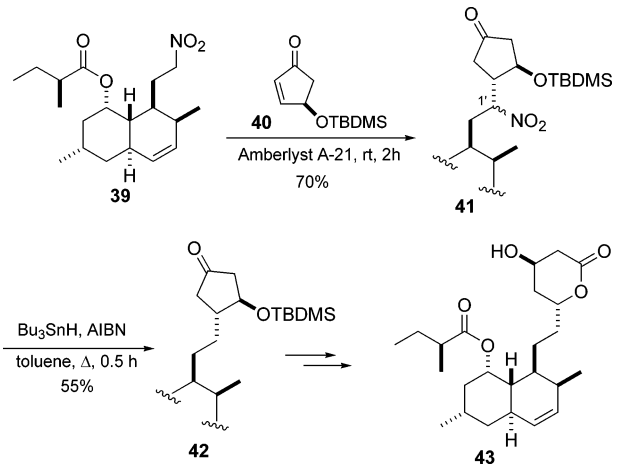
In a related procedure reaction of 2-nitropropane with chiral dehydroalanine **36** in the presence of TBAF gives a diastereomeric mixture of adducts with predominance of the *syn* isomer (Scheme 13).[72]

Scheme 13



As previously observed, stereocontrol at the carbon atom bearing the nitro group is hard to achieve, probably because of the consistent acidity of the related hydrogen that in basic conditions allows a thermodynamic equilibration between the epimers.[73] This drawback becomes ineffective when the nitro group needs to be eliminated from the molecular framework by means of a reductive denitration. A key step toward the total synthesis of the hypocholesterolemic agent dihydromevinolin **43** involves the conjugate addition of nitroalkane **39** to chiral cyclopentenone **40** (Scheme 14).[74] This addition is best effected

Scheme 14

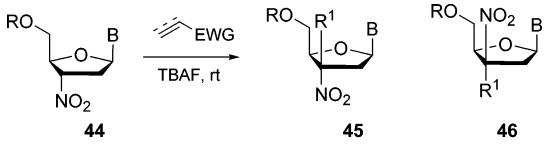


using Amberlyst A-21 in solventless conditions, and although it is highly diastereoselective in the formation of the carbon−carbon bond, product **41** is obtained as a mixture (3:2) of epimers at C-1′. However, radical-induced denitration of compound **41** affords derivative **42** as a single diastereomer that is converted into dihydromevinolin **43** after few synthetic manipulations.

Interesting stereoselectivities can be obtained when the nitro group is linked to a chiral cyclic structure that is able to produce consistent diastereofacial discrimination. Nitrothymidines **44** react with electron-poor alkenes from the less hindered α-face of the pentofuranose ring, giving compound **46** as major product (Scheme 15).[75]

Enantiomerically pure 5-glyco-4-nitrocyclohex-1-ene **47** reacts with various Michael acceptors with high diastereoselectivity, giving adducts **48** in which a *trans* relationship between the sugar chain and the added group is observed (Scheme 16).[76,77] The absence

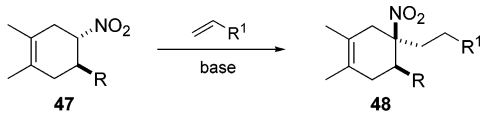
Scheme 15



B =

R^1	**45+46** yield(%)	**45:46**
CH_2CH_2CN	83	0:1
$CH{=}CHCO_2Et$	87	1:4
CH_2CH_2COMe	71	1:7

Scheme 16



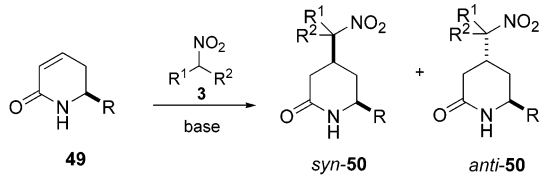
R =

R^1	base	**48** yield(%)
CO_2Me	DBU	60
COMe	TMG	82
CN	TMG	60
CHO	TMG	44

of enolizable hydrogen atoms near the nitro group probably avoids any epimerization of the addition products **48**.

Generally, because of the steric constraint present in rigid structures, chiral cycloalkenones are expected to react in conjugate additions with a consistent degree of diastereoselectivity. Chiral piperidinone **49** reacts with nitromethane with modest *syn* or no diastereoselectivity depending on the nature of the substituent present in the ring (Scheme 17).[78] Con-

Scheme 17

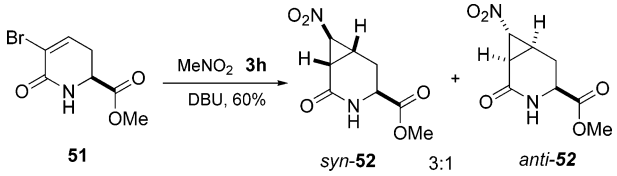


R	R^1	R^2	base	yield(%)	*syn:anti*
TBDPSO	H	H	DBU	85	1:1
TBDPSO	Me	Me	DBU	85	0:1
CO_2Me	H	H	DBU	85	3:1
CO_2Me	Me	Me	DBU	85	0:1
CO_2Me	$-(CH_2)_4-$		K_2CO_3	65	0:1
CO_2Me	$-(CH_2)_5-$		K_2CO_3	65	0:1

versely, secondary nitroalkanes add to piperidinone **49** with complete stereocontrol, giving exclusively the *anti* diastereomer.

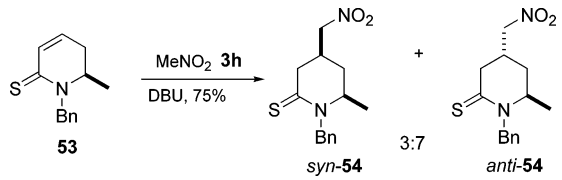
Reaction of 3-bromopiperidinone **51** with nitromethane takes place through a tandem conjugate addition−nucleophilic substitution by the corresponding nitronate anion, giving bicyclo derivatives **52**. Once again, the *syn*/*anti* ratio of the obtained compound **52** is 3:1 with a nitro group that adopts an *exo*-orientation with respect to the piperidinone ring (Scheme 18).

Scheme 18



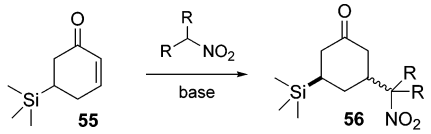
The *syn* diastereoselectivity observed in the conjugate addition of compounds **49** and **51** with nitromethane would be somewhat associated with the presence of a polar group in the 6-position that drives the nucleophilic attack from the same side of the substituent. Indeed, a structurally related thiolactam **53** bearing a 6-methyl group reacts with nitromethane in the presence of DBU with a *syn*/*anti* ratio of 3:7 (Scheme 19).[79]

Scheme 19



The steric hindrance of the incoming nitroalkane seems to have a deleterious effect on the diastereoselectivity displayed by 5-substituted cyclohexenones. Conjugate addition of 2-nitropropane on 5-trimethylsilyl cyclohexenone **55** occurs with high yield but unsatisfactory diastereoselectivity (Scheme 20).[80] On

Scheme 20

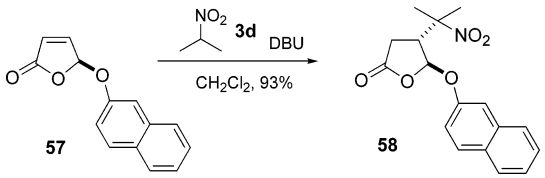


R	base	**56** yield(%)	*syn:anti*
Me, Me	DBU	80	2:3
Me, Me	KF/Al_2O_3	93	1:1
H, H	KF/Al_2O_3	80	1:20

the contrary, with the same substrate nitromethane gives excellent diastereoselectivity.

Chiral γ-aryloxybutenolide **57** prepared through dynamic kinetic asymmetric transformation of racemic acyloxybutenolides reacts with 2-nitropropane with high diastereoselectivity to give compound **58** as a single stereoisomer of *anti* configuration (Scheme 21).[81] In this context, butenolide **57** acts as a "chiral

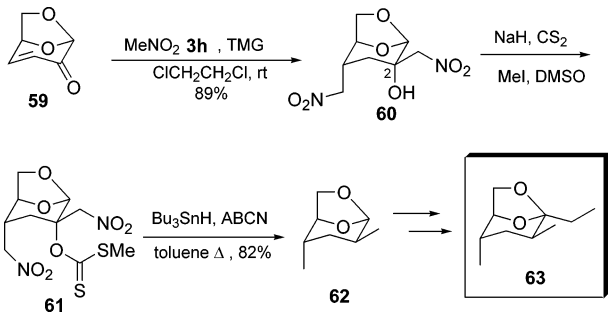
Scheme 21



aldehyde" equivalent for a number of synthetic transformations including conjugate additions and cycloadditions.

Rigid bicyclic structures are very effective in diastereoselective reactions as demonstrated by the reaction of levoglucosenone **59** with nitromethane **3h** (Scheme 22).[82]

Scheme 22

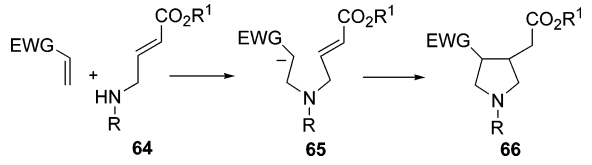


Using a large excess of nitromethane in the presence of TMG ensures a conjugate addition as well as a nitroaldol reaction on compound **59,** leading to adduct **60** in good yield and diastereoselectivity (10:1 at C-2). Deoxygenation and removal of the nitro functions can be made in a single step via thioxantate **61** using Bu_3SnH in a radical process. The obtained compound **62** is an advanced intermediate to the enantioselective synthesis of aggregation pheromone (−)-*δ*-multistriatin **63**.[83]

4.2. Intramolecular Additions

A viable strategy for the construction of pyrrolidine ring systems lies in the tandem conjugate additions of an amino derivative bearing a Michael acceptor **64** with an electron-poor olefin (Scheme 23). The

Scheme 23

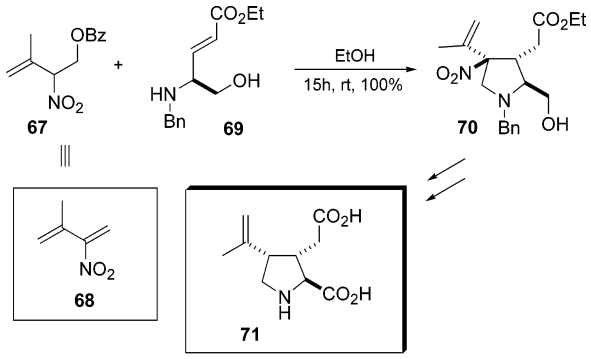


intermediate anion **65** undergoes to a further conjugate addition to give the final pyrrolidine **66**.

Nitroalkenes are ideal candidates as electrophilic olefins for this procedure, but sometimes their preparation and storage is made difficult by their instability and propensity to undergo polymerization processes. However, these reactive alkenes can be readily prepared *in situ* by an elimination reaction from a suitable *β*-acyloxy nitro derivative. This approach has been successfully applied to the enantioselective synthesis of neuroexcitatory amino acid (−)-α-kainic acid (Scheme 24).[84,85]

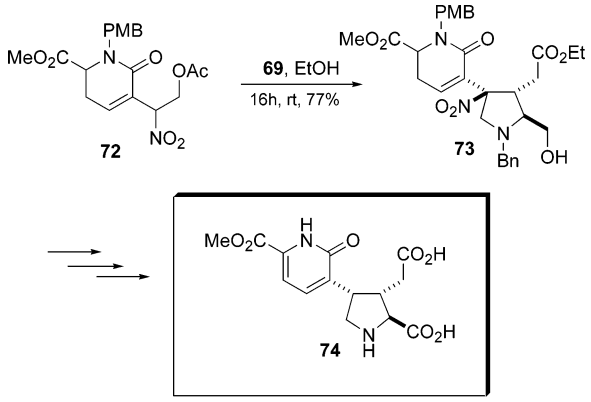
Benzyloxy nitroalkene **67** can be considered as a synthetic equivalent of nitrodiene **68** and by reaction with hydroxyester **69** in ethanol affords quantitatively pyrrolidine **70** as a sole diastereomer. The formation of nitrodiene **68** is presumably promoted by the amino group of **69**. Simple functional group transformations allow the total synthesis of (−)-α-kainic acid **71**. Using the same approach a structurally related compound, the neurotoxin acromelic acid A **74**, can be prepared using the nitroalkene pre-

Scheme 24



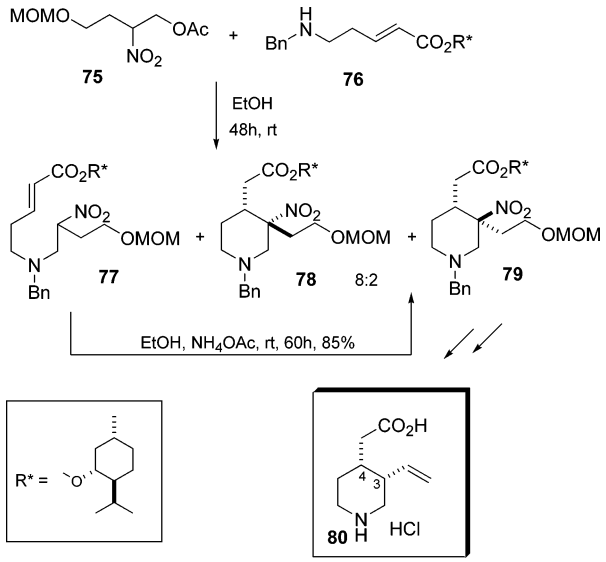
cursor **72** in the reaction with amino ester **69** (Scheme 25).[86]

Scheme 25



Ring closure to six-membered ring derivatives using the tandem conjugate addition previously described presents some remarkable differences compared to the assembling of five-membered rings. A synthetic plan to the enantioselective synthesis of (−)-meroquinene **80** requires the sequential inter- and intramolecular conjugate addition of chiral amino ester **76** to the nitroalkene precursor **75** (Scheme 26).[87] Surprisingly, only a partial cyclization of intermediate **77** is evidenced after 48 h at room temperature, and the diastereoselectivity of the obtained

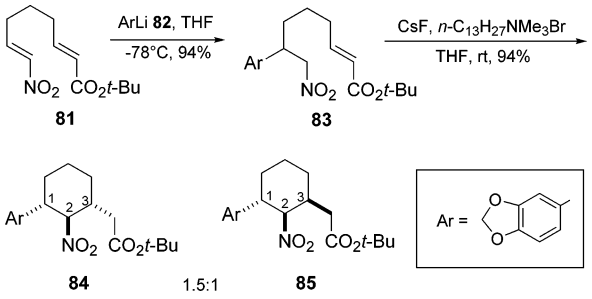
Scheme 26



piperidine ester is 8:2 in favor of diastereomer **78**. Open-chain adduct **77** can be forced to cyclize in the presence of ammonium acetate to give compounds **78** and **79** with the same diastereomeric ratio (8:2) previously obtained. The modest level of diastereoselectivity observed does not affect the efficiency of the process since removal of the nitro group in a subsequent step provides the correct stereochemistry at C-3; anyways, the chiral induction exerted by the L-menthyl group at C-4 during the cyclization step is noteworthy.

The difficulties associated with intramolecular six-membered ring closures by conjugate additions are also evident in a related procedure devoted to the synthesis of lycorane alkaloids. Addition of aryllithium **82** to the nitroalkene portion of **81** is completely chemoselective, but the intermediate nitronate anion does not add to the enoate group in a tandem process, so that compound **83** is obtained in high yield (Scheme 27).[88] Cyclization of **83** realized

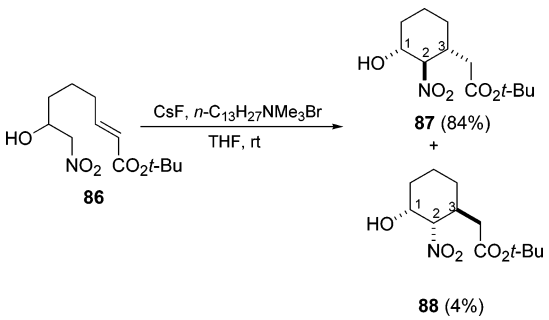
Scheme 27



using CsF is poorly diastereoselective at C-3 but displays a complete *trans* relationship between C-1 and C-2.

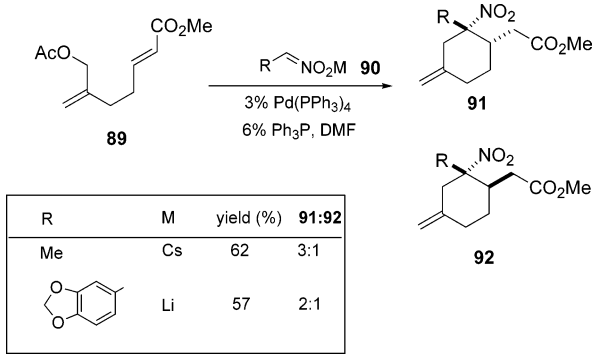
Better diastereoselections can be obtained starting from nitro alcohol **86** that in the same conditions (CsF, R_4NBr) produces a diastereomeric couple in which compound **87** strongly predominates (Scheme 28).[89]

Scheme 28



Allylic alkylation of nitro compounds catalyzed by Pd(0) can be associated with conjugate additions in order to prepare cyclohexane derivatives. Allyl acetate **89** reacts with metal nitronates **90** in the presence of $Pd(PPh_3)_4$ to give an open-chain homoallylic nitro derivative that as soon as it is formed cyclizes by means of a conjugate addition, leading to the diastereomeric couple of nitrocyclohexanes **91** and **92** (Scheme 29).[90−92] As for most of the six-membered ring cyclizations of this type, the diastereoselectivity

Scheme 29



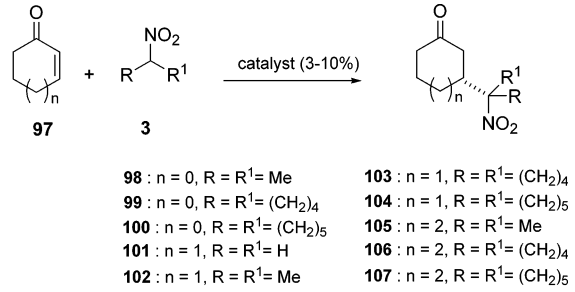
R	M	yield (%)	91:92
Me	Cs	62	3:1
	Li	57	2:1

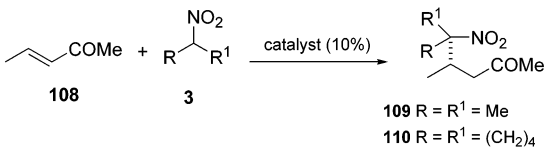
observed is quite modest but the yields of the overall transformation are respectable.

