Tributyltin Hydride Addition to Nitroalkenes: A Convenient Procedure for the Conversion of Nitroalkenes into Nitroalkanes and Carbonyl Compounds

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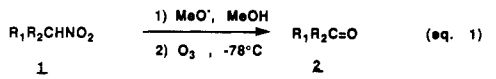
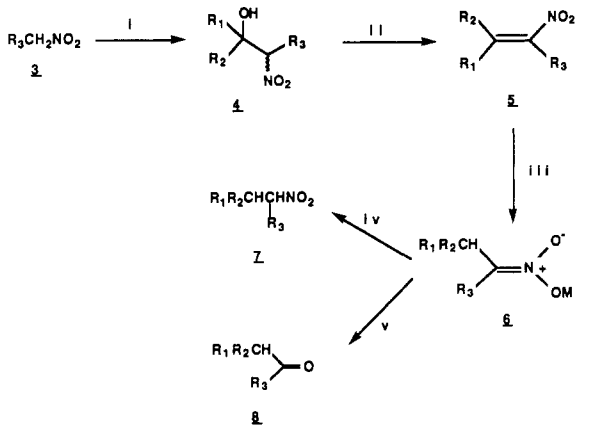
A new procedure for the reduction of nitroalkenes by using *n*-tributyltin hydride as reducing agent is described. The reaction proceeds under almost neutral conditions and works well even in the presence of other reduceable functionalities. Hydrolysis and Nef reaction of the resulting nitronates furnished nitroalkanes and carbonyl compounds respectively in high yields. Application of this methodology to the preparation of β-lactam building blocks is also made.

The conversion of nitroalkanes into carbonyl compounds, usually called the Nef reaction,[1] is a transformation of widespread utility in organic synthesis.[2] Several methods and reagents[3] have been developed to convert nitroalkanes **1** into aldehydes or ketones **2**, most notably McMurry's procedure[4] (eq 1). A convenient route

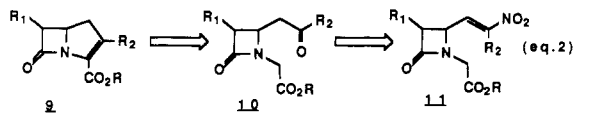


(Scheme I) for the preparation of higher primary and secondary nitroalkanes involves the condensation of aldehyde or ketone **2** with lower primary nitroalkane **3**, the Henry reaction,[5] followed by elimination of the resulting nitro aldol **4** and subsequent reduction of the product. This approach is a desirable synthetic transformation, because it can provide the expected nitroalkane **7** as well as the corresponding carbonyl compound **8** from common intermediate **6** and by the use of readily available starting materials. Among many suitable methods for the reduction of nitroalkenes,[2c,6] the most widely used involves sodium borohydride reduction.[7] Following this approach (eq 2), we have recently described[8a] the preparation of

Scheme I[a]



[a] Reagents and conditions: (i) **2**, NEt_3 or $KOBu^t$, THF; (ii) $MeSO_2Cl$, NEt_3, CH_2Cl_2; (iii) $NaBH_4$ or n-Bu_3SnH, CH_2Cl_2, room temperature; (iv) AcOH–MeOH; (v) O_3, –78 °C, CH_2Cl_2, then Me_2S.



4-phenacyl β-lactams **10** as synthetic precursors of bicyclic β-lactam compounds **9** according to Foxton's procedure.[8b] However, the yield in the reduction step was low, probably due to the strongly basic reaction conditions used. Moreover, borohydride reduction of nitroalkenes is often limited by the presence of other reduceable functionalities

(1) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 264. For a review, see: Noland, W. E. *Chem. Rev.* **1955**, *55*, 137.

(2) For reviews, see: (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. (b) *The Chemistry of the Nitro and Nitroso Groups*, Part 1; Fever, H., Ed.; John Wiley: New York, 1969. (c) Barret, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (d) *Umpoled Syntons*; Hase, T. A., Ed.; John Wiley: New York, 1987. (e) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.

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(4) McMurry, J. E.; Melton, J.; Padyett, H. *J. Org. Chem.* **1974**, *39*, 259.

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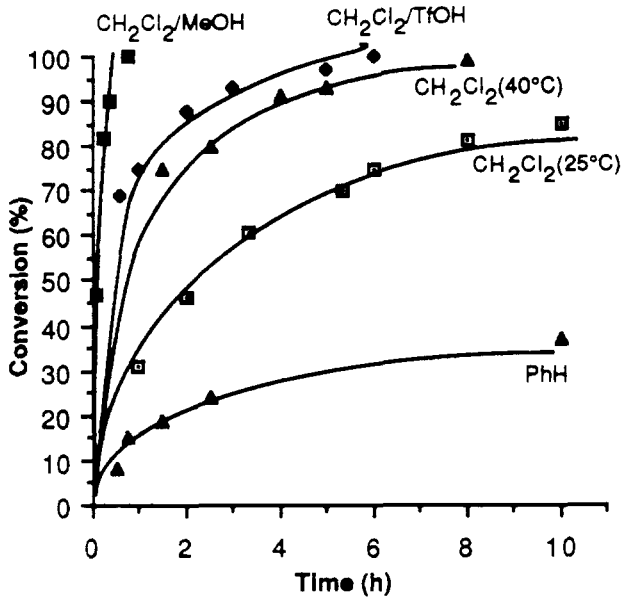

Figure 1. Tributyltin hydride reduction of *p*-chloro-β-nitrostyrene under different conditions.

such as carbonyl groups. Recently, we have found[9] that tributyltin hydride reduction of nitroalkenes afforded stannyl nitronates,[10] which upon oxidative Nef reaction furnished the expected carbonyl derivatives in excellent yields. Consequently we rationalized that we could utilize the tributyltin hydride procedure[11] for the preparation of **10** starting from nitroalkenes of type **11**. In this paper we report details of this new procedure for the conversion of nitroalkenes into carbonyl compounds as well as nitroalkanes with emphasis on its utility in β-lactam chemistry.

Results and Discussion

As previously described,[9] we found that treatment of nitroalkene **5** with tributyltin hydride in nearly equimolar amounts smoothly produced intermediate stannyl nitronate **6** (M = $SnBu_3$-*n*), which could be in situ oxidized to the corresponding carbonyl compound **8** or hydrolyzed to the corresponding nitroalkane **7** (Scheme I). Among the solvents examined, methanol and methylene chloride were found to be the most satisfactory to obtain the best results in terms of rapidity. For example, tributyltin hydride reduction of *p*-chloro-β-nitrostyrene (Figure 1) in methylene chloride gave a 50% conversion after 2 h of reaction at room temperature. The reduction could be accelerated either in refluxing methylene chloride or by the use of methanol as cosolvent. Tributyltin trifluoromethanesulfonate[12] also enhanced the reduction of nitroalkenes but in diethyl ether, tetrahydrofuran, and dimethoxyethane the reaction was extremely slow even in the presence of this catalyst.