5. Asymmetric Conjugate Additions Promoted by Chiral Catalysis

The utilization of chiral catalysts to produce enantiofacial discrimination in the conjugate addition of a nucleophile to electron-poor alkenes represents the optimum choice in terms of efficiency and stereoselectivity.[93−96] Conjugate additions of nitroalkanes to enones mediated by chiral catalysts have been known since at least the mid-1970s, but only in the past decade has their development provided important results in terms of efficiency and enantiomeric excess. Since these additions are prevalently base-promoted reactions, chiral amino derivatives have been among the first compounds to be used for this purpose. Ni(II) complexes of proline derivatives are able to catalyze the conjugate addition of nitromethane to chalcone, but the chemical yields are rather modest and the enantiomeric excesses (ee's) of the resulting adduct never exceed 61%.[97] Proline **93** and rubidium salt derivatives **94**−**96** are effective catalysts for the conjugate addition of various nitroalkanes **3** to enones **97** (Scheme 30).[98−100]

Scheme 30





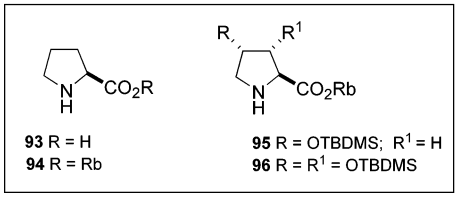


Table 5. Enantioselective Conjugate Addition of Nitroalkanes to Enones 97 and 108 Mediated by Proline Derivatives 93−96 as Chiral Catalysts

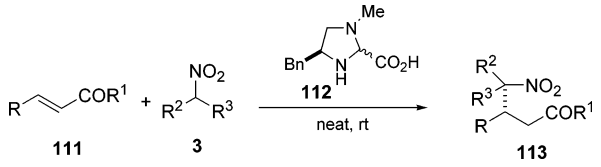
entry	enone	nitroalkane	catalyst[a]	product	yield (%)	ee % (config)	ref
1	2-cyclopentenone	*i*-$PrNO_2$	**93**	**98**	66	75(*R*)	101
2		*c*-$C_5H_9NO_2$	**93**	**99**	66	76(*R*)	101
3		*c*-$C_6H_{11}NO_2$	**93**	**100**	62	76(*R*)	101
4	2-cyclohexenone	$MeNO_2$	**93**	**101**	61	45(*R*)	101
5			**94**	**101**	55	45	98
6		*i*-$PrNO_2$	**93**	**102**	88	93*R*)	101
7			**94**	**102**	81	59(*R*)	98
8		*c*-$C_5H_9NO_2$	**93**	**103**	68	93(*R*)	101
9		*c*-$C_6H_{11}NO_2$	**93**	**104**	73	93(*R*)	101
10	2-cycloheptenone	*i*-$PrNO_2$	**93**	**105**	61	86(*R*)	101
11			**94**	**105**	79	73(*R*)	98
12			**95**	**105**	70	72(*R*)	98
13			**96**	**105**	73	76(*R*)	98
14		*c*-$C_5H_9NO_2$	**93**	**106**	71	87(*R*)	101
15			**94**	**106**	74	67	98
16		*c*-$C_6H_{11}NO_2$	**93**	**107**	49	89(*R*)	101
17			**94**	**107**	84	84	98
18	MeCH=CHCOMe	*i*-$PrNO_2$	**94**	**109**	74	68(*S*)	98
19		*c*-$C_5H_9NO_2$	**94**	**110**	64	59	98

[a] Proline **93** is used with 1 equiv of *trans*-2,5-dimethylpiperazine as an additive.

The ee's of the resulting adducts **98**−**107**, **109**, and **110** are quite modest (45−84%) and little affected by the substitution of the pyrrolidine ring (Table 5). (*S*)-Proline derivatives react efficiently with cycloalkenones, showing a marked preference for attack at the *si* face, leading to formation of the *R* enantiomer. A consistent improvement in these additions can be obtained using (*S*)-proline with a basic additive used in an equivalent amount.[101] Amino derivatives are particularly effective for this purpose, and *trans*-2,5-dimethylpiperazine is the most efficient catalyst.[102] Conjugate addition of primary nitroalkanes such as nitroethane or 1-nitro-4-butene to cycloalkenones occurs with poor diastereoselectivity and modest enantioselectivity of the obtained diastereomers.

Heterocyclic derivatives featured by the imidazolidine ring are also useful catalysts for conjugate addition of nitroalkanes to enones.[103] The level of enantioselection displayed by these catalysts is similar to that obtained with proline derivatives, and better results are usually obtained using secondary nitroalkanes (Scheme 31, Table 6).

Scheme 31



A possible explanation for the enantiofacial preference observed in this reaction would take into account the formation of an iminium ion intermediate between the enone and the catalyst (Scheme 32). The benzyl group in the catalyst in the more stable conformation assumed by the iminium ion would shield the *re* face of the reactive double bond, thus allowing a preferential attack of the nitroalkane from the *si* side of the molecule.

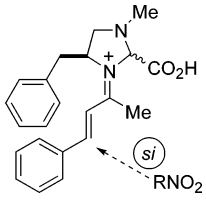
2-Nitrocycloalkanones **114** add to methyl vinyl ketone **115** in the presence of cinchonine **116,** which belongs to the class of *Cinchona* alkaloids.[104] The

Table 6. Enantioselective Conjugate Addition of Nitroalkanes to Enones Mediated by Imidazolidine 112 as Chiral Catalysts

entry	enone **111**	nitroalkane **3**	product **113** yield (%)	ee % (config)
1	PhCH=CHCOMe	$MeNO_2$	52	73(*S*)
2		$EtNO_2$	75	71/73[a]
3		*c*-$C_5H_9NO_2$	95	77(*S*)
4		*c*-$C_6H_{11}NO_2$	64	71(*S*)
5		*i*-$PrNO_2$	95	79(*S*)
6	PhCH=CHCOEt		69	83(*S*)
7	4-ClC_6H_4CH=CHCOMe		87	75(*S*)
8	4-OHC_6H_4CH=CHCOMe		86	75(*S*)
9	ArCH=CHCOMe[b]		69	70(*S*)
10	*n*-BuCH=CHCOMe		50	73(*S*)

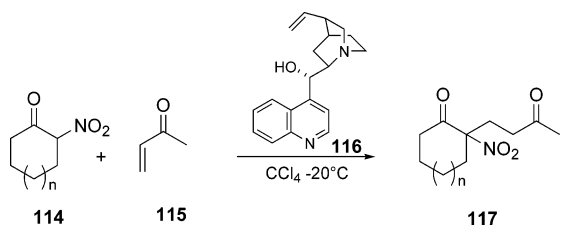
[a] Diastereomeric ratio 1:1. [b] Ar = 2-furyl.

Scheme 32



absolute configuration of the major enantiomer obtained of **117** is affected by the ring size of the 2-nitrocycloalkanone. Large rings ($n \geq 4$) give predominantly adducts with the *R* configuration, while the stereochemistry of medium rings does not follow a sharp trend (Scheme 33, Table 7).

Scheme 33



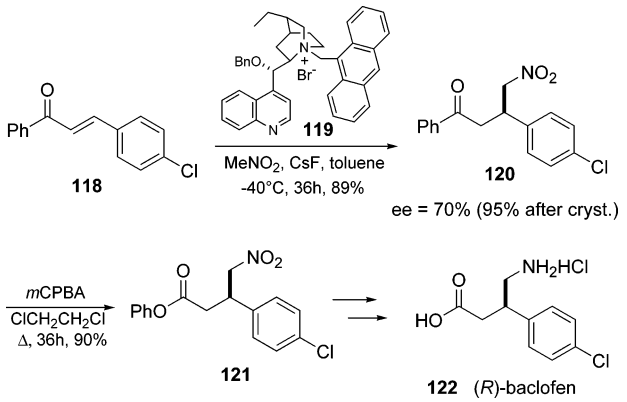
Chincona alkaloids can be easily transformed into quaternary ammonium salts that can be used for a

Table 7. Enantioselective Conjugate Addition of 2-Nitrocycloalkanones 114 to Methyl Vinyl Ketone 115 Mediated by Cinchonine 116 as Chiral Catalysts

entry	n	product yield (%)	ee % (config)
1	1	84	55(*S*)
2	2	95	45(*R*)
3	3	92	60(*S*)
4	4	95	25(*R*)
5	5	91	29(*R*)
6	7	87	25(*R*)
7	11	97	28(*R*)

variety of catalytic phase-transfer reactions. Conjugate addition of nitromethane to enone **118** in the presence of 10% chiral ammonium salt **119** produces nitro ketone **120** with modest enantioselectivity (Scheme 34).[105] The ee of **120** can be improved to 95%

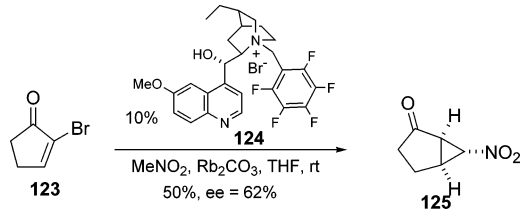
Scheme 34



after a single crystallization, and by means of a Baeyer−Villiger oxidation, ester **121** is obtained. This derivative can be easily transformed into (*R*)-baclofen hydrochloride, a γ-amino acid that acts as $GABA_B$ receptor agonist.

A tandem conjugate addition−nucleophilic substitution is experienced in the reaction of 2-bromo-2-cyclopentenone **123** with nitromethane (Scheme 35).

Scheme 35

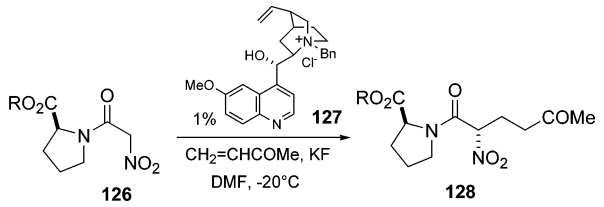


In the presence of 10% molar quinidine alkaloid **124** bicyclic nitro ketone **125** is formed in 50% yield and 62% ee.[106]

Conjugate addition of chiral nitroacetyl derivatives **126** to methyl vinyl ketone catalyzed by KF usually occurs with modest diastereoselectivity. However, addition of 1% *N*-benzylquinidinium chloride **127** slightly improves the diastereomeric excesses of the corresponding adducts **128** (Scheme 36).[107]

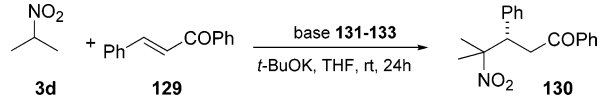
Amidine and guanidine bases are known to react with nitroalkanes in nonpolar solvents, giving tightly bound ion pairs whose structure has been determined by X-ray crystallography.[108,109] The utilization of complexes obtained using chiral amidines or guanidines has been tested for the conjugate addition of simple nitroalkanes with enones, but the adducts obtained using 2,8-disubstituted bicyclic guanidines have low ee's (9−12%).[110] Better results can be obtained using spirocyclic guanidines **131**−**133** that catalyze the addition of 2-nitropropane to chalcone with fair enantioselectivity (Scheme 37).[111]

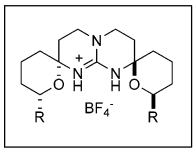
Scheme 36



R	yield(%)	**128** d.e.(%)
Bn	92	51
Et	72	51
t-Bu	40	36
Ph_2CH	50	40

Scheme 37

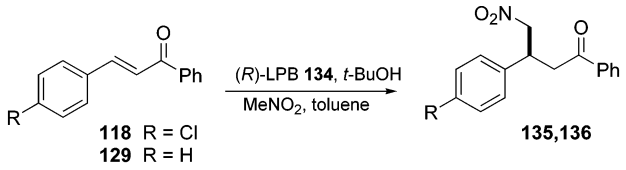


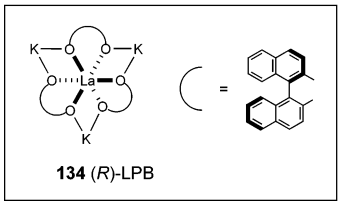


	R	conversion %	ee **3** %
131	Me	97	86
132	$TBDMSOCH_2$	70	65
133	$TBDPSOCH_2$	80	74

Chiral heterobimetallic complexes of lanthanum have been extensively used as catalysts for nitroaldol reactions but have found only a limited application to the corresponding conjugate additions. Nitromethane adds to chalcone derivatives **118** and **129** in the presence of (*R*)-LaK_3trisbinaphthoxide **134** with satisfactory yield and enantioselectivity (Scheme 38).[112] However the efficiency of this reaction is highly

Scheme 38





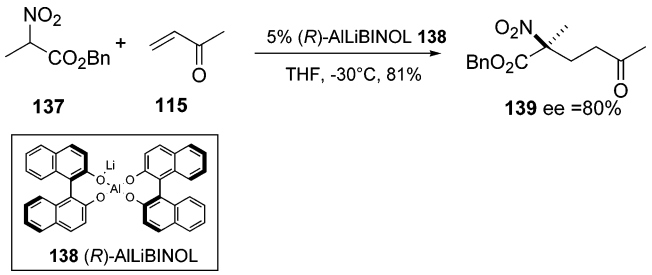
	R	yield %	ee %
135	Cl	71	95
136	H	59	97

substrate dependent since other enones react with moderate ee's (40−45%) and yields (up to 40%)

Addition of α-nitro esters to enones using chiral lanthanum complexes is poorly or nonenantioselective, but the efficiency of the reaction can be some-

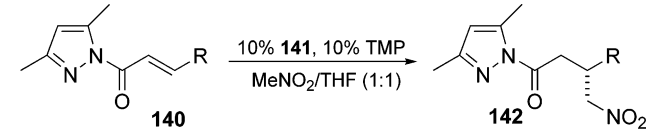
what improved moving to the Al−Li−BINOL complex **138** prepared in situ from $LiAlH_4$ and (*R*)-BINOL. The ee's of the resulting adducts lie in the range of 50% with a single example which reaches 80% (Scheme 39).[113]

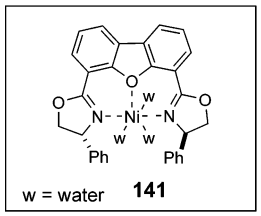
Scheme 39



The nickel complex of (*R,R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) **141** is an effective catalyst for the enantioselective addition of nitromethane to alkenoylpyrazoles **140** (Scheme 40).[114] The complex

Scheme 40



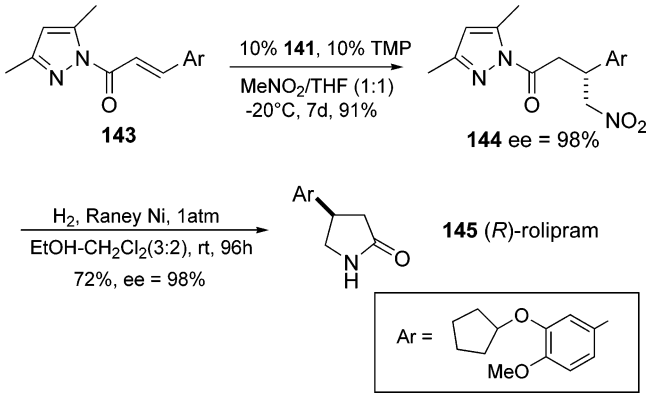


Entry	R	yield %	ee %
a	Me	85	94
b	*i*-Pr	74	97
c	*c*-C_6H_{11}	90	91
d	*t*-Bu	39	95
e	MeCH=CH	49	77
f	MeO_2C	91	83
g	Ph	90	93
h	2-furyl	75	97

alone is unable to catalyze the conjugate addition and requires a corresponding amount of TMP to be operative. Such a procedure is referred as a "catalytic double activation method" and usually works in a temperature range from −20 °C to room temperature with satisfactory yields and ee's.

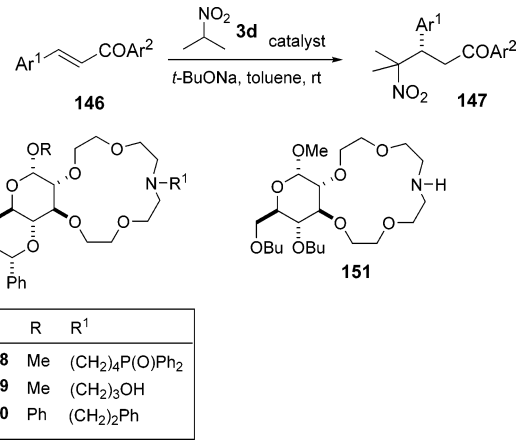
This approach has been successfully used for the total synthesis of the antidepressant agent (*R*)-rolipram **145** (Scheme 41).

Scheme 41



Azacrown ethers derived from D-glucose are able to catalyze the asymmetric conjugate addition of 2-nitropropane to chalcone derivatives **146**.[115−122] A consistent number of structural modifications have been introduced in the azacrown core as well as in the carbohydrate unit in order to obtain efficient results (Scheme 42, Table 8). Changing the ben-

Scheme 42



	R	R^1
148	Me	$(CH_2)_4P(O)Ph_2$
149	Me	$(CH_2)_3OH$
150	Ph	$(CH_2)_2Ph$

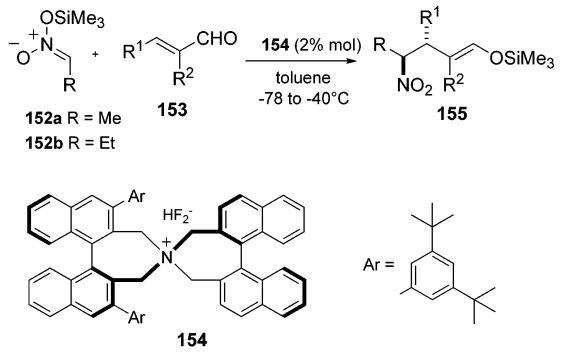
Table 8. Enantioselective Conjugate Addition of 2-Nitropropane 3d to Chalcones 129 Mediated by Azacrown Ethers 148−151 as Chiral Catalysts

entry	Ar^1	Ar^2	catalyst	product yield (%)	ee % (config)	ref
1	Ph	Ph	**148**	43	94(*R*)	115
2	Ph	Ph	**149**	53	85(*R*)	119
3	Ph	Ph	**150**	78	82(*R*)	120
4	Ph	Ph	**151**	82	89(*S*)	117
5	4-ClPh	Ph	**148**	75	56(*R*)	115
6	Ph	4-NO_2Ph	**148**	67	78(*R*)	115
7	4-NO_2Ph	4-MeOPh	**148**	52	67(*R*)	115
8	2-furyl	Ph	**148**	56	80(*S*)	115

zylidene function in catalysts **148**−**150** with two butyl groups in **151** provides a reversal in the enantiofacial preference for the reaction of 2-nitropropane with chalcone (Table 8, entries 1−4). A similar inversion in enantioselectivity is observed when the phenyl group is substituted with a furan ring (Table 8, entry 8).

Chiral quaternary ammonium fluorides are able to promote a consistent number of reactions involving nitroalkanes as nucleophiles with an outstanding degree of asymmetric induction.[123] Silyl nitronates **152** react with enals **153** in the presence of chiral *N*-spiro ammonium bifluoride **154** to give silyl enol ethers **155** (Scheme 43).[124,125] The conjugate addition occurs with high *anti* diastereoselectivity, and the ee's of the major diastereomer are also noteworthy. This procedure represents one of the first examples in which a consistent diastereocontrol in the formation of the adduct can be observed using nitroalkanes as nucleophiles. The utilization of quaternary ammonium salt **154** also has a beneficial effect on the regioselectivity of the nucleophilic addition. Indeed, in the presence of TBAF as catalyst, reaction of **152a** with *trans*-cinnamaldehyde **153** (R^1 = Ph and R^2 = H) gives a mixture of 1,4- and 1,2-adducts in a ratio of 1.1:1 with an overall yield of 76%.

Scheme 43



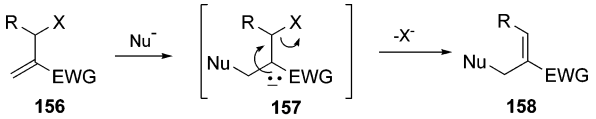
152	R^1	R^2	155 yield(%)	*syn:anti*	ee *anti*(%)
a	Ph	H	90	17:83	97
a	Ph	Me	90	5:95	95
a	-$(CH_2)_4$-		99	3:97	90
b	*n*-Pr	H	99	24:76	97

Ammonium bromides structurally related to compound **154** can be used as phase-transfer catalysts in the enantioselective conjugate addition of nitroalkanes to alkylidenemalonates.[126]

6. Conjugate Addition–Elimination Reactions

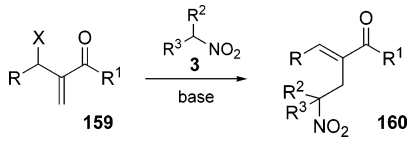
In conjugate additions the intermediate-stabilized anion that is produced by attack of the nucleophile to the electrophilic double bond is usually trapped with a proton or other electrophiles to give the final addition product. However, if a leaving group (X) is present in a suitable position of the substrate **156**, a subsequent elimination from the intermediate **157** can occur to produce a new unsaturation in molecule **158** (Scheme 44).

Scheme 44



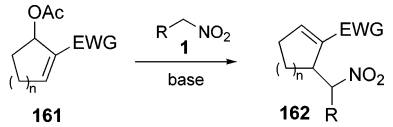
Derivatives of type **156** (X = acyloxy) are readily prepared by means of a base-catalyzed reaction of electron-poor olefins with aldehydes known as the Baylis–Hillman reaction.[127] Conjugate addition of nitroalkanes **3** with derivatives **159** leads to the expected products **160** with exclusive formation of the *E* stereoisomer (Scheme 45, Table 9).[128–132]

Scheme 45



The same procedure can be applied to cyclic derivatives **161** with formation of nitro derivatives **162** as a mixture of diastereomers and in fairy good yields (Scheme 46).[133]

Scheme 46



EWG	n	R	base	162 yield(%)
CO_2Et	1	Me	DBU	59
CO_2Et	2	Et	DBU	58
CN	1	Me	NaOH	58
CN	2	Et	DBU	80

Functionalization of the hydroxy group is mandatory for a successful addition–elimination mechanism since the corresponding alcohols **159** (X = OH) undergo a common conjugate addition with nitroalkanes.[134] The base used for this reaction may have a large influence on the related mechanistic route, so that the nature of the product obtained can be considerably different from that expected. Using DABCO as basic promoter involves a preliminary conjugate addition–elimination of the base to enoate **163,** giving salt **164** as an intermediate (Scheme 47).[130]

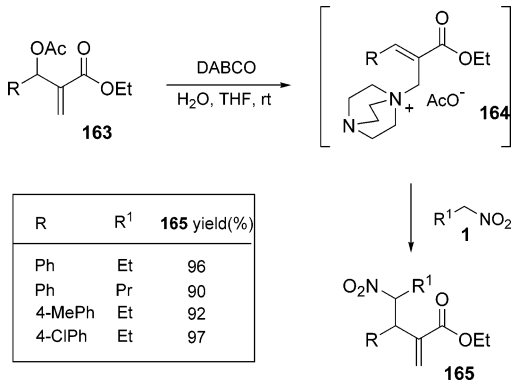
Compound **164** undergoes a conjugate addition by the nitroalkane followed by elimination of DABCO, leading to product **165** in a process that can be considered as a formal substitution of the acetoxy group by the nitroalkane. Enoates **166** bringing at least one halogen atom at C-2 of the aromatic ring react with nitroalkanes **1** in a tandem sequence that initially involves a conjugate addition–elimination leading to compound **167** (Scheme 48).[135] Nitro compound **167** reacts in an intramolecular aromatic nucleophilic substitution giving bicyclic derivative

Table 9. Conjugate Addition–Elimination of Nitroalkanes 3 to Baylis–Hillman Adducts 159

entry	R	R^1	R^2	R^3	X	base[a]	product **160** yield (%)	ref
1	Et	Me	Me	H	OAc	A	78	129
2	*i*-Pr	Me	Me	H	OAc	A	77	129
3	Pr	Me	Et	H	OAc	A	68	129
4	*c*-C_6H_{11}	Et	Me	H	OAc	A	64	129
5	2-furyl	OMe	Me	H	OAc	B	90	128
6	Ph	OMe	Me	Me	OAc	B	70	128
7	Ph	OEt	Et	H	OAc	C	73	129
8	4-MePh	OEt	Et	H	OAc	C	71	129
9	H	OEt	$MeO_2C(CH_2)_4$	H	Br	A	72	131
10	H	OEt	$HO(CH_2)_5$	H	Br	A	71	131
11	H	OEt	$CH_2{=}CH(CH_2)_8$	H	Br	A	80	131
12	H	OEt	$PhCH_2$	H	Br	A	78	131

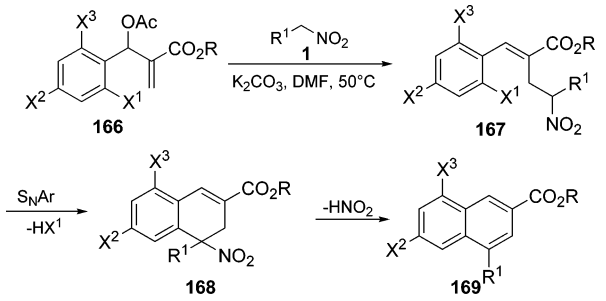
[a] A: 0.6 N NaOH, THF, room temperature. B: KF–Al_2O_3. C: K_2CO_3, DMF.

Scheme 47



R	R^1	**165** yield(%)
Ph	Et	96
Ph	Pr	90
4-MePh	Et	92
4-ClPh	Et	97

Scheme 48



R	R^1	X^1	X^2	X^3	**169** yield(%)
Et	Et	Cl	H	Cl	73
Et	Me	Cl	Cl	H	68
Et	CO_2Et	Cl	Cl	H	79
Me	Me	F	H	H	67

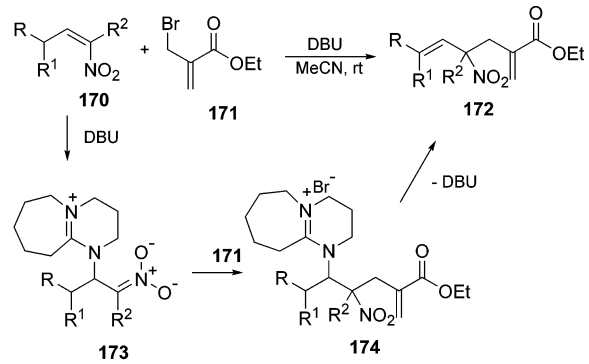
168 that quickly loses nitrous acid to afford functionalized naphthalene **169**. The final aromatization represents the key step of the whole process since its irreversibility ensures an efficient conversion of enoate **166** to naphthalene derivative **169**.

Nitroalkenes are widely known as reactive electrophilic substrates suitable for conjugate additions as well as cycloadditions reactions, but when involved in Baylis−Hillman processes, these compounds can act as allyl-type nucleophiles. Reaction of nitroalkenes **170** with bromomethyl acrylate **171** in the presence of DBU affords nitro dienes **172** (Scheme 49).[136] Conjugate addition of DBU to a nitroalkene gives a nitronate anion **173** that in the presence of acrylate **171** reacts as previously described, leading to ammonium salt **174** that upon elimination of DBU affords nitro diene **172**.

Electrophilic alkenes containing 1,2-electron-withdrawing substituents are particularly reactive toward conjugate additions. When alkenes **B** react with nucleophiles bearing a good leaving group **A** the intermediate adduct **C** undergoes a rapid base-catalyzed elimination to give an unsaturated derivative **D** (Scheme 50).

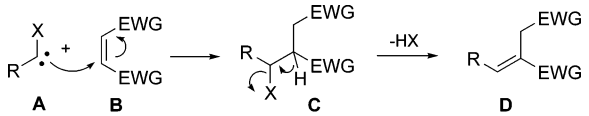
The nitro group in nitroalkanes is poorly reactive as a leaving group in nucleophilic substitutions but can be eliminated in basic conditions as nitrous acid. Enediones **175** react with nitro compounds **3** in the presence of DBU following this general mechanism to produce unsaturated carbonyl derivatives **176** (Scheme 51, Table 10).[137,138]

Scheme 49



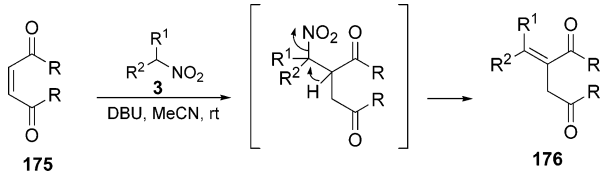
R	R^1	R^2	**172** yield(%)
Et	H	Et	80
H	H	Pr	80
H		$-(CH_2)_3-$	82
Et	H	$MeCO(CH_2)_2$	84
Et	H	$MeO_2C(CH_2)_4$	84

Scheme 50



X = leaving group EWG = electron-withdrawing group

Scheme 51



The elimination step is highly diastereoselective since only the *E* stereoisomer of compound **176** is formed, regardless the configuration of the double bond in the starting dienoate **175**. Chemoselective reduction of the carbon−carbon double bond in derivatives **176** can be carried out by a simple catalytic hydrogenation in the presence of Pd/C to give saturated diesters or keto esters.[139] Maleimides **177** are also reactive substrates for the same procedure, giving the corresponding 3-alkylidene derivatives **178** with *E* configuration (Scheme 52, Table 11).[140,141]

Reduction of the exocyclic double bond and the imido group provides a rapid entry to 3-substituted pyrrolidines.[141] Trimethyl *trans*-aconitate **179** reacts similarly with nitroalkanes **1** giving the corresponding unsaturated derivatives **180**, after elimination of nitrous acid, with good *E* diastereoselectivity (Scheme 53).[142]

This procedure when applied to 1-alkyl dienoates such as dimethyl citraconate **181** provides unexpected results, leading to the formation of keto diesters **182** (Scheme 54).[143] As observed by ^1H NMR analysis, in the presence of DBU there is an equilibrium between **181** and its regioisomer **183** that is probably more reactive toward conjugate addition with nitroalkanes. The adducts **184** formed by the

Table 10. Conjugate Addition−Elimination of Nitroalkanes 3 to Enediones 175

entry	R	R^1	R^2	**176** product yield (%)
1	OMe	H	Me	93
2	OMe	Me	Me	95
3	OMe	H	Me_2CHCH_2	89
4	OMe	H	$THPOCH_2$	80
5	OMe	H	$MeO_2C(CH_2)_3$	86
6	OMe	H		90
7	OMe	H	$MeCO(CH_2)_2$	90
8	OMe	H	$HO(CH_2)_4$	71
9	Me	H	n-C_4H_9	70
10	Me	H	$MeO_2C(CH_2)_3$	88
11	Me	Me	Me	65
12	Me	H	$MeCO(CH_2)_2$	95
13	Me	H	$HO(CH_2)_4$	85
14	Me	–$(CH_2)_5$–		85

Scheme 52

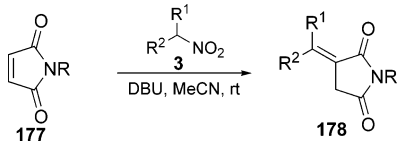


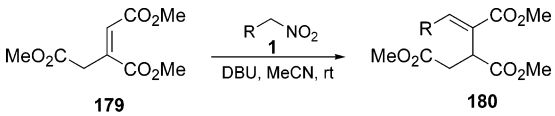
Table 11. Conjugate Addition−Elimination of Nitroalkanes 3 to *N*-Substituted Maleimides 177

entry	R	R^1	R^2	**178** product yield (%)
1	Ph	Me	Me	70
2	Ph	H	n-C_4H_9	56
3	Ph	H	$MeO_2C(CH_2)_3$	80
4	Ph	H	$MeCO(CH_2)_2$	73
5	Et	H	n-C_4H_9	88
6	Et	H		88
7	Et	H	$HO(CH_2)_4$	87
8	Et	–$(CH_2)_5$–		80

usual conjugate addition are therefore subsequently transformed into the keto diesters **182** by a Nef reaction promoted by DBU.[144]

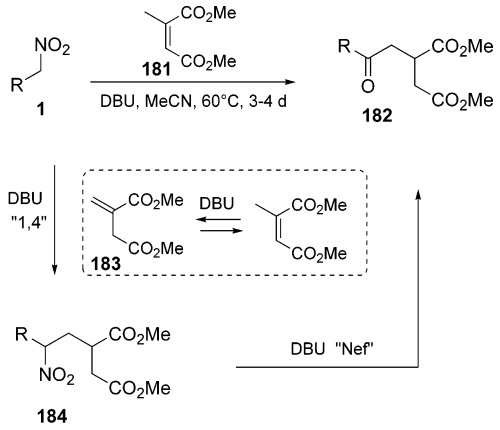
Conjugate addition of nitroalkanes to unsymmetrical 1,4-diketones usually leads to a regioisomeric mixture of products that endangers the efficiency of the synthetic procedure. However, (*Z*)-benzyl di-

Scheme 53



R	**180** yield %	*E*/*Z*
Et	79	88:12
$MeCO(CH_2)_2$	81	88:12
$MeO_2C(CH_2)_2$	90	95:5
2-furylmethyl	76	99:1
$HO(CH_2)_4$	66	87:13

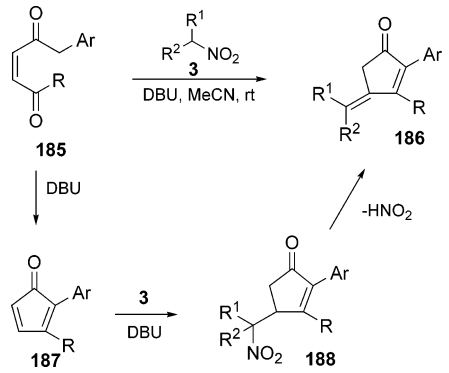
Scheme 54



R	**182** yield(%)
n-C_5H_{11}	81
CH_2=$CH(CH_2)_8$	54
$HO(CH_2)_5$	54
$MeCO_2(CH_2)_2$	56

enones **185** react with nitroalkanes in the presence of DBU in acetonitrile, affording 4-alkylidene-cyclopent-2-en-1-ones **186** in good yield and high *E* diastereoselectivity (Scheme 55, Table 12).[145] The overall

Scheme 55



synthetic transformation probably starts with a chemoselective intramolecular aldol condensation of enediones **185**, promoted by the presence of the aromatic ring, that gives cyclopentadienones **187**. Under the same conditions intermediates **187** react with nitroalkanes **3** to afford the Michael adducts **188** that eliminate nitrous acid to the final cyclopentenones **186**.

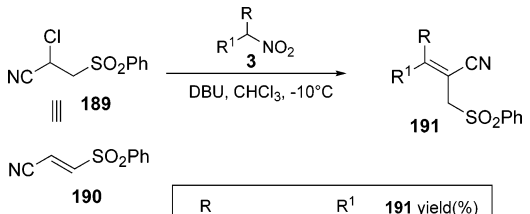
Regiochemical troubles can be avoided or minimized using 1,2-disubstituted alkenes bearing com-

Table 12. Synthesis of Cyclopentenones 186 by Tandem Aldol−Conjugate Addition−Elimination Process

entry	R	Ar	R^1	R^2	**186** product yield (%)
1	Me	Ph	Me	Me	77
2	Me	Ph	H	*n*-C_9H_{19}	76
3	Me	Ph	H	CH_2=$CH(CH_2)_3$	68
4	Me	Ph	H	$HO(CH_2)_5$	78
5	Me	Ph	H		73
6	Me	Ph	H	$MeCO(CH_2)_2$	84
7	Et	Ph	H	$MeO_2C(CH_2)_2$	79
8	Me	3-MeOPh	H	*n*-C_5H_{11}	87
9	Et	4-FPh	H	$MeO_2C(CH_2)_4$	73
10	Me	3-ClPh	H	*n*-C_5H_{11}	93

pletely different electron-withdrawing groups that are able to drive the conjugate attack selectively at one carbon atom. 2-Chloro-3-phenylsulfonylpropanenitrile **189** generates, in the presence of DBU, alkene **190** that reacts regioselectively with nitroalkanes **3** at −10 °C to afford, by the usual conjugate addition−elimination mechanism, the corresponding conjugated nitriles **191** (Scheme 56).[146] The double-bond

Scheme 56



R	R^1	**191** yield(%)
Me	Me	68
Et	H	61[a]
n-C_5H_{11}	H	71
$THPOCH_2$	H	51
$MeO_2C(CH_2)_4$	H	66
$-(CH_2)_5-$		63

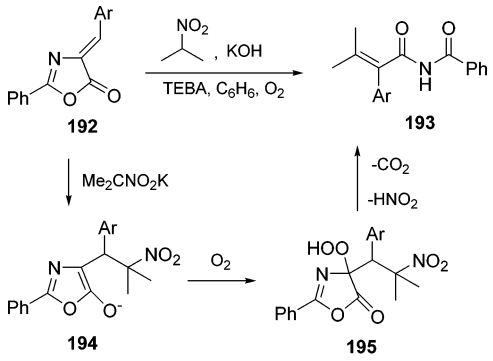
[a] *E/Z* = 7:3

configuration in most of the examples reported is *E,* but depending on the nature of the nitroalkane used, a certain amount of *Z* stereoisomer can sometimes be formed.

Potassium salt of 2-nitropropane reacts with 4-arylideneoxazol-5-ones **192** in the presence of molecular oxygen to afford 2-arylbutenoic acid imides **193** (Scheme 57).[147] The addition product **194** initially formed is believed to react with oxygen, giving a hydroperoxide intermediate **195** that decomposes with loss of CO_2 and HNO_2 to the final product **193**. An endoperoxide arising from a cycloaddition reaction between **194** and oxygen is also a possible intermediate in this process.