Results of reduction of some β-nitrostyrenes in methylene chloride as solvent are summarized in Table I. These results suggest that there is a remarkable influence on the rate of reduction by the substitution pattern of the aromatic ring. β-Nitrostyrenes with electron-donating substituents were reduced at a lower rate than nitroalkenes with electron-withdrawing groups or with deactivating substituents. In all cases the yields were high and no formation of dimer or other byproducts could be observed. Isolation of nitroalkanes **7** involved treatment of the tin nitronate **6** with methanol and addition of hydrofluoric acid (2 N in MeOH) at −15 °C. The precipitate tin compounds were filtered off and the nitroalkane **7** was separated by column chromatography on silica gel and purified by distillation. Tin nitronates **6** possessing substituents at the α-carbon were more stable than α-unsubstituted tin nitronates under the above workup conditions, and concomitant Nef reaction took place giving a mixture of the corresponding nitroalkane and carbonyl compound and, in some instances, accompanied with the corresponding oximes. For example, under these workup conditions the nitroalkane **7b** was obtained in 50% yield together with the corresponding ketone.[9] However, an excellent yield in nitroalkane **7b** could be obtained when the hydrolysis of the corresponding tin nitronate was carried out by means of aqueous acetic acid.

Table I. Tributyltin Hydride Reduction of β-Nitrostyrenes 5[a] to Nitroalkanes 7

	compound[b]					
	R_1	R_2	R_3	time, h	convn, %[c]	yield, %[d,e]
a	C_6H_5	H	H	2	46	
				15	91	
				20	97	90
b	C_6H_5	H	CH_3	24		90
c	4-MeC_6H_4	H	H	2	38	
				15	85	
				20	91	90
d	4-$MeOC_6H_4$	H	H	2	33	
				15	75	
				20	80	80
e	4-ClC_6H_4	H	H	2	50	
				15	92	
				20	95	92
f	4-NCC_6H_4	H	H	2	85	
				15	100	
				20	100	95

[a] These β-nitrostyrenes were prepared by the method described by J. Bourguignon, G. Le Nard, G. Queguiner, *Can. J. Chem.* **1985**, *63*, 2354. [b] All reactions were conducted on 3-mmol scale, 1:1.2 nitroalkene/tributyltin hydride. [c] Determined by ^1H NMR spectroscopy. [d] Yields based on weight of isolated product by column chromatography. [e] All compounds exhibited physical and spectral characteristics in accordance with the assigned structures, see ref 6a.

The established procedure for the reduction of β-nitrostyrenes was next extended to the preparation of some intermediates of interest in β-lactam chemistry.[8e] The β-lactams used in our study were prepared by known procedures according to Scheme II. The method involved preparation of β-lactams **12**[13] with a styryl group as the latent carbonyl functionality followed by ozonolysis and further treatment of the resulting aldehyde **13** with a lower primary nitroalkane.[14] Subsequent dehydration of the in situ formed nitro aldol by means of a methanesulfonyl chloride–triethylamine system[15] gave the corresponding nitroalkenes **14–16**. When the dehydration step was car-

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(10) (a) For other methods to generate stannyl nitronates, see: Guibé-Jampel, E.; Huet, F. *J. Organomet. Chem.* **1987**, *320*, 171. (b) Uno, H.; Watanabe, N.; Fujiki, S.; Suzuki, H. *Synthesis* **1987**, 471.
(11) For reviews on tributyltin hydride reductions, see: (a) Kuivila, H. G. *Acc. Chem. Res.* **1968**, 299. (b) Kuivila, H. G. *Synthesis* **1970**, 499. (c) Newman, W. P. *Synthesis*, **1987**, 665. (d) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987. (e) For a recent review on reduction, see: Hudlicky, M. *Reduction in Organic Chemistry*; Ellis Horwood Limited; John Wiley: New York, 1984.
(12) Xian, Y. T.; Four, P.; Guibé, F.; Balavoine, G. *Nouv. J. Chim.* **1984**, *8*, 611.
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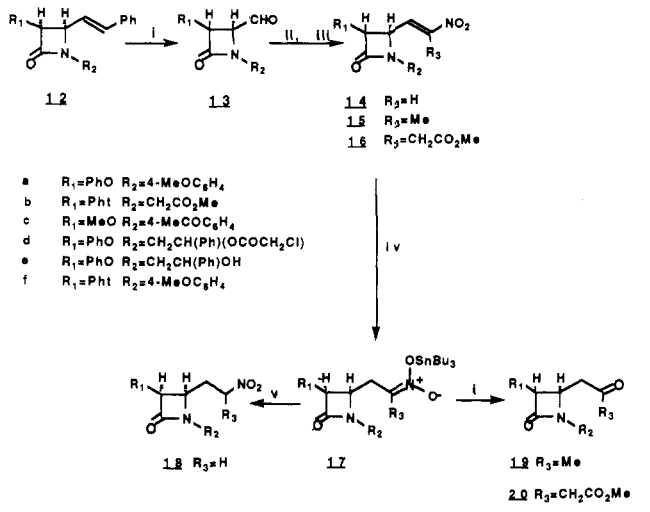
(15) (a) Melton, J.; McMurry, J. E. *J. Org. Chem.* **1975**, *40*, 2138. (b) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.

Scheme II[a]



[a] Reagents and conditions: (i) O_3 −78 °C, CH_2Cl_2, then Me_2S; (ii) $R_3CH_2NO_2$, NEt_3; (iii) $MeSO_2Cl$, NEt_3, CH_2Cl_2; (iv) n-Bu_3SnH, CH_2Cl_2, or CH_2Cl_2–MeOH, room temperature, 20–24 h; (v) EtOH or MeOH–H_2O–AcOH.

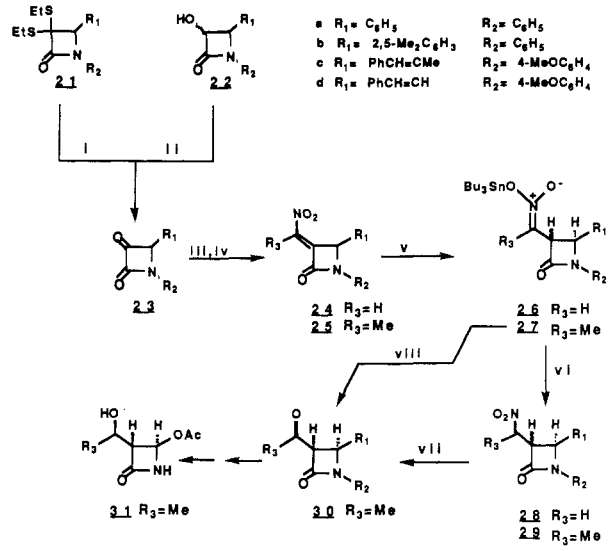
ried out by using McMurry's procedure,[15a] nitroalkenes were often produced as a mixture of cis and trans isomers at C_3–C_4 of the β-lactam ring, probably by the excess of base present in the reaction media, and generally in low yield. Better yields were obtained when dehydration of nitro aldols was carried out under Miyashita reaction conditions.[15b] In this case the expected nitroalkenes **14–16** were obtained as single cis isomers at C_3–C_4 of the β-lactam ring. The assignment of a cis or a trans stereochemistry to these compounds was made by examining the values of the coupling constant $J_{3,4}$. The typical values of $J_{3,4}$ for trans isomers are between 1.5 and 2.5 Hz and for the cis isomers larger than 5 Hz. Similarly, the geometrical assignment of the carbon–carbon double bond of these compounds was univocally determined by ^1H NMR spectroscopy.[16]