In the conjugate addition of bromonitromethane **197** with electrophilic alkenes **196** the intramolecular nucleophilic substitution of the intermediate anion

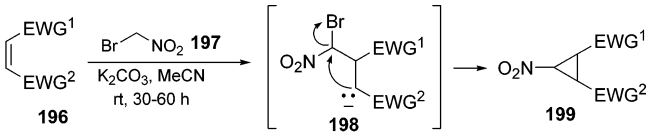
Scheme 57



Ar	yield **193** %
Ph	90
4-MeOPh	80
4-ClPh	80
4-NO_2Ph	60

198 is strongly favored over elimination of nitrous acid and ultimately leads to the synthesis of polyfunctionalized nitrocyclopropanes **199** as a mixture of diastereomers (Scheme 58).[148] Addition of bromoni-

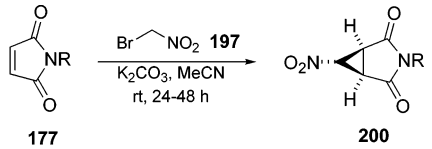
Scheme 58



EWG^1	EWG^2	**199** yield(%)
MeCO	MeCO	94
PhCO	MeCO	96
4-MePhCO	MeCO	96
PhCO	PhCO	75
CO_2Me	MeCO	86
CO_2Me	CO_2Me	88
CN	CN	78

tromethane in several portions is mandatory for the efficiency of the process. This cyclopropanation procedure can be extended to maleimido derivatives **177** that react with bromonitromethane in good yield and in a diastereoselective fashion giving *exo*-nitrocyclopropanes **200** as a single product (Scheme 59).

Scheme 59

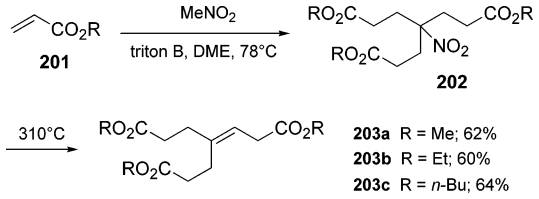


R	**200** yield(%)
Me	65
Et	70
t-Bu	82
Bn	70

Reduction of the nitro group to the corresponding amino derivative in compounds **200** provides an efficient entry to bicyclic intermediates employed for the synthesis of antibiotic trovafloxacin.[149] Elimina-

tion of nitrous acid can be obtained by thermolysis heating a quaternary nitro derivative **202** at 310 °C (Scheme 60).[150] The quaternary nitroalkane **202** can

Scheme 60



be obtained by triple conjugate addition of acrylate esters **201** to nitromethane in the presence of Triton B.[151,152]

Oxidation of the adducts between 3-nitropyrrolidines and Michael acceptors with NBS affords 3,4-substituted maleimides and involves elimination of HNO_2.[153]

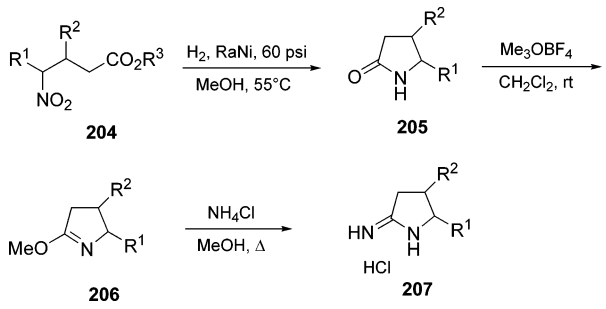
7. Synthetic Applications

As stated in the Introduction, the nitro group is amenable to many synthetic transformations once it has been inserted in a molecular framework. This feature has favored the utilization of functionalized nitro compounds in the preparation of various synthetic targets endowed of practical interest.

7.1. Pyrrolidines and Derivatives

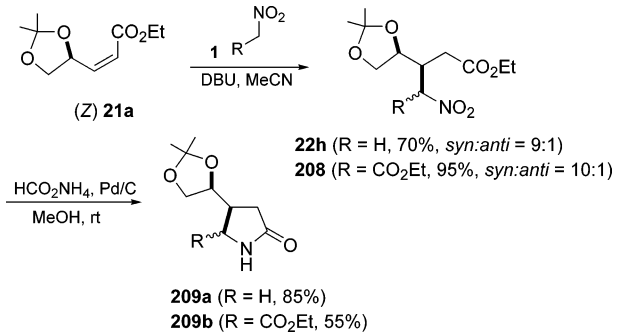
The most obvious transformation of the nitro group involves reduction of the nitrogen atom leading to an amino group. This process is often followed by a nucleophilic ring closure when a carbonyl or an ester function is present in the structure to afford directly pyrrolidinone derivatives.[154] A general method for the reduction of the nitro group in adducts **204** envisages the utilization of catalytic hydrogenation in the presence of Raney nickel (Scheme 61).[155] The ob-

Scheme 61



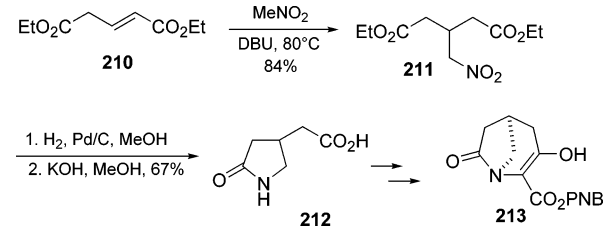
tained pyrrolidinones **205** can be transformed into 2-iminopyrrolidines **207** that act as potent and selective inhibitors of human inducible nitric oxide synthase. Diastereoselective conjugate addition of nitroalkanes **1** to chiral (*Z*)-enoate **21a** leads to the synthesis of compounds **22h** and **208** with predominance of the *syn* stereoisomer (Scheme 62).[156] Reduction of the nitro group and ring closure affords pyrrolidinones **209,** which can be used as synthetic intermediates in the preparation of several interesting compounds.

Scheme 62



Nitromethane addition to diester **210** affords product **211** that upon reduction of the nitro group and ester hydrolysis gives pyrrolidinone **212** (Scheme 63).[157] Acid **212** can be easily transformed in few

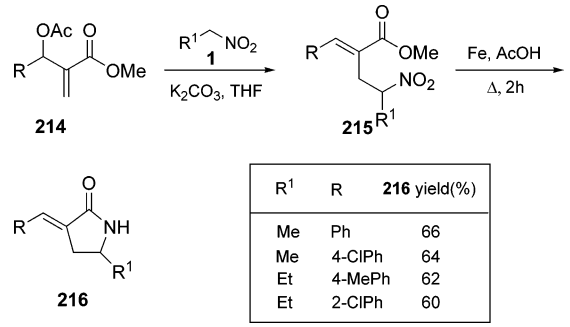
Scheme 63



steps into bicyclo-γ-lactam **213,** which acts as an inhibitor of penicillin-binding proteins. Disymmetric hydrolysis of racemic **211** using two enantiocomplementary enzymes allows the preparation of optically active **212** in both enantiomeric forms.[158]

Addition of nitroalkanes to Baylis−Hillman products **214** gives the corresponding unsaturated nitro esters **215** that are chemoselectively reduced by a 'one-pot' procedure to the corresponding pyrrolidinones **216** using Fe in boiling AcOH (Scheme 64).[159]

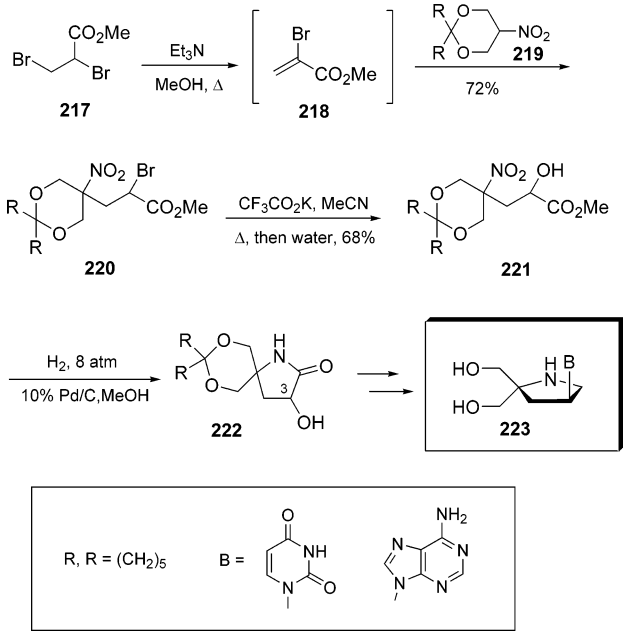
Scheme 64



R^1	R	**216** yield(%)
Me	Ph	66
Me	4-ClPh	64
Et	4-MePh	62
Et	2-ClPh	60

Methyl 2-bromoacrylate **218** can be generated in situ from the corresponding dibromo derivative **217** and then made to react with nitro compound **219** to give adduct **220** (Scheme 65).[160] Substitution of the halogen with a hydroxy group is followed by reduction of the nitro group using a catalytic hydrogenation to give pyrrolidinone **222**. This derivative can be converted into azaisonucleotide analogues **223** introducing the corresponding basic moiety using a Mitsunobu reaction and by further simple synthetic manipulations. 3,4-Dihydroxy pyrrolidinones structurally related to compound **223** can be obtained using the same strategy by conjugate addition of

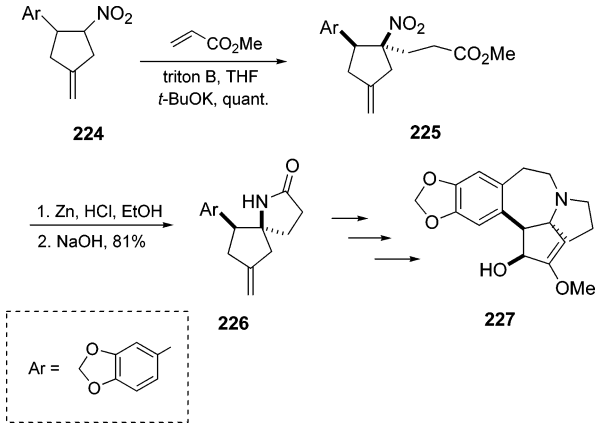
Scheme 65



nitroalkane **219** to ethyl propynoate followed by dihydroxylation of the resulting unsaturated derivative.[161]

Functionalized nitrocyclopentane **224** reacts with methyl acrylate in quantitative yield to give adduct **225** as a single diastereomer probably because of the stereodirecting effect of the vicinal phenyl group (Scheme 66).[162,163] Reduction of the nitro group using

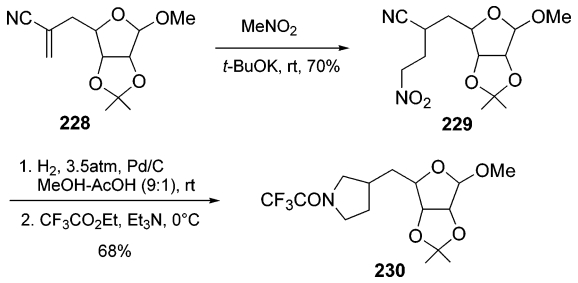
Scheme 66



zinc metal in ethanolic HCl affords spirolactam **226** without any migration of the exocyclic double bond. Lactam **226** is subsequently transformed into racemic alkaloid cephalotaxine **227**. A similar strategy can be adopted for the preparation of aza analogues of this natural alkaloid.[164,165]

Unsaturated nitrile **228** reacts with nitromethane giving the corresponding adduct **229** that upon catalytic hydrogenation with 10% Pd/C in MeOH/AcOH (9:1) and acylation furnishes *N*-trifluoroacetylpyrrolidine **230** (Scheme 67).[166] It is probable that the primary amine formed by reduction of the nitro group reacts with the intermediate imine formed by reduction of the nitrile to give the intermediate pyrrolidine. Compound **230** is an intermediate for the preparation of synthetic analogues of

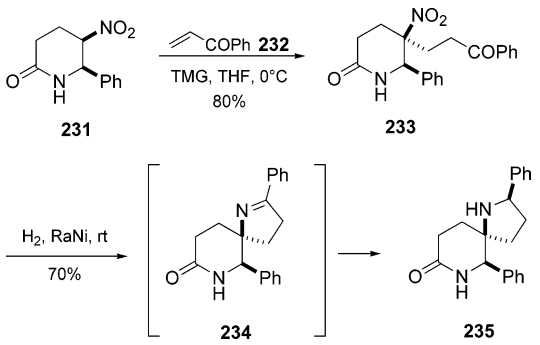
Scheme 67



sinefungin, a nucleoside active against viruses, fungi, and parasites.

Conjugate addition of nitrolactam **231** with acrylophenone **232** gives compound **233** with high diastereoselectivity (Scheme 68).[167] Catalytic hydrogena-

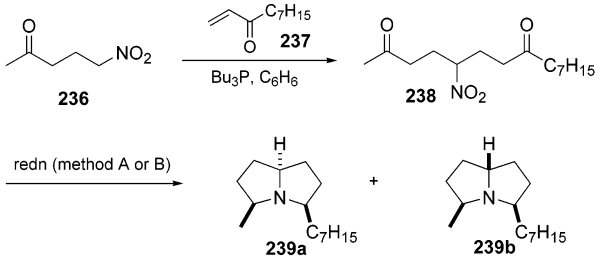
Scheme 68



tion of nitro ketone **233** occurs with concomitant formation of an intermediate imine **234** that is reduced in the same conditions to the spiropyrrolidine **235**. The presence of the phenyl group in the lactam ring hinders one face of the pyrroline ring in **234,** thus allowing complete diastereoselection in the imine reduction.

Nitro diketone **238** is readily obtained by addition of nitro ketone **236** to vinyl ketone **237** in the presence of Bu_3P (Scheme 69).[168] Reduction of compound

Scheme 69



method A: H_2 (8-10 atm), Pd/C, EtOH, **239a**:**239b** = 65:5

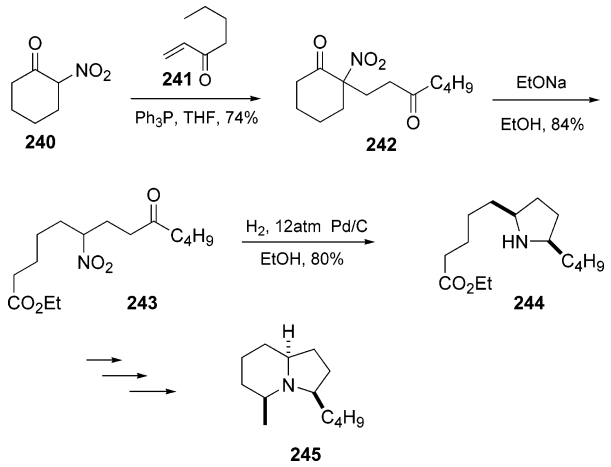
method B: NH_4OAc,KOH, MeOH, $NaBH_4CN$, then $NaBH_4$, **239a**:**239b** = 12:88

238 produces a mixture of pyrrolizidines **239** whose diastereomeric composition depends on the reducing system used. Catalytic hydrogenation (method A) provides the formation of compound **239a,** while utilization of complex hydrides (method B) favors isomer **239b**, an alkaloid known as xenovenine. It is highly probable that in the reduction with method B the nitro group in compound **238** is formerly trans-

formed by a Nef conversion into a carbonyl group and the nitrogen present in the final pyrrolizidine is provided by NH_4OAc.

2-Nitro ketones usually undergo conjugate additions in milder conditions with respect to simple nitroalkanes because of the enhanced acidity of the C-2 hydrogen atom.[169,170] 2-Nitrocyclohexanone **240** reacts with unsaturated ketone **241** in the presence of Ph_3P to give the corresponding adduct **242** (Scheme 70).[171]

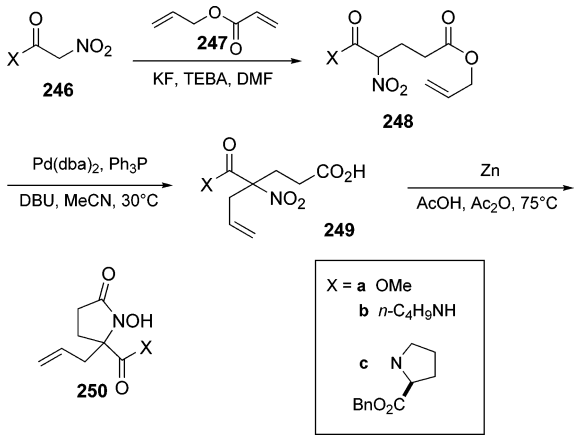
Scheme 70



The cyclohexanone moiety in **242** suffers a fast base-catalyzed retro-Claisen ring opening affording open-chain nitro derivative **243** that in reductive conditions chemoselectively furnishes *cis*-pyrrolidine **244**. This compound is a central intermediate for the synthesis of monomorine I **245,** a trail pheromone of the Pharao Ant and other similar biologically active substances.[172]

2-Nitro esters and 2-nitro amides **246** react with allyl acrylate **247** in the presence of KF to give adducts **248** (Scheme 71).[173,174] Intramolecular

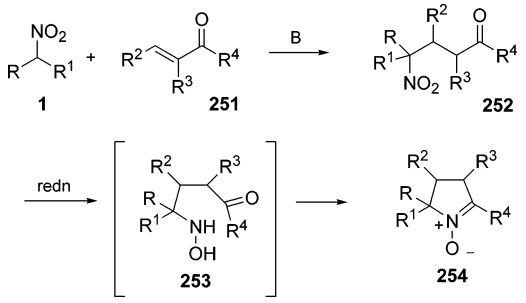
Scheme 71



Pd(0)-catalyzed allyl transfer converts esters **248** into acids **249** that, by carefully controlled reduction conditions, can be transformed into hydroxamic acids **250**.[175] The utilization of chiral nitro amides as **246c** does not produce significant levels of diastereoselection in the formation of acid **250c**.

Hydroxylamines are known intermediates in the reduction of nitro compounds to amines. Reduction of the adducts between nitroalkanes **1** and enones or enals **251** directly produces cyclic nitrones **254** by an intramolecular reaction of the intermediate hydroxylamine **253** and the carbonyl group (Scheme 72, Table 13).[176−183]

Scheme 72



A new entry for the 2-isoxazoline nucleus makes use of the conjugate addition of ethyl nitroacetate **256** with 2-bromoketones **255** (Scheme 72).[184] The intermediate adduct **257** undergoes an intramolecular nucleophilic substitution involving the oxygen of the nitronate anion and the bromine atom. The reaction can be realized in homogeneous (Et_3N, ether) as well as heterogeneous conditions (basic alumina), and the 2-isoxazolines **258** are formed predominantly as *trans* isomers (Scheme 73).