As expected, conversion of nitroalkenes **14–16** into their tin nitronates **17** proceeds completely at room temperature within 20 and 24 h in methylene chloride or in methylene chloride–methanol. The conversion could be monitored by TLC analysis of the reaction mixture and, after completion, primary nitroalkanes **18** were separated by evaporation of the solvent, trituration of the resulting oil with methanol or ethanol, and further crystallization or isolation by column chromatography. The results obtained illustrate the efficiency, the applicability, and the scope of the present method. As shown in Scheme II the reaction conditions are mild enough to be applied to compounds possessing other reduceable functionalities such as keto and alkoxycarbonyl groups.

The generality of the method can be further shown in the conversion of tin nitronates **17** into carbonyl compounds **19–20**. Thus, when a α-substituted nitroalkene **15** was subjected to treatment with tributyltin hydride in methylene chloride as solvent followed by ozonolysis of the in situ generated tin nitronate **17** the corresponding carbonyl compound **19** was obtained in good yield. Similarly, nitroalkene **16** upon treatment with tributyltin hydride and further oxidative Nef reaction afforded the β-keto ester **20** in good yield. The transformations depicted in Scheme II illustrate the wide scope of the method. For example,

(16) Hayama, T.; Tomoda, S.; Takeuch, Y.; Nomura, Y. *Tetrahedron Lett.* **1982**, *23*, 4733.

Scheme III[a]



[a] Reagents and conditions: (i) I_2, CH_3CN–H_2O; (ii) Me_2SBr_2, NEt_3, CH_2Cl_2; (iii) $R_3CH_2NO_2$, NEt_3, or $R_3CH_2NO_2$, t-BuOK, THF; (iv) $MeSO_2Cl$, NEt_3, CH_2Cl_2; (v) n-Bu_3SnH, CH_2Cl_2; (vi) AcOH, MeOH–H_2O; (vii) $ClSiMe_3$ or BSA, DBU, CH_2Cl_2, then MCPBA; (viii) O_3, −78 °C, CH_2Cl_2, then Me_2S.

the nitroalkene **15d**, which posseses the labile chloroacetyl moiety, could be transformed into the ketone **19e** in good overall yield. It is also worth noting that the *N*-(*p*-anisyl) group in these β-lactams can be removed under mild conditions with cerium(IV) ammonium nitrate (CAN)[17] and the resulting N-H azetidin-2-ones further elaborated to the corresponding bicyclic compounds.[8e] Particularly, the β-keto ester **20** thus prepared provides a new entry to the bicyclic ring system following Merck's methodology.[18]

In view of the results obtained we next extended the tin hydride reduction of nitroalkenes to β-lactams **24** and **25** in order to obtain side chains at the C_3 position of the β-lactam ring suitable for further chemical elaboration to potentially valuable intermediates for β-lactam antibiotic synthesis.[19] Our approach (Scheme III) involved first the preparation of azetidine-2,3-diones **23** followed by the Henry reaction and subsequent dehydration of the resulting nitro aldol. The starting products **23** were prepared either by oxidative hydrolysis of 3,3-bis(ethylthio) β-lactams **21**[8c] or by oxidation of 3-hydroxy β-lactams **22**[20] by means of a dimethylbromosulfonium bromide–triethylamine system.[21] Formation of nitroalkenes **24** was achieved according to Sheehan's procedure[19b] and preparation of nitroalkenes **25** could be carried out in high yields by using the same procedure as described for nitroalkenes **14**. The stereochemistry of the double bond on these nitroalkenes was deduced on the basis of ^1H NMR nuclear Overhauser effect experiments in which presaturation of the α-methyl group did not lead to any detectable enhancement of the signal corresponding to the C_4-H proton. This result suggests that these groups are in a trans relationship. This high stereoselectivity could be attributed

(17) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(18) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *20*, 31.

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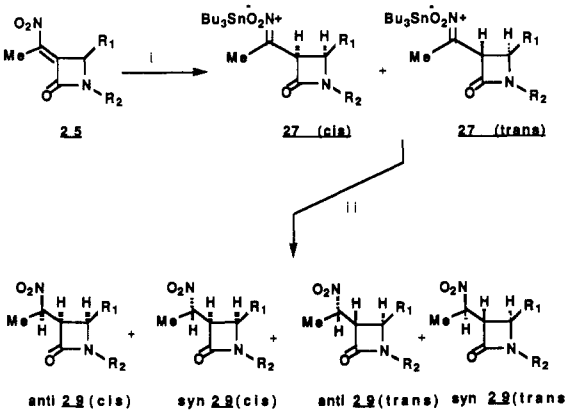
(20) (a) Cossío, F. P.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 4239. (b) Cossío, F. P.; López, C.; Oiarbide, M.; Palomo, C.; Aparicio, D.; Rubiales, G. *Tetrahedron Lett.* **1988**, *29*, 3133.

(21) Corey, E. J.; Kim, C. V. *J. Am. Chem. Soc.* **1972**, *24*, 758.

Scheme IV[a]



[a] Reagents and conditions: (i) n-Bu_3SnH, Cl_2CH_2; (ii) AcOH, MeOH–H_2O.

to electrostatic and steric repulsions between the nitro group and the β-lactam carbonyl that could prevent the formation of the *Z* isomer.

Reaction between **24** and tributyltin hydride in methylene chloride for 20–24 h followed by addition of methanol to the in situ generated tin nitronate **26** furnished the expected nitroalkane **28**. As mentioned above, α-substituted tin nitronates were stable under these workup conditions and isolation of secondary nitroalkanes **29** might be accomplished under acetic acid conditions. Hydrofluoric acid and hydrochloric acid caused formation of oximes and ketones as byproducts. In all cases the yields were high and the nitro compounds were generally obtained as a mixture of cis and trans isomers at C_3–C_4 of the β-lactam ring. The isomer ratio of these β-lactams was easly determined, from the crude reaction mixture, by examining the coupling constants between the C_3 and C_4 protons in either the intermediate tin nitronates or nitroalkanes. Although the configuration of the double bond in tin nitronates was not determined, we found that the stereoselectivity of the hydride addition reaction seems to be dependent of the bulkness of the substituents at the C_4 position of the β-lactam ring. For example, while compound **24a** upon treatment with tributyltin hydride gave a mixture of cis and trans isomers of **28a** in approximately equal amounts, compound **24c** provided the nitro compound **28c** as a cis isomer. Similar results were obtained when the hydride addition was performed on nitroalkenes **25**. For instance, whereas nitro compound **29a** was produced as a mixture of cis and trans isomers in nearly equal amounts, the *cis*-β-lactam **29b** was formed as main product (cis:trans ratio 80/20). As expected, the hydride reagent showed marked stereoselectivity for the nitroalkene **25c**, producing **29c** as a single cis isomer. The stereoselectivity of the reaction could be attributed to the preference of the hydride attack from the less hindered face of the starting nitroalkenes. The change of the α-methylstyryl group in **25c** by the less hindered styryl one caused a loss of selectivity and a mixture of cis and trans isomers of **29d** was produced in a 40:60 ratio, respectively. Particularly, nitroalkanes **29** were obtained as a mixture of diastereoisomers epimeric about the nitro group, except **29c**, which was obtained as a single diastereoisomer (Scheme IV).