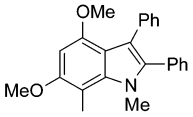
Alkylidene diesters and keto esters **260** obtained by the conjugate addition−elimination procedure can be suitably converted into 3-alkylidenepyrrolidines **262** by a simple synthetic procedure (Scheme 74).[185] Chemoselective reduction of the ester or keto functions leads to the corresponding diols that are subsequently converted into their mesylates **261**.[186] Ring closure is best realized using $TsNH_2$ in basic conditions to afford pyrrolidines **262**. Benzylamine can also be used for this purpose, but the process is less efficient and requires a large excess of the amine.

Reaction of nitroalkanes with dimethyl α-(bromomethyl)fumarate **263** follows the usual addition−elimination mechanism giving diene derivative **264** (Scheme 75).[187,188] Aliphatic amines react with diene **264** by means of a conjugate addition−cyclization process to afford alkylidene lactams **265**.

Oxidative cleavage of the furan **266** gives (*Z*)-enedione **267** that reacts with nitroalkanes **1** to afford the alkylidene derivatives **268** (Scheme 76). Double-bond reduction of these compounds provides diketones **269,** which are central intermediates for the synthesis of pyrroles **270** and furans **271** using a Paal−Knorr reaction.[189,190]

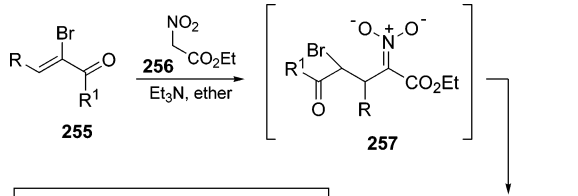
A three-component coupling among enones or enals **251**, nitroalkanes **1,** and primary amines **272** leads to the straightforward synthesis of *N*-alkylpyrroles **273** (Scheme 77, Table 14).[191] The reaction is carried out on solid support (SiO_2) without any solvent and is promoted by microwave irradiation. A Nef conversion of the nitro group in one of the possible intermediates of this process probably occurs, allowing the formation of the pyrrole ring through a Paal−Knorr-type reaction.[192] In a related procedure, 3-nitropyr-

Table 13. Synthesis of Cyclic Nitrones 254

entry	R	R^1	R^2	R^3	R^4	**254** yield (%)[a]	ref.
1	Me	Me	H	$(CH_2)_2CO_2Me$	H	-	176
2	Me	Me	H	Me	H	64	177
3	Me	Me	Me	H	H	62	177
4	Me	Me	Ph	H		55[b]	178
5	Me	Me	H	MeOH	Me	72	179
6	H	H	H	H	Me	61	180
7	Me	Ph	H	H	H	28	180
8	Me	Me	H	H	H	51	181
9	H	CO_2Et	H	H	Ph	70	182
10	H	CO_2Et	H	H	Me	46	182
11	Me	$(EtO)_2(O)P$	H	Ph	H	52	183

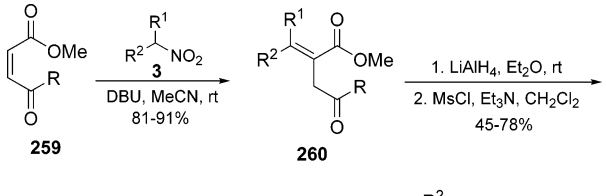
[a] Reductions are carried out using Zn metal in acidic conditions. [b] Reduction is carried out using Fe metal in acidic aqueous ethanol.

Scheme 73



R	R^1	yield **258** %
H	Me	93
H	Et	95
Me	Et	99
i-Pr	Et	63
-$(CH_2)_3$-		89
-$(CH_2)_2$-		92

Scheme 74



R	R^1	R^2	yield **262** %
Me	H	C_5H_{11}	84
Me	Me	Me	70
H	H	Et	78
H	H	Pr	81
H	H	C_5H_{11}	88
H	H	Ph	80
H	-$(CH_2)_5$-		94

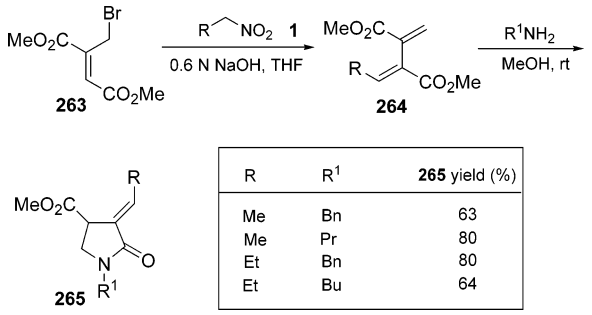
roles are prepared by reaction of nitromethane with 1-isocyano-1-tosyl-1-alkenes in the presence of *t*-BuOK.[193]

Conjugate addition of nitromethane to acrylate esters produces 4-nitrobutanoate derivatives that can be readily transformed into 5-nitro-2-oxopentanoate esters. These compounds can be enantioselectively reduced at the keto group using enzymes and then converted into optically active 3-hydroxypiperidin-2-ones.[194,195]

7.2. Lactones and Oxygenated Heterocycles

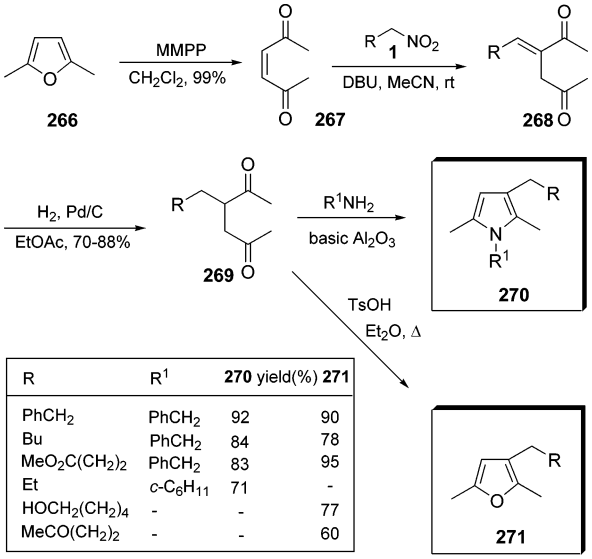
Lactones and cyclic derivatives bearing an oxygen atom in the ring are of considerable importance as both synthetic intermediates and compounds showing interesting biological properties. Preparation of lactone derivatives from Michael adducts of nitroalkanes generally involves a preliminary elimination of the nitro group to give an alkene derivative[196] or conversion of the nitro group into a carbonyl function by a Nef reaction. The former approach is especially useful for the preparation of small ring lactones, while the nitro to carbonyl conversion is mainly used for the synthesis of macrolactones and spirocyclic compounds. Unsaturated keto ester **274** obtained by a conjugate addition−elimination process is a central intermediate for the synthesis of various butyrolactone systems (Scheme 78). Reduction of the alkene and carbonyl groups in **274** allows the preparation of α-substituted-γ-methyl-γ-lactones **275** (Table

Scheme 75



R	R^1	**265** yield (%)
Me	Bn	63
Me	Pr	80
Et	Bn	80
Et	Bu	64

Scheme 76



R	R^1	**270** yield(%)	**271**
$PhCH_2$	$PhCH_2$	92	90
Bu	$PhCH_2$	84	78
$MeO_2C(CH_2)_2$	$PhCH_2$	83	95
Et	c-C_6H_{11}	71	-
$HOCH_2(CH_2)_4$	-	-	77
$MeCO(CH_2)_2$	-	-	60

Scheme 77

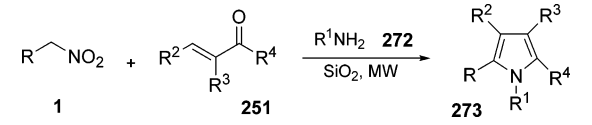


Table 14. Synthesis of *N*-Alkylpyrroles by Three-Component Coupling

entry	R	R^1	R^2	R^3	R^4	**273** yield (%)
1	Me	Bn	Ph	H	H	60
2	Me	Bn	Ph	H	Me	64
3	Me	c-C_6H_{11}	H	H	Me	60
4	Me	(*S*)-PhCHMe	Ph	H	H	62
5	Me	*i*-Pr	Ph	H	H	64
6	Me	Bn	2-furyl	H	Me	72
7	Et	*n*-Bu	2-furyl	H	Me	68
8	Me	Bn	*n*-Pr	Et	H	60
9	Me	*n*-Bu	Ph	H	H	61

15).[197,198] Alternatively, the alkene function can be retained in the lactone moiety of **276** by a chemoselective reduction of the carbonyl function using the $NaBH_4/Na_2HPO_4{\cdot}12H_2O$ system.[199] Finally, nucleophilic attack of the carbonyl function can be selectively realized using a Grignard reagent in the presence of $CeCl_3$ with consequent formation of γ,γ-disubstituted lactones **277**.

Similarly, 2-alkylidene dimethyl succinates **278** can be hydrolyzed to the parent carboxylic acids and then converted into the corresponding anhydrides by reaction with acetyl chloride at reflux (Scheme 79).[200]

Scheme 78

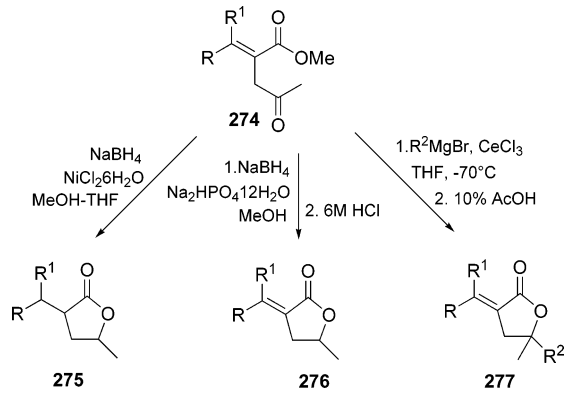
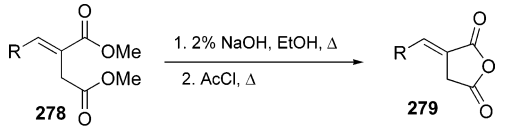


Table 15. Synthesis of Lactones 275−277 from Unsaturated Keto Ester 274

entry	R	R^1	R^2	**275** yield (%)	**276** yield (%)	**277** yield (%)
1	Ph	H	*n*-Pr	70	70	53
2	*n*-Pr	H	Bn	85	67	65
3	$-(CH_2)_2-$		Me	66	85	75
4	$MeO_2C(CH_2)_2$	H		84	80	
5	$MeCH(OH)(CH_2)_2$	H		75	87	
6	Me	Me	Me		55	65
7	*n*-Bu	H	*n*-Pr			52

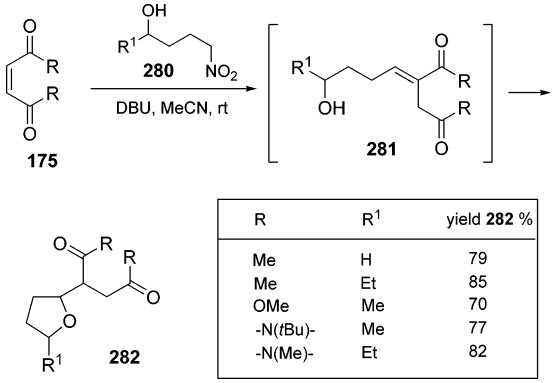
Scheme 79



R	yield **279** %
Et	71
$MeCO(CH_2)_2$	71
$HO(CH_2)_5$	72
i-Pr	64

Conjugate addition of δ-nitroalkanols **280** to dienones and dienoates **175** occurs with the usual mechanism giving an intermediate alkenol **281** that is not isolated since it undergoes to a rapid ring closure leading to tetrahydrofuran derivative **282** (Scheme 80).[201]

Scheme 80

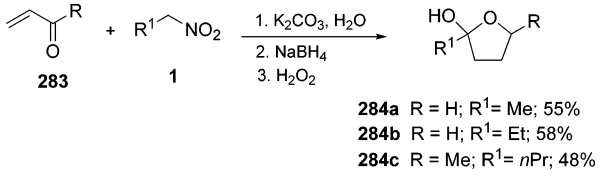


R	R^1	yield **282** %
Me	H	79
Me	Et	85
OMe	Me	70
-N(*t*Bu)-	Me	77
-N(Me)-	Et	82

Lactols **284** can be prepared by one-pot synthesis carried out in water as solvent involving a sequential conjugate addition of enones **283** with nitroalkanes **1**, reduction of the resulting γ-nitro ketone, and

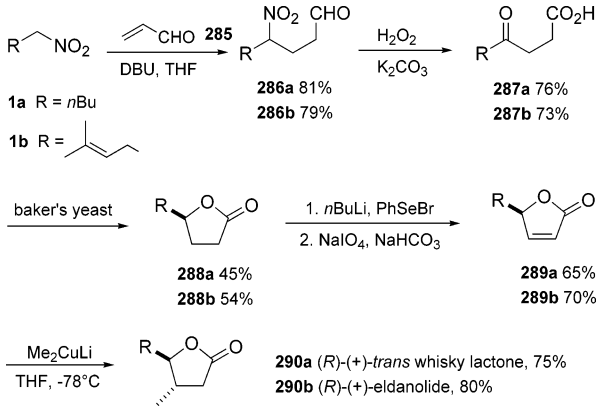
oxidative nitro to carbonyl conversion with concomitant cyclization (Scheme 81).[202]

Scheme 81



As previously stated, conjugate addition of nitroalkanes to α,β-unsaturated carbonyls coupled with the Nef reaction represents a rapid entry to a series of γ-keto derivatives that are useful intermediates for lactone syntheses. Structurally related compounds such as the flavor compound *trans* whisky lactone and the pheromone eldanolide can be prepared following the same synthetic strategy starting from the conjugate addition of nitroalkanes **1** to acrolein **285** (Scheme 82).[203] The addition products **286** are oxi-

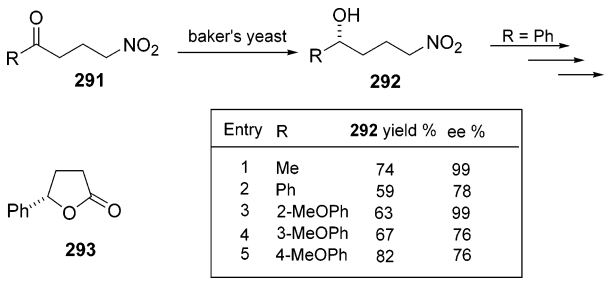
Scheme 82



dized with hydrogen peroxide in basic media that provides the Nef reaction and the aldehyde oxidation to give ketoacid **287**. Enantioselective reduction of the carbonyl group by Baker's yeast leads to lactone **288** that is easily converted into (*R*)-*trans* whisky lactone **290a** and (+)-eldanolide **290b**.

Baker's yeast reduction can also be applied to a series of γ-nitro ketones **291** with variable levels of enantioselectivity (Scheme 83).[204,205] Hydroxy alcohols

Scheme 83

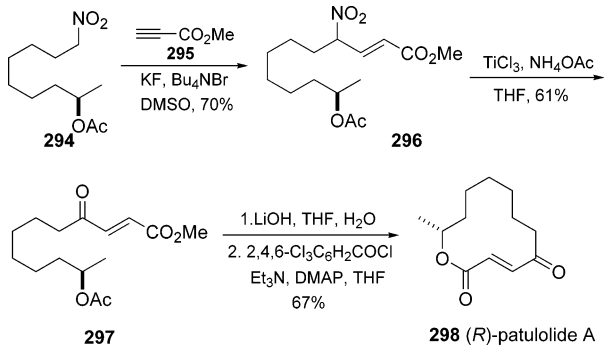


Entry	R	292 yield %	ee %
1	Me	74	99
2	Ph	59	78
3	2-MeOPh	63	99
4	3-MeOPh	67	76
5	4-MeOPh	82	76

292 (entry 2) can be transformed into lactones **293** by a simple sequence involving Nef reaction of the primary nitro group and lactonization in acidic conditions.

Optically active nitroacetate **294** can be readily prepared by enzymatic resolution from the corresponding nitro alcohol and reacts efficiently with methyl propiolate **295** giving the corresponding adduct (*E*)-**296** (Scheme 84).[206] The nitro group is then

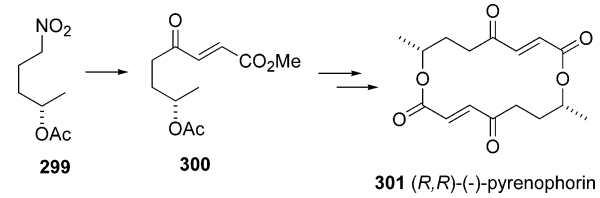
Scheme 84



converted into keto ester **297** using the McMurry method, and after ester hydrolysis the resulting hydroxy acid is lactonized to macrolide (*R*)-patulolide A. A similar strategy can be used to prepare (*Z*)-**296** and (*R*)-patulolide B.

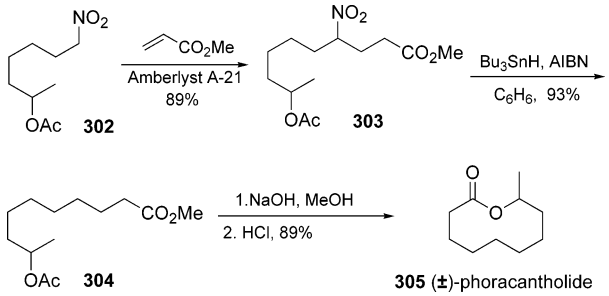
The enantioselective synthesis of macrolide dilactone (*R,R*)-(−)-pyrenophorin **301** can be realized using the usual conjugate addition−Nef reaction to produce keto ester **300** as a monomeric intermediate (Scheme 85).[207]

Scheme 85



Radical denitration allows a complete removal of the nitro group by its replacement with a hydrogen atom. Tertiary nitroalkanes and activated nitro compounds such as α-nitro ketones give the best results in this process.[208] This synthetic operation is particularly useful when simple macrolactones must be prepared using the chemistry of nitro compounds, as illustrated for the preparation of racemic phoracantholide (Scheme 86).[209] Conjugate addition of

Scheme 86

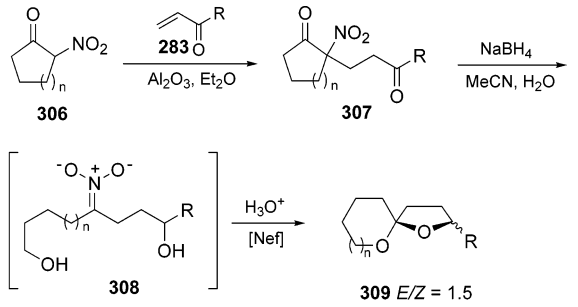


nitroalkane **302**[210] in solventless conditions using macroreticular resin Amberlyst A-21 affords adduct **303,** which is denitrated using Bu_3SnH to diester **304** and finally hydrolyzed to give phoracantholide **305**.

Spiroketalization of hydroxyketones is a spontaneous process that occurs in mild acidic conditions

because of the great stability of the resulting bicyclic system. This aptitude can be suitably used in a cascade reaction that involves some consecutive transformations. Conjugate addition of 2-nitrocycloalkanones **306** with enones **283** gives products **307** that are reduced with $NaBH_4$ in acetonitrile−water (Scheme 87).[211] This process also implies a retro-

Scheme 87

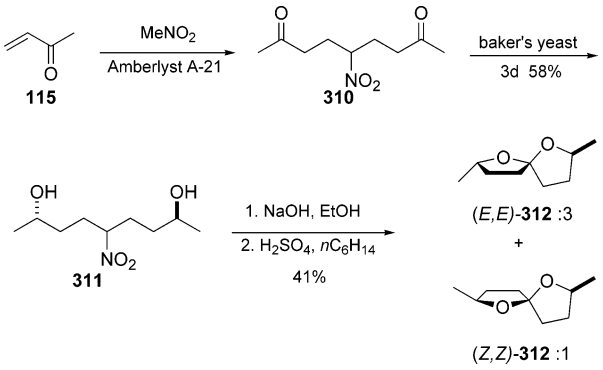


n	R	yield **309** %
1	Me	65
1	Et	70
2	Me	75
2	H	80

Claisen cleavage of the cycloalkanone ring giving hydroxynitronate **308** as an intermediate. Upon acidification of the reaction mixture a Nef reaction occurs, followed by a spontaneous cyclization to give spiroketals **309**.

Double conjugate addition of nitromethane to two equivalents of enones leads to the formation of symmetrical nitro diketones that upon reduction and Nef reaction afford the corresponding spiroketals.[212] Asymmetric reduction of the diketone **310** with Baker's yeast leads to the optically active alcohol **311** that after the nitro to carbonyl conversion gives the spiroketal system as a mixture of diastereomers (Scheme 88).[213] Reduction of symmetrical nitro dike-

Scheme 88



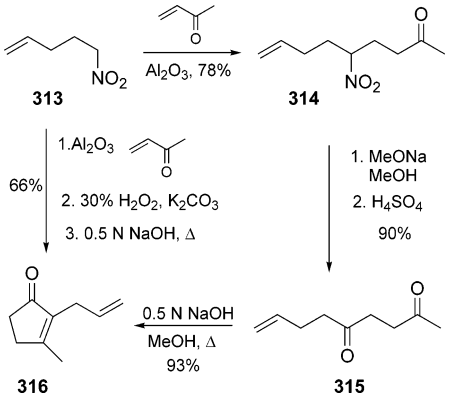
tones can also be realized using chiral reducing agents such as (+) or (−)-diisopinocampheylchloroborane with good results in terms of enantioselectivity of the obtained nitro alcohols.[214]

Asymmetric reduction using Baker's yeast can be successfully used with unsymmetrical nitro diketones to give optically active spiroketals featuring different ring sizes.[215]

7.3. Carbocycles

Allylrethrone **316** is an important component of an insecticidal pyrethroid, and its preparation can be realized in three distinct steps, starting from the nitroalkene **313** and methyl vinyl ketone (Scheme 89).[216] The obtained Michael adduct **314** is converted

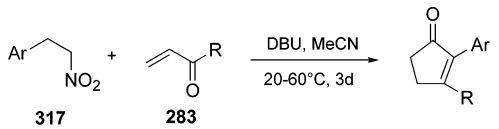
Scheme 89



into the diketone **315** by a hydrolytic Nef reaction and is then cyclized to allylrethrone **316** under basic conditions. Alternatively, the same process can be realized in a 'one-pot' reaction using hydrogen peroxide to carry out the nitro to carbonyl conversion.

The ability of DBU to promote a conjugate addition of nitroalkanes to enones as well as a Nef reaction on secondary nitroalkanes can be suitably used in a tandem process that allows the direct synthesis of cyclopentenone derivatives **318** (Scheme 90).[217]

Scheme 90



318a Ar = Ph; R= Me; 68%
318b Ar = Ph; R= Et; 65%
318c Ar = 4-MePh; R= Me; 78%

Double conjugate addition of nitroalkanes **1** with enones **283** in the presence of K_2CO_3 initially gives nitro diketone **319,** which undergoes an intramolecular aldol condensation to produce 2-acyl-4-nitrocyclohexanol derivatives **320** in a diastereoselective fashion (Scheme 91, Table 16).[218,219] Heating com-

Scheme 91

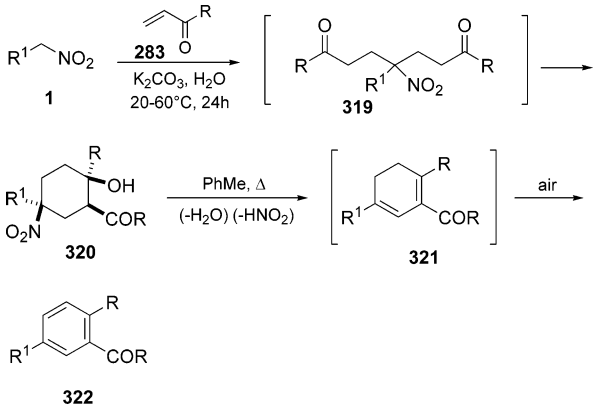


Table 16. Synthesis of Nitrocyclohexanols 320 and Their Oxidation to Aromatic Compounds 322

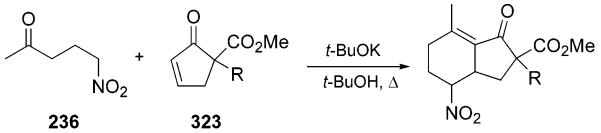
entry	R	R^1	**320** yield (%)	**322** yield (%)[c]
1	Me	Me	90[a]	53
2	Et	Me	85[a]	55
3	*n*-Pr	Me	93[a]	65
4	*n*-Bu	Me	95[b]	72
5	*n*-C_5H_{11}	Me	95[b]	61
6	*i*-Pr	Me	75[b]	50
7	Ph	Me	70[b]	80[d]
8	Me	Et	77[b]	50

[a] Reaction performed at room temperature. [b] Reaction performed at 60 °C. [c] Reaction time 15 h. [d] Reaction time 3 h.

pounds **320** in toluene at reflux in the presence of bubbling air provides a double elimination of water and nitrous acid to diene **321** that is subsequently oxidized by oxygen to the aromatic derivative **322**.

A related process occurs upon reaction of 2-nitrocycloalkanones with acrolein, leading to the synthesis of nitrocyclohexene derivatives.[220] Reaction of γ-nitro ketone **236** with cyclic β-keto esters **323** directly affords bicyclic compounds **324** through a conjugate addition−aldol condensation reaction (Scheme 92).[221,222] These derivatives are important precursors

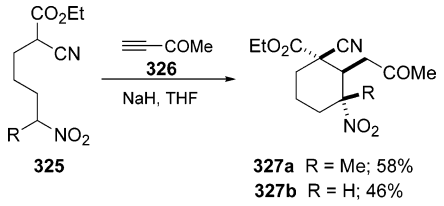
Scheme 92



of the germination stimulant strigol and its synthetic analogues.

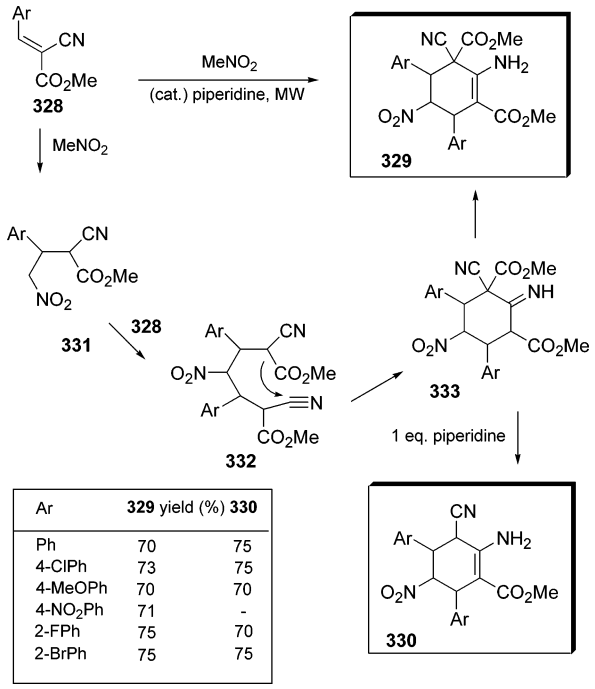
Nitro compounds **325** present two nucleophilic sites; therefore, by reaction with 3-butyn-2-one **326** a double conjugate addition occurs with formation of cyclohexyl derivative **327** as the main product (Scheme 93).[223] Compounds **327** are pivotal intermediates for the synthesis of *trans* decalines and hydrindanes.

Scheme 93



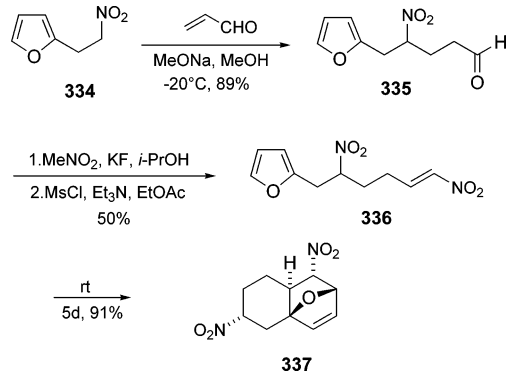
Functionalized cyclohexene derivatives **329** or **330** are obtained by reaction of arylidene cyanoacetate **328** with nitromethane in the presence of piperidine and under microwave irradiation (Scheme 94).[224,225] Double addition of alkene **328** to nitromethane affords compound **332,** which undergoes an intramolecular nucleophilic addition to give cyclic derivative **333**. If a catalytic amount of piperidine is used, tautomerization of imino derivative **333** occurs giving compound **329** as the main product. Alternatively, utilization of one equivalent of the basic promoter causes a decarboxylation of this intermediate, giving cyclohexene derivative **330** as the final product.

Scheme 94



Functionalized tricyclic derivative **337** is an intermediate for the synthesis of ergot alkaloids and valienamine analogues (Scheme 95).[226] Conjugate

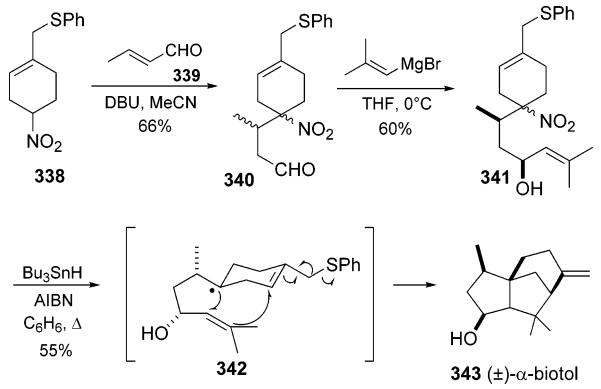
Scheme 95



addition of 2-furylnitroethane **334** to acrolein is followed by a Henry (nitroaldol) reaction−elimination of the obtained aldehyde **335** to afford nitroalkene **336**. This compound on standing at room temperature for 5 days undergoes to an intramolecular Diels−Alder reaction giving derivative **337** in good yield as a single diastereomer.

Denitration of nitroalkanes can be easily carried out in radical conditions using Bu_3SnH/AIBN. The intermediate radical produced may be reduced by hydrogen abstraction or alternatively react with alkenes giving an addition reaction. A synthetic approach to cedranoid sesquiterpene α-biotol **343** starts with a conjugate addition of nitrocyclohexene **338** to crotonaldehyde **339** to give nitro aldehyde **340** that upon reaction with isobutenylmagnesium bromide affords nitro alcohol **341** (Scheme 96).[227−229] The radical intermediate **342** formed upon reaction with Bu_3SnH/AIBN reacts through a cascade cyclization giving α-biotol **343**. The stereochemistry of the obtained tricyclic compound **343** is totally controlled

Scheme 96

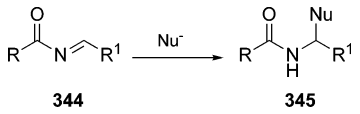


by the configuration of the carbon bearing the hydroxy group. Nitrocyclohexitols can be prepared from the adducts of nitroalkanes to acrolein using an enzymatic aldol reaction followed by a highly stereoselective intramolecular nitroaldol reaction.[230]

7.4. Amino Acids and Derivatives

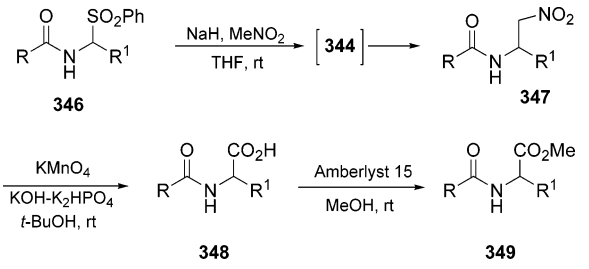
The synthesis of α-amino acid derivatives cannot be accomplished by usual conjugate addition of nitroalkanes to common Michael acceptors. However, keeping in mind that a primary nitro group can be easily converted into a carboxylic group using the Nef reaction, some alternative strategies can be devised to realize the synthesis of α-amino acids using a conjugate addition process. *N*-Acylimines **344** are powerful electrophilic substrates that upon reaction with nucleophilic reagents undergo to a conjugate addition giving the corresponding product **345** (Scheme 97).

Scheme 97



N-Acyl- and *N*-carbamoylimines **344** are too unstable to be stored when prepared from aliphatic aldehydes (R^1 = alkyl) since they rapidly decompose or tautomerize to the corresponding enecarbamate. However, imines **344** can be generated *in situ* starting from α-amidoalkylphenyl sulfones **346** by a base-induced elimination of benzenesulfinic acid (Scheme 98).[231] In the presence of a nucleophilic reagent as

Scheme 98



the nitromethane anion, a conjugate addition occurs giving the corresponding nitro derivative **347**. The nitro group of compound **347** can be readily converted into a carboxylic acid **348** using alkaline $KMnO_4$ solutions giving, after methylation, *N*-acyl-α-amino acid esters **349**. The utilization of α-carbamoylalkylphenyl sulfones (**346** R = OBn, O*t*-Bu) allows a rapid cleavage of the *N*-protecting group of the final acid **348** to give the free amino acid compound (Table 17).

This procedure can be extended to optically active α-amidoalkylphenyl sulfones that using the same synthetic approach lead to the preparation of interesting target molecules featured by the α-amino acid moiety. Chiral sulfones **350** react with the anion of nitromethane with high diastereoselectivity, preferentially giving the *anti* adducts **351** that upon Nef conversion produce *β*-hydroxy-α-amino acid esters **352** (Scheme 99).[232]

Similarly, sulfone **353** featuring a pyrrolidine ring can be transformed into nitro derivative **354** and α-amino acid ester **355,** which is a precursor of chiral piperazine-2-carboxylic acids **356** that are useful catalysts in asymmetric synthesis (Scheme 100).

Stable isotope-labeled L-glutamic acid can be prepared from ^{13}C-enriched compounds following a strategy involving the conjugate addition of ethyl nitroacetate **256** to ethyl acrylate (Scheme 101).[233] Oxidative Nef conversion of the 2-nitroglutarate **357** to diethyl 2-oxoglutarate and ester hydrolysis gives 2-oxoglutaric acid **358**. This diacid is trasformed into L-glutamic acid **359** using the commercially available enzyme glutamic dehydrogenase in the presence of ammonium ions.

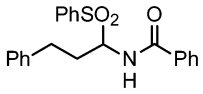
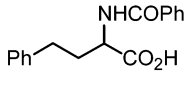
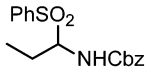
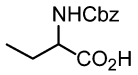
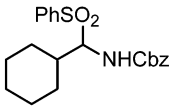
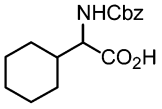
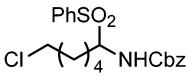
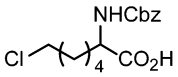
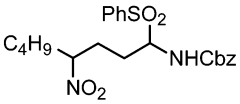
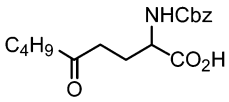
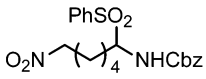
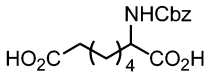
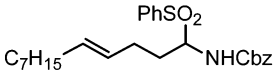
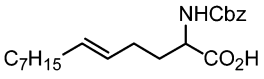
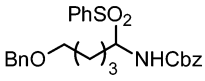
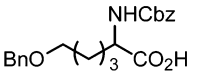
Conjugate addition of nitroalkanes to dehydroalanine **360** affords *γ*-nitro-α-amino acids such as **361** in racemic form (Scheme 102).[234] This adduct is further elaborated by converting the nitro group into a carbonyl moiety that can be reduced *in situ* to a diastereomeric pair of *γ*-hydroxy-α-amino acids **362** in a 1:1 ratio. The acid-catalyzed cyclization of these hydroxy derivatives gives the 2-aminolactones **363**.

Conjugate addition of nitroalkanes to enoates results in the formation of *γ*-nitro ester derivatives that can be reduced at the nitro group to give the corresponding *γ*-amino esters. Enzymatic resolution of product **365** obtained by conjugate addition of nitromethane to benzyl 2-trifluoromethylpropenoate **364** provides acid **366** and ester **367** that after simple separation can be reduced at the nitro group to afford *γ*-amino acid **368** and *γ*-amino ester **369** in almost enantiomerically pure form (Scheme 103).[235]

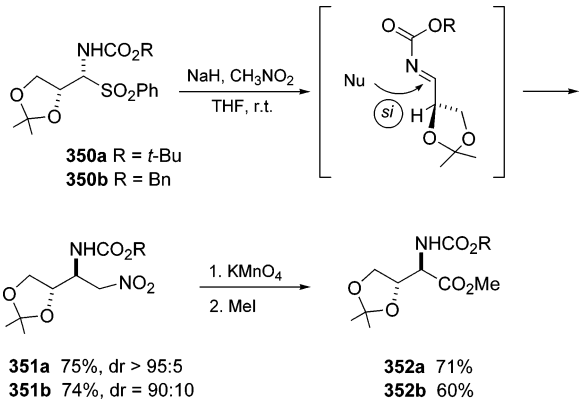
7.5. Other Applications

Polyfunctionalized compounds can be easily prepared combining the conjugate addition process with other transformations involving the nitro group in sequential reactions that can be often realized by a one-pot procedure, thus avoiding the isolation of any intermediate.[236] Addition of 2-nitrocycloalkanones **114** with enones **283** occurs in mild conditions to give 1,5-dicarbonyl derivatives **370** (Scheme 104).[237,238] A retro-Claisen cleavage of the 2-nitrocycloalkanones **370** can be realized by addition to the reaction mixture of a methanolic solution of KOH giving open-chain nitronates **371** that are oxidized to trioxo derivatives **372**−**374** simply adding aqueous permanganate solution.