The relative stereochemistry of diastereoisomeric β-lactams **29**, anti and syn, respectively according to the nomenclature introduced by Masamune[22] (Figure 2), was

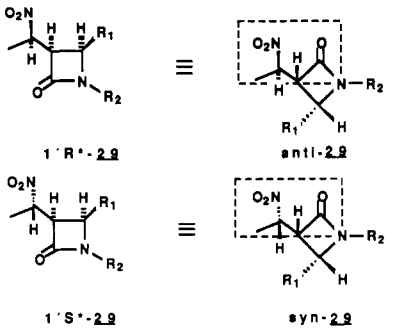
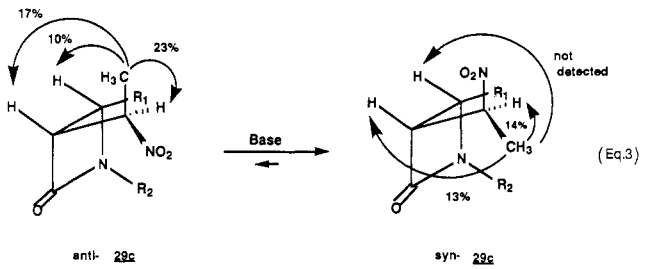


Figure 2. Different representations of epimeric β-lactams **29**. Only one enantiomer of each diastereoisomer is drawn.

established on the basis of their respective ^1H NMR spectra. As can be seen by inspection of Dreiding models, the cis relationship between the C_3 and C_4 substituents on tin nitronates restricts strongly the number of accessible conformations for the epimers of the β-lactam **29**. Assuming that intermediate **27U** (Figure 3) is unfavorable by steric and electrostatic repulsions, it is possible to rationalize the behavior of intermediate **27F** toward protonation. Thus, from a kinetic point of view, protonation of this intermediate should occur preferentially from the less-hindered *si* face, leading to *anti*-**29** as the main diastereomer. This assignment explains the fact that the selectivity diminishes when the substituents at C_3–C_4 of the β-lactam ring are in a trans relationship or when the substituent at C_4 has a major degree of conformational freedom. From a thermodynamic point of view, we have the reverse situation because of the repulsion between the nitro group and the β-lactam carbonyl of the major epimer *anti*-**29**. In fact, *anti*-**29c** (eq 3) upon treatment with



(Eq.3)

triethylamine led to complete isomerization into the thermodynamically more stable *syn*-**29c**. These arguments are consistent with NOE experiments made on both epimers. Thus, presaturation of their respective methyl groups led to the enhancements indicated in eq 3 (R^1 = α-methylstyryl, R^2 = *p*-methoxyphenyl). Particularly interesting is the fact that in the case of the isomer *syn*-**29c** no nuclear Overhauser enhancement was detected at the C_4-H signal when the methyl group was irradiated. The assignment for the anti and syn isomers of β-lactams **29** could also be established by examining the coupling constants between the H-3 and H-1′ protons in both isomers. Thus, in our compounds $J_{1',3}$ for the syn cis isomer is greater than that for the anti cis isomer and $J_{1',3}$ for the syn trans isomer is lower than that for the anti trans isomer, in agreement with similar values made on related compounds.[23] On the basis of this assignment for the stereochemistry at the $C_3(1')$ position, we tried to correlate the structure of these epimeric β-lactams with their ^{13}C NMR spectra as Seebach et al.[5c] and Kamimura and Ono[24] did in the case of O-silylated and O-benzylated nitro aldols,

(22) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

(23) (a) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (b) Cainelli, G.; Panunzio, M.; Basile, Y.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2637.

(24) Kamimura, A.; Ono, N. *Tetrahedron Lett.* **1989**, *30*, 731.

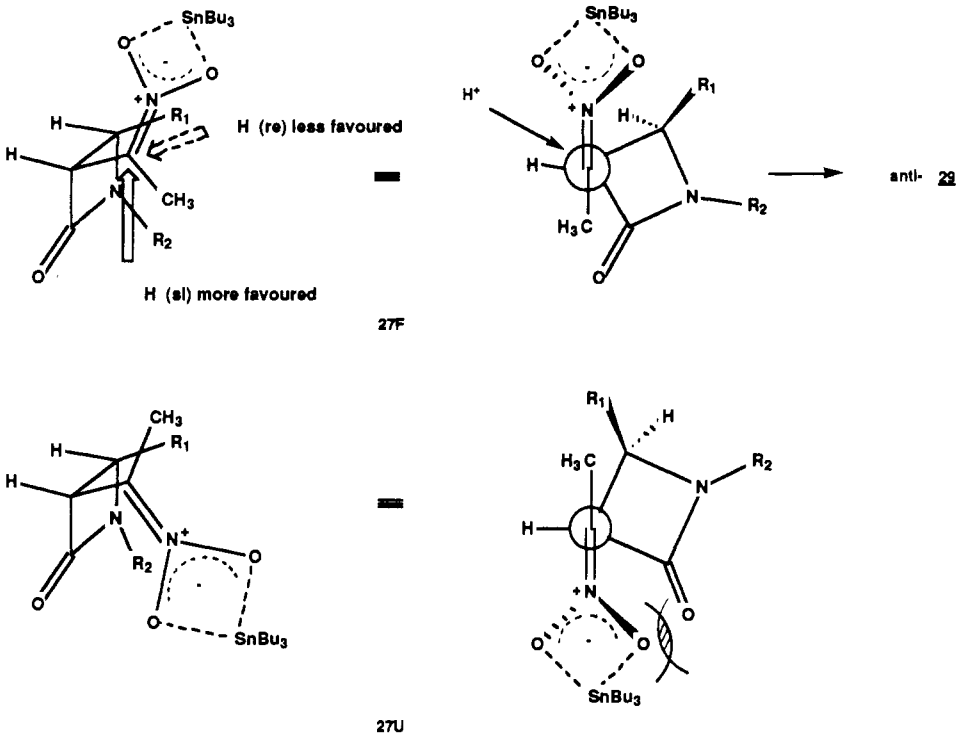


Figure 3. Different possible conformations of cis nitronates **27** showing the diastereofacial selectivity toward protonation. Only one enantiomer is drawn.