Table 17. Base-Assisted Substitutions of Sulfones 346 into Nitro Derivatives 347 and Their Conversion to α-Amino Acids 348

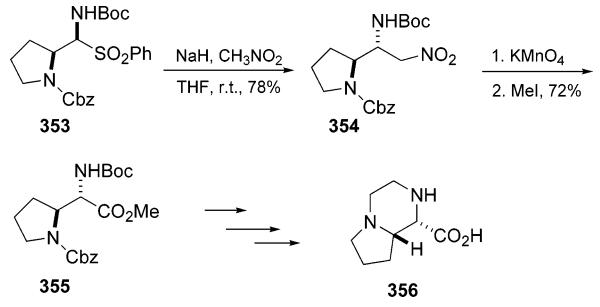
entry	sulfone **346**	nitro **347** yield (%)	amino acid **348**	yield (%) (methyl ester **349**)
a		87		90 (95)
b		78		81 (93)
c		90		88 (97)
d		77		85 (92)
e		80		83 (90)
f		83		78 (92)
g		85		72[a] (91)
h		79		70[a] (88)

Scheme 99



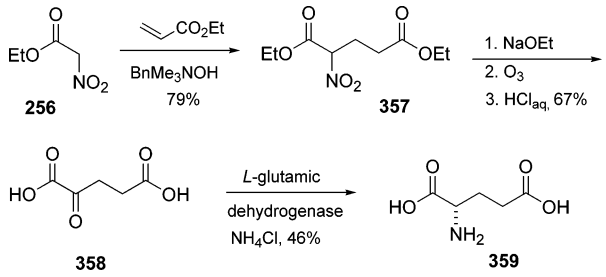
1,3-Dinitroalkanes **376** can be prepared heating at reflux an aldehyde **375** with an excess of nitromethane in the presence of basic alumina (Scheme 105).[239] Dinitro derivatives **376** are obtained by a tandem process involving a preliminary nitroaldol condensation followed by a dehydration to the corresponding nitroalkenes **378** that undergo a conjugate addition of the nitromethyl anion to the final compounds **376**.

Scheme 100

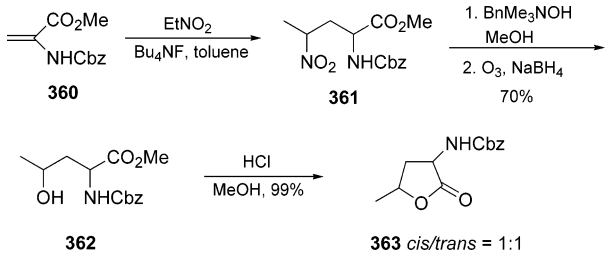


Diesters of (*E*)-2-alkylidenesuccinic acids **379** obtained by conjugate addition of nitroalkanes to dimethyl maleate can be selectively monohydrolyzed at the more reactive carboxyl group to the corresponding half-ester **380** (Scheme 106).[240] Alternatively, total hydrolysis to the diacid **381** allows a subsequent selective methyl esterification of the alkanoic carboxyl group to give the other regioisomeric half-ester **382**. 2-Alkylsuccinic monoesters can be also obtained by catalytic hydrogenation of the unsaturated derivatives **380**−**382**.

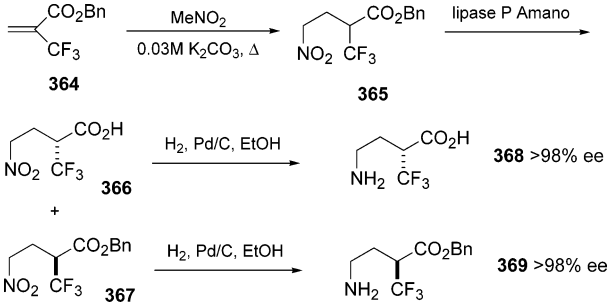
Scheme 101



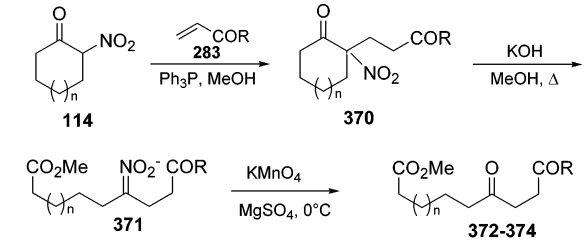
Scheme 102



Scheme 103

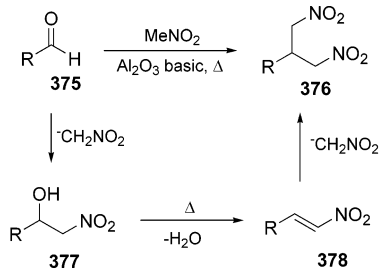


Scheme 104



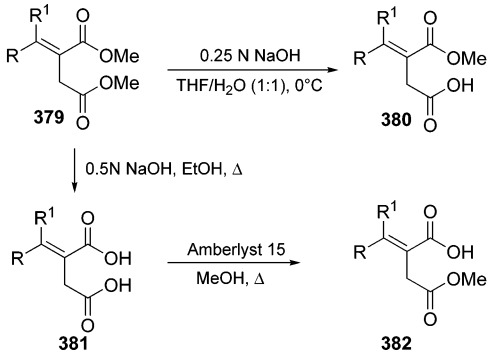
n	R	yield **372** %	R	yield **373** %	R	yield **374** %
1	Me	87	H	92	OMe	70
2	Me	75	H	75	OMe	67
7	Me	93	H	73	OMe	50
10	Me	80	H	70	OMe	50

Scheme 105



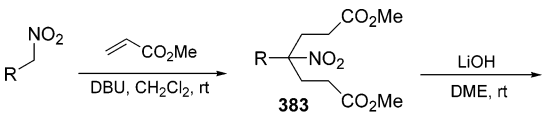
R	yield **376** %	R	yield **376** %
$Ph(CH_2)_2$	78	4-CF_3Ph	73
Me_2CH	62	4-MeOPh	74
$Me(CH_2)_2$	68	3-pyridyl	60
Ph	71	2-furyl	70

Scheme 106

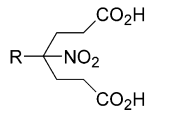


R	R^1	**380** yield(%)	**381** yield(%)	**382** yield(%)
Et	H	95	98	86
$-(CH_2)_5-$		85	92	80
$HO(CH_2)_5$	H	74	89	76
$MeCO(CH_2)_2$	H	73	91	71

Scheme 107



1a R = $CH_3(CH_2)_{16}$
1b R = (*Z,Z,Z,Z*)-$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2$



384a (86% overall)
384b (76% overall)

The reactivity of nitroalkanes toward multiple addition can be profitably used for the preparation of nitro-substituted fatty acids, which are interesting derivatives resistant to β-oxidation in living systems.

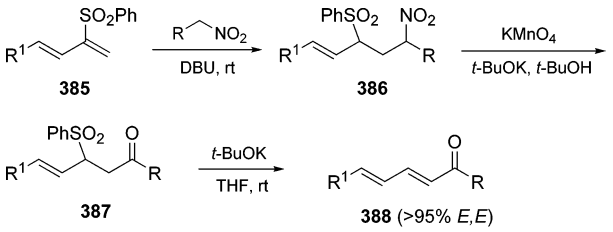
Nitro derivatives **1** obtained from the corresponding fatty alcohols are made to react with a large excess of methyl acrylate in the presence of DBU giving bis adducts **383** that upon hydrolysis afford diacids **384** in good overall yield (Scheme 107).[241]

An interesting approach to the preparation of conjugated dienones involves as first step the Michael addition of nitroalkanes to 2-phenylsulfonyl-1,3-dienes **385** to give nitro sulfones **386** (Scheme 108).[242] Conversion of the nitro group into a ketone **387** is followed by a base-induced elimination of benzenesulfinic acid giving dienone **388** with high diastereoselectivity (>95% *E,E*).

Substituted allylnitro compounds **389** are regiochemically stable derivatives that undergo to a conjugate addition to methyl vinyl ketone giving nitroalkenes **390** (Scheme 109).[243] Despite the basic conditions the reaction occurs without any observed migration of the double bond.

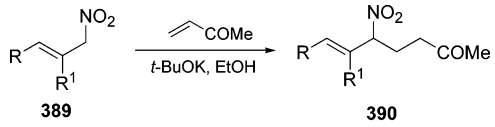
Conjugated nitrosoalkenes **394** are typical electron-poor olefins that can be generated *in situ* by reaction of fluoride ions with *N,N*-bis(silyloxy)enamines **391** at low temperature (Scheme 110).[244] In the presence

Scheme 108



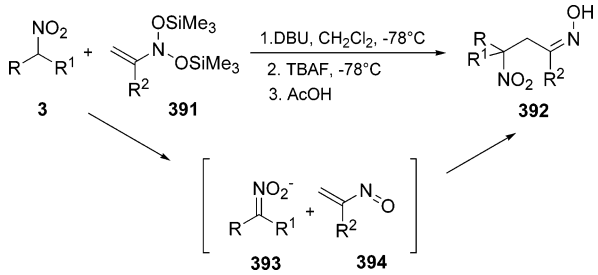
R	R^1	**386** yield(%)	**387** yield(%)	**388** yield(%)
Me	Me	92	81	76
H	Me	81	56	67
Me	n-C_5H_{11}	60	79	69
H	n-C_5H_{11}	43	77	64

Scheme 109



R	R^1	**390** yield (%)
Me	Me	83
Et	Me	61
n-C_5H_{11}	Me	64
Me	Et	70

Scheme 110



of nitronate anions **393** formed from the corresponding nitroalkanes **3** a conjugate reaction occurs leading, after acidic quenching, to β-nitro oximes **392** (Table 18).

Table 18. Synthesis of β-Nitro Oximes 392 from *N,N*-Bis(silyloxy)Enamines 391

entry	R	R^1	R^2	**392** yield (%)
1	Et	H	Me	78
2	$MeO_2C(CH_2)_2$	H	Me	90
3	MeO_2C	H	Me	64
4	MeO_2CCH_2	H	H	88
5	Et	H	$MeO_2C(CH_2)_2$	76
6	MeO_2C	H	$MeO_2C(CH_2)_2$	78
7	Me	Me	Me	72
8	MeO_2CCH_2	Me	Me	71
9	MeO_2CCH_2	Me	H	62
10	$MeO_2C(CH_2)_2$	Me	$MeO_2C(CH_2)_2$	70

8. Conclusion

Nitroalkanes are a convenient source of stabilized carbanions that react with electron-poor alkenes giving the corresponding 1,4-adducts with high regioselectivity. The addition process is usually realized in basic media that strongly affects the selectivity and efficiency achievable in carbon−carbon bond formation. The presence of chiral centers in the nitroalkane or in the α,β-unsaturated derivative allows a certain degree of stereocontrol in the formation of the corresponding adducts. Enantioselective processes can be realized with the aid of chiral catalysts, although only recently satisfactory results in terms of ee's have been obtained. Besides the formation of simple carbon−carbon bonds, the conjugate addition of nitroalkanes to dienones and dienoates permits the creation of new carbon−carbon double bonds by means of a tandem elimination of nitrous acid that occurs after the primary addition process. The nitro group, once it has been introduced in the molecular framework by the conjugate addition, really acts as a chemical chameleon since it can be reduced to the amino group, replaced by a hydrogen atom, or transformed into a carbonyl group. For these reasons an increasing number of synthetic procedures devoted to the preparation of important target molecules profitably include the conjugate addition of nitroalkanes to electron-deficient alkenes into some crucial step of the overall synthetic plan.

9. Abbreviations

ABCN	azobiscyclohexylnitrile
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butoxycarbamoyl
Bz	benzoyl
Cbz	benzylcarbamoyl
CTAB	cetyltrimethylammonium bromide
CTACl	cetyltrimethylammonium chloride
CTAOH	cetyltrimethylammonium hydroxide
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DME	1,2-dimethoxyethane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EWG	electron-withdrawing group
HMS	hexagonal mesoporous silica
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
Ms	methanesulfonyl
MW	microwave
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium
PMB	4-methoxybenzyl
PNB	4-nitrobenzyl
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEBA	triethylbenzylammonium chloride
THF	tetrahydrofuran
TMG	tetramethylguanidine
TMP	2,2,6,6-tetramethylpiperidine
Ts	4-toluenesulfonyl

10. Acknowledgments

The authors are greatly indebted to their coworkers whose names are cited in the references, for their enthusiasm and dedication. Financial support has been granted by M.I.U.R. and the University of Camerino. This review is dedicated to Professor

Goffredo Rosini (University of Bologna) on the occasion of his 65th birthday.

11. References

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Pergamon: Oxford, 1992.
(2) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179.
(3) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
(4) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
(5) *Nitro Compounds Recent Advances in Synthesis and Chemistry*; Feuer, H., Nielsen, A. T., Eds.; VCH: Weinheim, 1990.
(6) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
(7) *The Chemistry of Amino, Nitroso, Nitro and Related Groups;* Patai, S., Ed.; Wiley: Chichester, 1996.
(8) Adams, J. P. *J. Chem. Soc., Perkin Trans.1* **2002**, 2586.
(9) Seebach, D.; Lehr, F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 505.
(10) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon: Oxford, 1991; Vol. 2, p 321.
(11) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
(12) Rosini, G.; Ballini, R.; Zanotti, V. *Synthesis* **1983**, 137.
(13) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
(14) Pinnick, H. W. *Org. React.* **1990**, *38*, 655.
(15) Simpkins, N. S. *Sulphones in Organic Synthesis;* Pergamon: Oxford, 1993.
(16) Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 941.
(17) Oshida, J.; Okamoto, M.; Azuma, S.; Tanaka, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2579.
(18) Nakagawa, M.; Tsuruoka, A.; Yoshida, J.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1990**, 603.
(19) Nakamura, K.; Kitayama, T.; Inoue, Y.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 91.
(20) Kitayama, T. *Tetrahedron* **1996**, *52*, 6139.
(21) Lubineau, A.; Augé, J. *Tetrahedron Lett.* **1992**, *33*, 8073.
(22) Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1999**, *55*, 3937.
(23) Nan, F.; Bzdega, T.; Pshenichkin, S.; Wroblewski, J. T.; Wroblewska, B.; Neale, J. H.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 772.
(24) Nakashita, N.; Hesse, M. *Helv. Chim. Acta* **1983**, *66*, 845.
(25) Derri Alcantara, M. P.; Escribano, F. C.; Gómez-Sánchez, A.; Diánez, M. J.; Estrada, M. D.; López-Castro, A.; Pérez-Garrido, S. *Synthesis* **1996**, 64.
(26) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.
(27) Grimm, E. L.; Zschiesche, R.; Reissig, H. U. *J. Org. Chem.* **1985**, *50*, 5543.
(28) Chasar, D. W. *Synthesis* **1982**, 841.
(29) Chetia, A.; Saikia, C. J.; Lekhok, K. C.; Boruah, R. C. *Tetrahedron Lett.* **2004**, *45*, 2649.
(30) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis* **1984**, 226.
(31) Pollini, G. P.; Barco, A.; De Giuli, G. *Synthesis* **1972**, 44.
(32) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879.
(33) Zia-Ebrahimi, M.; Huffman, G. W. *Synthesis* **1996**, 215.
(34) Rosini, G.; Marotta, E.; Ballini, R.; Petrini, M. *Synthesis* **1986**, 237.
(35) Bergbreiter, D. F.; Lalonde, J. J. *J. Org. Chem.* **1987**, *52*, 1601.
(36) Ballini, R.; Petrini, M.; Rosini, G. *Synthesis* **1987**, 711.
(37) Baasner, B.; Marhold, A.; Negele, M. *J. Fluorine Chem.* **1990**, *46*, 161.
(38) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897.
(39) Ballini, R.; Bosica, G.; *Tetrahedron Lett.* **1996**, *37*, 8027.
(40) Ballini, R.; Bosica, G.; Livi, D.; Palmieri, A.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **2003**, *44*, 2271.
(41) Mdoe, J. E. G.; Clark, J. H.; Macquarrie, D. J. *Synlett* **1998**, 625.
(42) Mudaliar, C. D.; Nivalkar, K. R.; Mashraqui, S. H. *Org. Prep. Proc. Int.* **1997**, *29*, 584.
(43) da Silva, F. M.; Gomes, A. K.; Jones, J. *Can. J. Chem.* **1999**, *77*, 624.
(44) Choudary, B. M.; Kantam, M. L.; Kavita, B.; Reddy, C. V.; Figueras, F. *Tetrahedron* **2000**, *56*, 9357.
(45) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **1996**, 965.
(46) Ranu, B. C.; Bhar, S. *Tetrahedron* **1992**, *48*, 1327.
(47) Costantino, U.; Marmottini, F.; Curini, M.; Rosati, O. *Catal. Lett.* **1993**, *22*, 333.
(48) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553.
(49) Bergbreiter, D. E.; Li, C. *Org. Lett.* **2003**, *5*, 2245.
(50) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555.
(51) Jouglet, B.; Blanco, L.; Rousseau, G. *Synlett* **1991**, 907.
(52) Sebti, S.; Boukhal, H.; Hanafi, N.; Boulaajaj, S. *Tetrahedron Lett.* **1999**, *40*, 6207.
(53) Michaud, D.; Abdallah-El Ayoubi, S.; Dozias, M.-J.; Toupet, L.; Texier-Boullet, F.; Hamelin, J. *Chem. Commun.* **1997**, 1613.
(54) Michaud, D.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* **1997**, *38*, 7563.
(55) Ballini, R.; Marziali, P.; Mozzicafreddo, A. *J. Org. Chem.* **1996**, *61*, 3209.
(56) Niyazymbetov, M. E.; Evans, D. H. *J. Org. Chem.* **1993**, *58*, 779.
(57) Keller, E.; Feringa, B. L. *Synlett* **1997**, 842.
(58) Ballini, R.; Fiorini, D.; Gil, M. V.; Palmieri, A. *Green Chem.* **2003**, *5*, 475.
(59) Miranda, S.; López-Alvarado, P.; Giorgi, G.; Rodriguez, J.; Avedaño, C.; Menéndez, J. C. *Synlett* **2003**, 2159.
(60) Laikhter, A. L.; Niyazymbetov, M. E.; Evans, D. H.; Samet, A. V.; Semenov, V. V. *Tetrahedron Lett.* **1993**, *34*, 4465.
(61) Samet, A. V.; Niyazymbetov, M. E.; Semenov, V. V.; Laikhter, A. L.; Evans, D. H. *J. Org. Chem.* **1996**, *61*, 8786.
(62) Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* **2001**, *42*, 8471.
(63) Ballini, R.; Fiorini, D.; Gil, M. V.; Palmieri, A. *Tetrahedron* **2004**, *60*, 2799.
(64) Patrocinio, V.; Costa, P. R. R.; Correia, C. R. D. *Synthesis* **1994**, 474.
(65) Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002.
(66) Pinto, A. C.; Freitas, C. B. L.; Dias, A. G.; Pereira, V. L. P.; Tinant, B.; Declercq, J.-P.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2002**, *13*, 1025.
(67) Krief, A.; Provins, L.; Froidbise, A. *Synlett* **1999**, 1936.
(68) Plummer, J. S.; Emery, L. A.; Stier, M. A.; Suto, M. J. *Tetrahedron Lett.* **1993**, *34*, 7529.
(69) Ballini, R.; Fiorini, D.; Palmieri, A.; Petrini, M. *Lett. Org. Chem.* **2004**, *1*, 335.
(70) Camps, P.; Muñoz-Torrero, D.; Sánchez, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2039.
(71) Bartels, A.; Jones, P. G.; Liebscher, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1545.
(72) Crossley, M. J.; Tansey, C. W. *Aust. J. Chem.* **1992**, *45*, 479.
(73) Versleijen, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803.
(74) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766.
(75) Garg, N.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 5189.
(76) Areces, P.; Gil, M. V.; Higes, F. J.; Román, E.; Serrano, J. A. *Tetrahedron Lett.* **1998**, *39*, 8557.
(77) Ballini, R.; Bosica, G.; Gil, M. V.; Román, E.; Serrano, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1773.
(78) Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.* **2002**, *43*, 1991.
(79) Sosnicki, J. G.; Liebscher, J. *Synlett* **1996**, 1117.
(80) Asaoka, M.; Sonoda, S.; Fujii, N.; Takei, H. *Tetrahedron* **1990**, *46*, 1541.
(81) Trost, B. M.; Crawley, M. L. *Chem. Eur. J.* **2004**, *10*, 2237.
(82) Forsyth, A. C.; Gould, R. O.; Paton, R. M.; Sadler, I. H.; Watt, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2737.
(83) Witczak, Z. J.; Li, Y. *Tetrahedron Lett.***1995**, *36*, 2595.
(84) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *J. Chem. Soc., Chem. Commun.* **1991**, 390.
(85) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279.
(86) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *Gazz. Chim. Ital.* **1993**, *123*, 185.
(87) Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Spalluto, G.; Zanirato, V. *Tetrahedron* **1994**, *50*, 2583.
(88) Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.; Muraoka, O.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1123.
(89) Yasuhara, T.; Osafune, E.; Nishimura, K.; Yamashita, M.; Yamada, K.; Muraoka, O.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 3043.
(90) Jousse, C.; Mainguy, D.; Desmaële, D. *Tetrahedron Lett.* **1998**, *39*, 1349.
(91) Jousse, C.; Desmaële, D. *Eur. J. Org. Chem.* **1999**, 909.
(92) Jousse-Karinthi, C.; Zhouiri, F.; Mahuteau, J.; Desmaële, D. *Tetrahedron* **2003**, *59*, 2093.
(93) Cristoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.
(94) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.
(95) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
(96) Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051.
(97) Botteghi, C.; Paganelli, S.; Schionato, A.; Boga, C.; Fava, A. *J. Mol. Catal.* **1991**, *66*, 7.
(98) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223.
(99) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.
(100) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233.