Table II. Distribution of the Products Corresponding to the Sequence Indicated in Scheme IV

	nitronates **27** (%)[a]		nitro compounds **29** (%, ^{13}C δ ppm)[b]			
			cis		trans	
substr **25**	cis	trans	syn	anti	syn	anti
a	48	52	4 (78.39)[d]	46 (79.60)	23 (79.37)	27 (81.66)
b	80	20	31 (78.52)	69 (79.56)	0 *c*	0 *c*
c	100	0	0 (78.90)[d]	100 (79.45)	0	0
d	41	59	28 (79.00)	15 (79.41)	20 (79.22)	37 (81.49)

[a] Stereochemistry assigned by measuring $J_{3,4}$ coupling constants and applying Karplus equation. [b] ^{13}C NMR signals corresponding to the $CHNO_2$ group assigned by correlation with the corresponding ^1H NMR spectra of both isomers and by isomerization (see text for details). [c] Hydrolysis not observed: the starting tin nitronate *trans*-**27** was recovered unchanged. [d] Chemical shifts obtained by basic isomerization of the kinetic product *anti*-**29**.

respectively. These authors made their assignments for the syn and anti isomers on the basis of the major ^{13}C chemical shifts of the carbon signals corresponding to the methine-NO_2 group of the syn isomers. However in our case, Table II, the ^{13}C chemical shifts of the methine signals are in the inverse relative relationship for all compounds **29**.

Compounds **29** thus prepared could be transformed into ketones **30** by silylation and further oxidation by means of *m*-chloroperbenzoic acid (MCPBA).[8a] These methyl ketones could be directly obtained from the corresponding tin nitronates **27** according to the McMurry procedure.[4] In all cases ozonolysis of tin nitronates led to oxidation and concomitant isomerization at C_3–C_4 of the β-lactam ring, affording trans methyl ketones **30** in good yields. Particularly, the 3-acetyl β-lactam **30c** bearing a C_4-styryl moiety can be further elaborated to the known (±)-thienamycin precursor **31** according to an established protocol.[25]

Conclusion

From the results reported here the tributyltin hydride reduction of nitroalkenes seems to be of general application since a wide range of nitroalkanes, including those bearing reduceable or base-sensitive functionalities, could be prepared. As demonstrated here, the method has been successfully applied to the elaboration of β-lactams leading to a variety of bicyclic β-lactam precursors. The procedure is experimentally simple and may be readily extended to further applications, not only in the β-lactam area but also in other fields of chemistry.

Experimental Section

Commercially available compounds were used without further purification unless otherwise noted. Hexane was purified by distillation. Tetrahydrofuran was distilled over sodium with benzophenone as indicator. Methylene chloride was shaken with concentrated H_2SO_4, dried over K_2CO_3, and distilled. β-Lactams **12** were prepared by our procedure[13] and ozonized by using a Fischer 502 ozone generator. All compounds prepared are racemic mixtures. Melting points were determined on either Büchi SMP-20 or Mettler FP61 instruments and are uncorrected. Proton magnetic resonance (^1H NMR) spectra were recorded on a Varian VXR 300 spectrometer; chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. The nuclear Overhauser enhancement experiments were run at 300 MHz by preirradiating the desired signals for 15 s with the decoupler channel turned on at 20 db below 1 W and acquiring the spectrum with the decoupler turned off. A control experiment was created by setting the irradiation away from any signal. The acquisitions

(25) Palomo, C.; Cossío, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1989**, *54*, 5736.

were carried out in groups of four for each irradiated signal, until 32 accumulations were performed. The FID's, acquired with 16K (3000 Hz sweep width), were Fourier transformed with 32K (zero-filling) and with a line broadering of 5 Hz. The NOE's were measured by integration of the signals resulting from the respective difference spectra. Infrared (IR) spectra were obtained on a Shimadzu IR-435 spectrometer. For new compounds microanalytical data were obtained in these laboratories on a Perkin-Elmer Model 240 C instrument.

Reduction of β-Nitrostyrenes 5 to Nitroalkanes 7. General Procedure. To a solution of the corresponding nitrostyrene **5** (R_1 = Ar, R_2 = R_3 = H) (3 mmol) in methylene chloride (7.5 mL) was added tributyltin hydride (0.95 mL, 3.6 mmol), and the resulting mixture was stirred at room temperature. The conversion of the reaction was monitored by ^{1}H NMR spectroscopy from an aliquot of the reaction mixture. When the conversion was total the solvent was evaporated under reduced pressure. The resulting oil was dissolved in methanol and treated with a solution of H_2F_2 in methanol. The resulting precipitate tin compounds were filtered off and the residue was subjected to column chromatography to afford the corresponding nitroalkane, which was purified by distillation or crystallization. All compounds exhibited physical an spectral characteristics in accordance with the assigned structures.[6a]

Preparation of Nitroalkenes 14–16. General Procedure. To a solution or suspension of the β-lactam **13** (10 mmol) in nitromethane or nitroethane (15 mL) was added triethylamine (0.2 mL, 1.5 mmol), and the resulting mixture was stirred at room temperature until completion (1–3 h). Evaporation of the solvent under reduced pressure gave a residue, which was dissolved in methylene chloride (40 mL) and dropwise added at −78 °C to a mixture of triethylamine (4.14 mL, 30 mmol) and methanesulfonyl chloride (2.34 mL, 30 mmol) and was stirred for 30 min at −78 °C. Triethylamine (4.14 mL, 30 mmol) was added to the solution at −50 °C and the resulting mixture was gradually warmed to 0 °C during 3 h, poured into water, and extracted with methylene chloride. The organic layer was washed with 0.1 N HCl (3 × 40 mL) and then with aqueous $NaHCO_3$ (40 mL, saturated solution). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure gave the nitroalkenes **14–16**, which were purified by crystallization or chromatography on silica gel (eluent methylene chloride–hexane).

***cis*-1-(4-Methoxyphenyl)-4-(2-nitrovinyl)-3-phenoxyazetidin-2-one (14a).** Following the general procedure starting from 4-formyl-1-(4-methoxyphenyl)-3-phenoxyazetindin-2-one (**13a**) (2.97 g, 10 mmol) and nitromethane, the title compound was obtained: yield 2.89 g (85%); mp 120–123 °C (EtOH); IR (KBr) ν 1746, 1515, 1396, 1351 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–6.89 (m, 11 H, Ar and CH=CHNO$_2$), 5.59 (d, 1 H, J = 5.0 Hz, H-3), 5.08 (m, 1 H, H-4), 3.81 (s, 3 H, OCH_3). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 63.53; H, 4.74; N, 8.23. Found: C, 63.71; H, 4.67; N, 8.21.

***cis*-1-[(Methoxycarbonyl)methyl]-4-(2-nitrovinyl)-3-phthalimidoazetidin-2-one (14b).** Following the general procedure starting from *cis*-4-formyl-1-[(methoxycarbonyl)-methyl]-3-phthalimidoazetidin-2-one (**13b**) (3.16 g, 10 mmol) and nitromethane, the title compound was obtained: yield 1.80 g (50%); syrup; IR (CH_2Cl_2) ν 1785, 1748, 1747, 1534, 1380, 1358 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88–7.16 (m, 6 H, Ar and CH=CHNO$_2$), 5.78 (d, 1 H, J = 5.5 Hz, H-3), 4.98 (dd, 1 H, J = 7.3 Hz, J' = 5.6 Hz, H-4), 4.48 (d, 1 H, J = 18.3 Hz, CH_ACH$_B$), 3.90 (d, 1 H, J = 18.3 Hz, CH$_A$CH_B), 3.78 (s, 3 H, $COOCH_3$).

***cis*-1-(4-Acetylphenyl)-3-methoxy-4-(2-nitrovinyl)azetidin-2-one (14c).** Following the general procedure starting from *cis*-1-(4-acetylphenyl)-4-formyl-3-methoxyazetidin-2-one (**13c**) (2.47 g, 10 mmol) and nitromethane, the title compound was obtained: yield 2.38 g (82%); syrup; IR (CH_2Cl_2) ν 1772, 1681, 1534, 1374, 1358 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2 H, J = 8.7 Hz, Ar), 7.40 (d, 2 H, J = 8.7 Hz, Ar), 7.32 (dd, 1 H, J = 13.6 Hz, J' = 6.8 Hz, CH=CHNO$_2$), 7.21 (d, 1 H, J = 13.7 Hz, CH=CHNO$_2$), 5.03 (dd, 1 H, J = 6.8 Hz, J' = 5.2 Hz, H-4), 4.93 (d, 1 H, J = 5.2 Hz, H-3), 3.58 (s, 3 H, OCH_3), 2.57 (s, 3 H, CH_3CO).

***cis*-4-(2-Methyl-2-nitrovinyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (15a).** Following the general procedure starting from 4-formyl-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**13a**) (2.97 g, 10 mmol) and nitroethane, the title compound was obtained: yield 2.13 g (60%); mp 125–127 °C (EtOH); IR (KBr) ν 1757, 1514, 1393, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–6.87 (m, 10 H, Ar and CH=CNO$_2$), 5.58 (d, 1 H, J = 4.9 Hz, H-3), 5.04 (dd, 1 H, J = 9.2 Hz, J' = 4.9 Hz, H-4), 3.79 (s, 3 H, OCH_3), 2.30 (d, 3 H, J = 1.0 Hz, CH_3). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.90. Found: C, 63.99; H, 5.04; N, 7.76.

***cis*-4-(2-Methyl-2-nitrovinyl)-1-[(methoxycarbonyl)-methyl]-3-phthalimidoazetidin-2-one (15b).** Following the general procedure starting from *cis*-4-formyl-1-[(methoxycarbonyl)methyl]-3-phthalimidoazetidin-2-one (**13b**) (3.16 g, 10 mmol) and nitroethane, the title compound was obtained: yield 2.50 g (67%); mp 155–158 °C (EtOH); IR (KBr) ν 1767, 1752, 1728, 1717, 1518, 1396 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.89–7.76 (m, 4 H, Ar), 7.15 (d, 1 H, J = 8 Hz, CH=C(Me)NO$_2$), 5.81 (d, 1 H, J = 5.7 Hz, H-3), 5.06 (dd, 1 H, J = 5.7 Hz, J' = 8.1 Hz, H-4), 4.54 (d, 1 H, J = 18.3 Hz, CH_2COOCH$_3$), 3.88 (d, 1 H, J = 18.3 Hz, CH_2COOCH$_3$), 3.80 (s, 3 H, CH$_2$COOCH_3), 2.11 (s, 3 H, CH=C(CH_3)NO$_2$). Anal. Calcd for $C_{17}H_{15}N_3O_7$: C, 54.69; H, 4.06; N, 11.26. Found: C, 54.21; H, 3.92; N, 11.40.

***cis*-1-[2-(Chloroacetoxy)-2-phenylethyl]-4-(2-methyl-2-nitrovinyl)-3-phenoxyazetidin-2-one (15d).** Following the general procedure starting from *cis*-1-[2-(chloroacetoxy)-2-phenylethyl]-4-formyl-3-phenoxyazetidin-2-one (**13d**) (3.83 g, 10 mmol) and nitroethane, the title compound was obtained: yield 2.58 g (58%); syrup; IR (CH_2Cl_2) ν 1761, 1753, 1515, 1392, 1365 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (both diastereoisomers) 7.75–7.02 (m, 11 H, Ar and CH=C(Me)NO$_2$), 6.15 (m, 1 H, HCO), 5.55 (d, 1 H, J = 4.7 Hz, H-3) and 5.50 (d, 1 H, J = 4.5 Hz, H-3), 4.72 (dd, 1 H, J = 9.5 Hz, J' = 4.6 Hz, H-4) and 4.51 (dd, 1 H, J = 9.7 Hz, J' = 4.5 Hz, H-4), 4.45 and 4.28 (s, 2 H, CH_2Cl), 4.20 and 3.50 (m, 2 H, CH_2CO), 2.29 and 2.14 (s, 3 H, CH_3).

***cis*-4-[2-[(Methoxycarbonyl)methyl]-2-nitrovinyl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (16f).** To a suspension of the β-lactam **13f** (3.50 g, 10 mmol) in acetonitrile, methyl 3-nitropropionate (2.66 g, 20 mmol) and triethylamine (1.4 mL, 10 mmol) were added, and the resulting mixture was stirred at room temperature overnight. The solution was poured into methylene chloride (150 mL). The organic layer was successively washed with 1 N HCl (2 × 40 mL) and water (40 mL), separated, and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure afforded an oil, which was used without further purification. Following the general procedure for nitroalkene formation, the title compound **16f** was obtained: yield 1.40 g (30%); mp 208–211 °C (EtOH); IR (KBr) ν 1758, 1737, 1710, 1513, 1390 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91–6.92 (m, 9 H, Ar and CH=CNO$_2$), 5.93 (d, 1 H, J = 6 Hz, H-3), 5.52 (dd, 1 H, J = 6 Hz, J' = 7.8 Hz, H-4), 3.81 (s, 3 H, p-CH_3OPh), 3.54 (s, 3 H, CCH$_2$COOCH_3), 3.30 (d, 1 H, J = 7.5 Hz, CCH_2COOCH$_3$), 3.11 (d, 1 H, J = 7.5 Hz, CCH_2COOCH$_3$). Anal. Calcd for $C_{23}H_{19}N_3O_8$: C, 59.35; H, 4.12; N, 9.03. Found: C, 59.72; H, 4.28; N, 8.87.

Preparation of Azetidine-2,3-diones 23.[17] Method A. General Procedure. To a solution of 3,3-bis(ethylthio) β-lactam **21**[8c] (20 mmol) in acetonitrile (200 mL) and water (50 mL) was added iodine (30.45 g, 120 mmol), and the resulting mixture was stirred under reflux for 30–45 min until completion. Then the mixture was cooled at room temperature and diluted with methylene chloride (400 mL) and washed with 40% aqueous sodium hydrosulfite (100 mL). The organic layer was separated and the aqueous phase was extracted with methylene chloride (2 × 100 mL). The methylene chloride solutions were combined and washed with water (2 × 200 mL) and then with aqueous $NaHCO_3$ (200 mL, saturated solution). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure gave the title compound, which was purified by column chromatography or crystallized from hexane/chloroform.