(101) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.
(102) Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, 4014.
(103) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331.
(104) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4*, 173.
(105) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257.
(106) Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4215.
(107) Thomas, A.; Manjunatha, S. G.; Rajappa, S. *Helv. Chim. Acta* **1992**, *75*, 715.
(108) Boyle, P. H.; Convery, M. A.; Davis, A. P.; Hosken, G. D.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1992**, 239.
(109) van Aken, E.; Wynberg, H.; van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1992**, 629.
(110) Davis, A. P.; Dempsey, K. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2829.
(111) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677.
(112) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557.
(113) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403.
(114) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.
(115) Bakó, T.; Bakó, P.; Szöllõsy, M.; Czugler, M.; Keglevich, G.; Tõke, L. *Tetrahedron: Asymmetry* **2002**, *13*, 203.
(116) Novák, T.; Tatai, J.; Bakó, P.; Czugler, M.; Keglevich, G.; Tõke, L. *Synlett* **2001**, 424.
(117) Bakó, P.; Bajor, Z.; Tõke, L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3651.
(118) Bakó, P.; Novák, T.; Ludányi, K.; Pete, B.; Tõke, L.; Keglevich, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2373.
(119) Bakó, P.; Czinege, E.; Bakó, T.; Czugler, M.; Tõke, L. *Tetrahedron: Asymmetry* **1999**, *10*, 4539.
(120) Bakó, P.; Vizvárdi, K.; Bajor, Z.; Tõke, L. *Chem. Commun.* **1998**, 1193.
(121) Bakó, P.; Szöllõsy, M.; Bombicz, P.; Tõke, L. *Synlett* **1997**, 291.
(122) Bakó, P.; Kiss, T.; Tõke, L. *Tetrahedron Lett.* **1997**, *38*, 7259.
(123) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526.
(124) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.
(125) Ooi, T.; Morimoto, K.; Doda, K.; Maruoka, K. *Chem. Lett.*. **2004**, *33*, 824.
(126) Ooi, T.; Fuijoka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790.
(127) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
(128) Bauchat, P.; Le Rouillé, E.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1991**, *128*, 267.
(129) Chamakh, A.; M'hirsi, M.; Villiéras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295.
(130) Kim, J. M.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Kor. Chem. Soc.* **2002**, *23*, 657.
(131) Ballini, R.; Bosica, G.; Livi, D. *Synthesis* **2001**, 1519.
(132) Ballini, R.; Bosica, G. *Eur. J. Org. Chem.* **1998**, 355.
(133) Kraïem, H.; Turki, T.; Amri, H. *Synth. Commun.* **2003**, *33*, 3261.
(134) Wang, W.; Yu, M. *Tetrahedron Lett.* **2004**, *45*, 7141.
(135) Kim, J. N.; Im, Y. J.; Gong, J. H.; Lee, K. Y. *Tetrahedron Lett.* **2001**, *42*, 4195.
(136) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* **2004**, *60*, 4995.
(137) Ballini, R.; Rinaldi, A. *Tetrahedron Lett.* **1994**, *35*, 9247.
(138) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213.
(139) Ballini, R.; Bosica, G.; Petrelli, L.; Petrini, M. *Synthesis* **1999**, 1236.
(140) Kakiuchi, T.; Kato, H.; Jayasundera, K. P.; Higashi, T.; Watabe, K.; Sawamoto, D.; Kinoshita, H.; Inomata, K. *Chem. Lett* **1998**, 1001.
(141) Ballini, R.; Bosica, G.; Cioci, G.; Fiorini, D.; Petrini, M. *Tetrahedron* **2003**, *59*, 3603.
(142) Ballini, R.; Bosica, G.; Fiorini, D.; Gil, M. V.; Palmieri, A. *Synthesis* **2004**, 605.
(143) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Gil, M. V. *Synlett* **2002**, 1706.
(144) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233.
(145) Ballini, R.; Bosica, G.; Fiorini, D.; Gil, M. V.; Petrini, M. *Org. Lett.* **2001**, *3*, 1265.
(146) Ballini, R.; Fiorini, D.; Gil, M. V.; Palmieri, A. *Tetrahedron Lett.* **2003**, *44*, 9033.
(147) Lalitha, N.; Bhalerao, U. T.; Iyengar, D. S. *J. Chem. Soc., Chem. Commun.* **1991**, 897.
(148) Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* **2003**, 1704.
(149) Braish, T. F.; Castaldi, M.; Chan, S.; Fox, D. A.; Keltonic, T.; McGarry, J.; Hawkins, J. M.; Norris, T.; Rose, P. R.; Sieser, J. E.; Sitter, B. J.; Watson, H., Jr. *Synlett* **1996**, 1100.
(150) Weis, C. D.; Newkome, G. R. *J. Org. Chem.* **1990**, *55*, 5801.
(151) Newkome, G. R.; Weis, C. D. *J. Org. Chem.* **1991**, *56*, 4798.
(152) Newkome, G. R.; Weis, C. D. *Org. Prep. Proc. Int.* **1996**, *28*, 495.
(153) Bajpal, L. K.; Bhanduri, A. P. *J. Chem. Res. (S)* **1996**, 522.
(154) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729.
(155) Hagen, T. J.; Bergmanis, A. A.; Kramer, S. W.; Fok, K. F.; Schmelzer, A. E.; Pitzele, B. S.; Swenton, L.; Jerome, G. M.; Kornmeier, C. M.; Moore, W. M.; Branson, L. F.; Connor, J. R.; Manning, P. T.; Currie, M. G.; Hallinan, E. A. *J. Med. Chem.* **1998**, *41*, 3675.
(156) Domingos, J. L. O.; Lima, E. C.; Dias, A. G.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2313.
(157) Aszodi, J.; Rowlands, D. A.; Mauvais, P.; Collette, P.; Bonnefoy, A.; Lampilas, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2489.
(158) Felluga, F.; Gombac, V.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2004**, *15*, 3323.
(159) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621.
(160) Mironiuk-Puchalska, E.; Kołaczkowska, E.; Sas, W. *Tetrahedron Lett.* **2002**, *43*, 8351.
(161) Kuciak, R.; Sas, W. *Tetrahedron Lett.* **1994**, *35*, 8647.
(162) Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436.
(163) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276.
(164) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Töke, L. *Tetrahedron Lett.* **1994**, *35*, 4413.
(165) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Töke, L. *Tetrahedron* **1995**, *51*, 11489.
(166) Mouna, A. M.; Blanchard, P.; Fourrey, J.-L.; Robert-Gero, M. *Tetrahedron Lett.* **1990**, *31*, 7003.
(167) Desai, M. C.; Lefkowitz, S. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2083.
(168) Vavreka, M.; Janowitz, A.; Hesse, M. *Tetrahedron Lett.* **1991**, *32*, 5543.
(169) Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Righi, P. *Org. Prep. Proc. Int.* **1990**, *22*, 707.
(170) Ballini, R. *Synlett.* **1999**, 1009.
(171) Vavreka, M.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 438.
(172) Francke, W.; Schröder, F.; Walter, F.; Sinnwell, V.; Baumann, H.; Kaib, M. *Liebigs Ann.* **1995**, 965.
(173) Chittari, P.; Thomas, A.; Rajappa, S. *Tetrahedron Lett.* **1994**, *35*, 3793.
(174) Thomas, A.; Rajappa, S. *Tetrahedron* **1995**, *51*, 10571.
(175) Krawczyk, H.; Wolf, W. M.; Śliwiński, M. *J. Chem. Soc., Perkin Trans 1* **2002**, 2794.
(176) Zhang, Y.-K.; Xu, G.-Z. *J. Chem. Res.(S)* **1990**, 104.
(177) Zhang, Y.-K.; Lu, D.-H.; Xu, G.-Z. *J. Chem. Soc., Perkin Trans 2* **1991**, 1855
(178) Black, D. S. C.; Deb-Das, R. B.; Kumar, N. *Austr. J. Chem.* **1992**, *45*, 1051.
(179) Gibson, N. J.; Forrester, A. R.; Brown, C. *J. Chem. Soc., Perkin Trans 1* **1995**, 507.
(180) Sankuratri, N.; Janzen, E. G.; West, M. S.; Poyer, J. L. *J. Org. Chem.* **1997**, *62*, 1176.
(181) Le, D. D.; Zhang, Y.; Nguyen, D.; Moravek, J. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 1107.
(182) Black, D. S. C.; Edwards, G. L.; Evans, R. H.; Keller, P. A.; Laaman, S. M. *Tetrahedron* **2000**, *56*, 1889.
(183) Nsanzumuhire, C.; Clément, J.-L.; Ouari, O.; Karoui, H.; Finet, J.-P.; Tordo, P. *Tetrahedron Lett.* **2004**, *45*, 6785.
(184) Galli, C.; Marotta, E.; Righi, P.; Rosini, G. *J. Org. Chem.* **1995**, *60*, 6624.
(185) Ballini, R.; Bosica, G.; Masè, A.; Petrini, M. *Eur. J. Org. Chem.***2000**, 2927.
(186) Ballini, R.; Bosica, G.; Damiani, M.; Righi, P. *Tetrahedron* **1999**, *55*, 13451.
(187) Béji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959.
(188) Béji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Synth. Commun.* **2002**, *32*, 3273.
(189) Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. *Synlett* **2000**, 391.
(190) Ballini, R.; Bosica, G.; Fiorini, D.; Giarlo, G. *Synthesis* **2001**, 2003.
(191) Ranu, B. C.; Hajra, A. *Tetrahedron* **2001**, *57*, 4767.
(192) Lui, K.-H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans 1* **1990**, 457.
(193) van Leusen, D.; Flentge, E.; van Leusen, A. M. *Tetrahedron* **1991**, *47*, 4639.
(194) Gibbs, G.; Hateley, M. J.; McLaren, L.; Welham, M.; Willis, C. L. *Tetrahedron Lett.* **1999**, *40*, 1069.
(195) Crosby, S. R.; Hateley, M. J.; Willis, C. L. *Tetrahedron Lett.* **2000**, *41*, 397.
(196) Sil, D.; Sharon, A.; Maulik, P. R.; Ram. V. J. *Tetrahedron Lett.* **2004**, *45*, 6273.
(197) Ballini, R.; Bosica, G. *Synlett* **1996**, 1115.
(198) Ballini, R.; Bosica, G. *Liebigs Ann.* **1996**, 2087.
(199) Ballini, R.; Marcantoni, E.; Perella, S. *J. Org. Chem.* **1999**, *64*, 2954.
(200) Ballini, R.; Bosica, G.; Fiorini, D.; Righi, P. *Synthesis* **2002**, 681.

(201) Ballini, R.; Fiorini, D.; Gil, M. V.; Palmieri, A.; Román, E.; Serrano, J. A. *Tetrahedron Lett.* **2003**, *44*, 2795.
(202) Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2003**, *68*, 9173.
(203) Sarmah, B. K.; Barua, N. C. *Tetrahedron* **1993**, *49*, 2253.
(204) Guarna, A.; Occhiato, E. G.; Spinetti, L. M.; Vallecchi, M. E.; Scarpi, D. *Tetrahedron* **1995**, *51*, 1775.
(205) Fantin, G.; Fogagnolo, M.; Guerzoni, E. M.; Marotta, E.; Medici, A.; Pedrini, P. *Tetrahedron: Asymmetry* **1992**, *3*, 947.
(206) Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron* **1999**, *55*, 5177.
(207) Kalita, D.; Khan, A. T.; Saikia, A. K.; Bez, G.; Barua, N. C. *Synthesis* **1998**, 975.
(208) Ballini, R.; Bosica, G. *J. Nat. Prod.* **1994**, *57*, 1462.
(209) Saikia, A. K.; Hazarika, M. J.; Barua, N. C.; Bezbarua, M. S.; Sharma, R. P.; Ghosh, A. C. *Synthesis* **1996**, 981.
(210) Bez, G.; Saikia, A. K.; Kalita, D.; Bezbarua, M. S.; Barua, N. C. *Indian J. Chem.* **1998**, *37B*, 325.
(211) Ballini, R.; Petrini, M.; Rosini, G. *Tetrahedron* **1990**, *46*, 7531.
(212) Ballini, R.; Bosica, G.; Uselli, A. *J. Heterocycl. Chem.* **1994**, *31*, 259.
(213) Occhiato, E. G.; Guarna, A.; De Sarlo, F.; Scarpi, D. *Tetrahedron: Asymmetry* **1995**, *6*, 2971.
(214) Occhiato, E. G.; Scarpi, D.; Menchi, G.; Guarna, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1929.
(215) Bez, G.; Bezbarua, M. S.; Saikia, A. K.; Barua, N. C. *Synthesis* **2000**, 537.
(216) Ballini, R. *Synthesis* **1993**, 687.
(217) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**, 2725.
(218) Ballini, R.; Barboni, L.; Bosica, G.; Filippone, P.; Peretti, S. *Tetrahedron* **2000**, *56*, 4095.
(219) Ballini, R.; Barboni, L.; Bosica, G. *J. Org. Chem.* **2000**, *65*, 6261.
(220) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Gil, M. V.; Petrini, M. *Tetrahedron* **2001**, *57*, 6079.
(221) Kádas, I.; Árvai, G.; Töke, L.; Tóth, G.; Szöllöszy, Á.; Bihari, M. *Tetrahedron* **1994**, *50*, 2895.
(222) Mikló, K.; Jaszberenyi, J. C.; Kádas, I.; Árvai, G.; Töke, L. *Tetrahedron Lett.* **1996**, *37*, 3491.
(223) Grossman, R. B.; Rasne, R. M.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7173.
(224) Michaud, D.; Hamelin, J.; Texier-Boullet, F.; Toupet, L. *Tetrahedron* **2002**, *58*, 5865.
(225) Correc, O.; Guillou, K.; Hamelin, J.; Paquin, L.; Texier-Boullet, F.; Toupet, L. *Tetrahedron Lett.* **2004**, *45*, 391.
(226) Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998**, *54*, 1773.
(227) Chen, Y.-J.; Lin, W.-Y. *Tetrahedron Lett.* **1992**, *33*, 1749.
(228) Chen, Y.-J.; Chen, C. M.; Lin, W.-Y. *Tetrahedron Lett.* **1993**, *34*, 2961.
(229) Chen, Y.-J.; Chang, W.-H. *J. Org. Chem.* **1996**, *61*, 2536.
(230) El Blidi, L.; Crestia, D.; Gallienne, E.; Demuynck, C.; Bolte, J.; Lemaire, M. *Tetrahedron: Asymmetry.* **2004**, *15*, 2591.
(231) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449.
(232) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.
(233) Cappon, J. J.; Baart, J.; van der Walle, G. A. M.; Raap, J.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 158.
(234) Crossley, M. J.; Fung, Y. M.; Kyriacopoulos, E.; Potter, J. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1123.
(235) Yamazaki, T.; Ohnogi, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1990**, *1*, 215.
(236) Ballini, R.; Bosica, G. *Org. Prepr. Proc. Int.* **1995**, *27*, 561.
(237) Ballini, R.; Petrini, M.; Polzonetti, V. *Synthesis* **1992**, 355.
(238) Ballini, R.; Bosica, G.; Gigli, F. *Tetrahedron* **1998**, *54*, 7573.
(239) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Synthesis* **2004**, 1938.
(240) Ballini, R.; Bosica, G.; Palmieri, A.; Petrini, M.; Pierantozzi, C. *Tetrahedron* **2003**, *59*, 7283.
(241) Easton, C. J.; Xia, L.; Pitt, M. J.; Ferrante, A.; Poulos, A.; Rathjen, D. A. *Synthesis* **2001**, 451.
(242) Bäckvall, J.-E.; Ericsson, A. M.; Plobeck, N. A.; Juntunen, S. K. *Tetrahedron Lett.* **1992**, *33*, 131.
(243) Schneider, R.; Gerardin, P.; Loubinoux, B.; Rihs, G. *Tetrahedron* **1995**, *51*, 4997.
(244) Dilman, A. D.; Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **1999**, 1767.

CR040602R