Method B. General Procedure. To a solution of dimethyl sulfide (0.6 mL, 8.4 mmol) in methylene chloride (10 mL) was added bromine (0.4 mL, 8.4 mmol) in methylene chloride (5 mL) with the inmediate formation of a yellow precipitate. The resulting mixture was stirred at room temperature for 5 min and the corresponding 3-hydroxy β-lactam **22** (8 mmol) was added. The stirring was continued for 2 min at the same temperature and then the solution was cooled at 0 °C. To the above mixture was added triethylamine (2.24 mL, 16 mmol) in methylene chloride (4 mL) dropwise, and the stirring was continued for 1–1.5 h at

the same temperature until completion. The reaction mixture was washed with H_2O (40 mL) and 0.1 N HCl (2 × 10 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure gave the azetidine-2,3-dione **23**, which was purified by crystallization.

Preparation of Nitroalkenes 24. General Procedure. A solution of nitromethane (1.35 mL, 20.6 mmol) in tetrahydrofuran (30 mL) under nitrogen was cooled to 0 °C and potassium *tert*-butoxide (0.53 g, 4.7 mmol) was added. After 15 min a solution of the azetidine-2,3-dione **23** (10 mmol) in tetrahydrofuran (30 mL) was added, and the resulting mixture was stirred at 0 °C for 1–2 h. The mixture was diluted with methylene chloride (150 mL) and washed with H_2O (60 mL) and NaCl (60 mL, saturated solution). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave an oil, which was dissolved in methylene chloride (80 mL). To the above solution cooled at −40 °C and under nitrogen was added triethylamine (3.5 mL, 25 mmol) first, and then methanesulfonyl chloride (1.17 mL, 15 mmol) was added dropwise for 5 min. The resulting mixture was stirred for 20–30 min at −40 °C and then was diluted with methylene chloride (100 mL) and was washed with 1 N HCl–ice (2 × 50 mL), H_2O (50 mL), and then with NaCl (25 mL, saturated solution). After drying over $MgSO_4$, the solution was evaporated at reduced pressure to give the nitroalkene **24** which was purified by column chromatography and crystallized.

1,4-Diphenyl-3-(nitromethylene)azetidin-2-one (24a). Following the general procedure starting from **23a** (2.37 g, 10 mmol) the title compound was obtained: yield 2.16 g (78%); IR (KBr) ν 1760, 1520, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.7 (m, 11 H, Ar CH); 6.1 (d, 1 H, CH, J = 1.4 Hz). Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.28; N, 10.00. Found: C, 68.32; H, 4.02; N, 9.87.

4-(α-Methylstyryl)-1-(4-methoxyphenyl)-3-(nitromethylene)azetidin-2-one (24c). Following the general procedure starting from **23c** (3.07 g, 10 mmol), the title compound was obtained: yield 1.96 g (56%); mp 136–138 °C ($CHCl_3$–hexane); IR (KBr) ν 1741, 1533, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52, 6.90 (AB, J = 6.9 Hz, 4 H, Ar), 7.48 (d, 1 H, CH, J = 1.4 Hz), 7.40–7.26 (m, 5 H, Ar), 7.06 (s_b, 1 H, CH), 5.57 (d, 1 H, CH, J = 1.3 Hz), 3.80 (s, 3 H, OCH_3), 1.80 (d, 3 H, CH_3, J = 1.4 Hz). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.34; H, 5.12; N, 7.67.

Preparation of Nitroalkenes 25. The same procedure as that used for the preparation of **14** was followed.

1,4-Diphenyl-3-(1-nitroethylidene)azetidin-2-one (25a). Following the general procedure starting from **23a** (2.37 g, 10 mmol) and nitroethane, the title compound was obtained: yield 2.35 g (80%); mp 200–202 °C; IR (KBr) ν 1749, 1526, 1489, 1375, 1329 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55–7.20 (m, 10 H, Ar), 5.85 (s, 1 H, CH), 2.50 (s, 3 H, CH_3). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.27; H, 4.70; N, 9.37.

4-(2,5-Dimethylphenyl)-3-(1-nitroethylidene)-1-phenylazetidin-2-one (25b). Following the general procedure starting from **23b** (2.65 g, 10 mmol) and nitroethane, the title compound was obtained: yield 2.16 g (67%); mp 169–171 °C (EtOH); IR (KBr) ν 1740, 1528, 1371, 1332 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–6.93 (m, 8 H, Ar), 6.11 (s, 1 H, CH), 2.64 (s_b, 3 H, CH_3), 2.55 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.37; H, 5.81; N, 8.93.

4-(α-Methylstyryl)-1-(4-methoxyphenyl)-3-(1-nitroethylidene)azetidin-2-one (25c). Following the general procedure starting from **23c** (3.07 g, 10 mmol) and nitroethane, the title compound was obtained: yield 3.28 g (90%); mp 126–128 °C (EtOH); IR (KBr) ν 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, 2 H, Ar, J = 9 Hz), 7.35–7.25 (m, Ar, 5 H), 7.01 (s, 1 H, CH), 6.89 (d, Ar, 2 H, J = 9 Hz), 5.49 (s, 1 H, CH), 3.79 (s, 3 H, OCH_3), 2.57 (s, 3 H, CH_3), 1.76 (d, 3 H, CH_3, J = 1.5 Hz). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.68. Found: C, 69.63; H, 5.47; N, 7.51.

1-(4-Methoxyphenyl)-3-(1-nitroethylidene)-4-styrylazetidin-2-one (25d). Following the general procedure starting from **23d** (2.93 g, 10 mmol) and nitroethane, the title compound was obtained: yield 3.13 g (86%); mp 173–175 °C (EtOH); IR (KBr) ν 1730, 1523, 1508, 1331 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (d, 2 H, Ar, J = 8.6 Hz), 6.22 (dd, 1 H, CH, J = 7.3 Hz, J' = 15.9 Hz), 5.54 (d, 1 H, CH, J = 7.3 Hz), 3.78 (s, 3 H, OCH_3), 2.53 (s, 3 H, CH_3). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.52; H, 5.10; N, 7.87.

Preparation of Primary Nitroalkanes. General Procedure. To a solution of the corresponding nitroalkene (6 mmol) in methylene chloride (20 mL) and methanol (2 mL) was added tributyltin hydride (1.85 mL, 7.2 mmol), and the mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave an oil, which was triturated with ethanol and filtered off to give the corresponding nitroalkane. An analytical sample was obtained by crystallization from ethanol.

Preparation of Secondary Nitroalkanes. General Procedure. To a solution of the corresponding α-substituted nitroalkene (6 mmol) in methylene chloride (20 mL) was added tributyltin hydride (1.9 mL, 7.2 mmol), and the mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave an oil, which was dissolved in methanol (15 mL). To this solution was added H_2O (2 mL), and two phases appeared. To this mixture was added glacial acetic acid (1.2 mL), and the resulting solution was stirred at room temperature for 30 min from which a white precipitate appeared. Stirring was continued for 5 h at the same temperature and the precipitate was filtered off to give the nitroalkane, which was purified by crystallization from ethanol.

***cis*-1-(4-Methoxyphenyl)-4-(2-nitroethyl)-3-phenoxyazetidin-2-one (18a).** Following the general procedure starting from **14a** (2.04 g, 6 mmol), the title compound was obtained: yield 1.81 g (88%); mp 112–114 °C (EtOH); IR (KBr) ν 1733, 1549, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–6.91 (m, 9 H, Ar), 5.43 (d, 1 H, J = 5.14 Hz, H-3), 4.56 (m, 3 H, H-4 and CH_2NO_2), 3.80 (s, 3 H, OCH_3), 2.83 (m, 1 H, CH_AH_B), 2.58 (m, 1 H, CH_ACH_B). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.75; H, 5.33; N, 8.12.

***cis*-1-[(Methoxycarbonyl)methyl]-4-(2-nitroethyl)-3-phthalimidoazetidin-2-one (18b).** Following the general procedure starting from **14b** (2.16 g, 6 mmol), the title compound was obtained: yield 1.73 g (80%); mp 151–154 °C (EtOH); IR (KBr) ν 1766, 1752, 1717, 1714, 1548, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92–7.82 (m, 4 H, Ar), 5.54 (d, 1 H, J = 5.4 Hz, H-3), 4.48 (m, 2 H, $CH_AH_BNO_2$), 4.36 (d, 1 H, J = 18.1 Hz, CH_AH_BCO), 4.28 (m, 1 H, H-4), 4.06 (d, 1 H, J = 18.1 Hz, CH_AH_BCO), 3.78 (s, 3 H, OCH_3), 2.48 (m, 1 H, CH_AH_B), 2.26 (m, 1 H, CH_AH_B). Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.23; H, 4.32; N, 12.51.

***cis*-1-(4-Acetylphenyl)-3-methoxy-4-(2-nitroethyl)azetidin-2-one (18c).** Following the general procedure starting from **14c** (1.74 g, 6 mmol), the title compound was obtained: yield 1.23 g (70%); mp 97–99 °C (EtOH); IR (KBr) ν 1736, 1667, 1552, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10–7.25 (m, 4 H, Ar), 4.75–4.30 (m, 4 H, H-3 and CH_2NO_2), 3.70 (m, 1 H, H-4), 3.63 (s, 3 H, OCH_3), 2.65 (m, 2 H, CH_2), 2.55 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 58.06; H, 5.76; N, 9.48.

1,4-Diphenyl-3-(nitromethyl)azetidin-2-one (28a). Following the general procedure starting from **24a** (2.8 g, 10 mmol), the title compound was obtained as a 40:60 mixture of cis and trans isomers: yield 2.54 g (90%); IR (KBr) ν 1740, 1550, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.00 (m, 10 H, Ar); diastereoisomer cis 5.38 (d, 1 H, H-4, J = 5.7 Hz), 4.54 (dd, 1 H, CH_AH_B, J = 15.4 Hz, J' = 3.3 Hz), 4.41 (m, 1 H, H-3), 4.12 (dd, 1 H, CH_AH_B, J = 15.4 Hz, J' = 10.9 Hz); diastereoisomer trans 4.97 (d, 1 H, H-4, J = 2.4 Hz), 4.85 (dd, 1 H, CH_AH_B, J = 14.4 Hz, J' = 4.2 Hz), 4.77 (dd, 1 H, CH_AH_B, J = 14.4 Hz, J' = 10.0), 3.66 (m, 1 H, H-3). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 4.96; N, 9.92. Found: C, 67.98; H, 4.98; N, 9.93.

***cis*-1-(4-Methoxyphenyl)-4-(α-methylstyryl)-3-(nitromethyl)azetidin-2-one (28c).** Following the general procedure startaing from **24c** (1.05 g, 3 mmol), the title compound was obtained: yield 0.80 (76%); mp 147–149 °C (EtOH); IR (KBr) ν 1737, 1551, 1369 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–6.86 (m, 9 H, Ar), 6.50 (s_b, 1 H, =CH), 4.81 (d, 1 H, H-4, J = 5.62 Hz), 4.75 (m, 2 H, CH_2NO_2), 4.44 (m, 1 H, H-3), 3.79 (s, 3 H, OCH_3), 1.90 (d, 3 H, CH_3, J = 1.28 Hz). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.94; H, 5.76; N, 7.75.

1,4-Diphenyl-3-(1-nitroethyl)azetidin-2-one (29a). Following the general procedure starting from **25a** (2.94 g, 10 mmol), the title compound was obtained: yield 2.66 g (90%); IR (KBr) ν 1744, 1553, 1495, 1392 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.07 (m,

10 H, Ar); anti,trans diastereoisomer 5.02 (d, 1 H, H-4, J = 2.4 Hz), 4.97 (m, 1 H, $CHNO_2$, J = 6.6 Hz, J' = 11 Hz), 3.50 (dd, 1 H, H-3, J = 2.4 Hz, J' = 11 Hz), 1.82 (d, 3 H, CH_3, J = 6.6 Hz); syn,trans diastereoisomer 5.05 (d, 1 H, H-4, J = 2.5 Hz), 5.04 (m, 1 H, $CHNO_2$), 3.71 (dd, 1 H, H-3, J = 2.5 Hz, J' = 5.1 Hz), 1.78 (d, 3 H, CH_3, J = 6.9 Hz); anti,cis diastereoisomer 5.35 (d, 1 H, H-4, J = 6 Hz), 4.51 (m, 1 H, $CHNO_2$, J = 6.6 Hz, J' = 10.2 Hz), 4.07 (dd, 1 H, H-3, J = 6 Hz, J' = 10.2 Hz), 1.21 (d, 3 H, CH_3, J = 6.9 Hz); syn,cis diastereoisomer 5.37 (d, 1 H, H-4, J = 5.2 Hz), 4.42 (m, 1 H, $CHNO_2$, J = 6.9 Hz, J' = 11.7 Hz), 4.27 (dd, 1 H, H-3, J = 5.2 Hz, J' = 11.7 Hz), 1.78 (d, 3 H, CH_3, J = 6.9 Hz). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.44; N, 9.45. Found: C, 69.10; H, 5.43; N, 9.51.

***cis,syn*-4-(2,5-Dimethylphenyl)-3-(1-nitroethyl)-1-phenylazetidin-2-one (29b).** Following the general procedure starting from **25b** (0.93 g, 3 mmol), a mixture of epimeric β-lactams was obtained in a ratio of 69:31. After crystallization from ethanol the sole syn diastereoisomer of **29b** was obtained: yield 0.29 g (30%); mp 188–191 °C (EtOH); IR (KBr) ν 1742, 1556, 1362 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–7.02 (m, 8 H, Ar), 5.50 (d, 1 H, H-4, J = 5.6 Hz), 4.55 (m, 1 H, $CHNO_2$), 4.28 (dd, 1 H, H-3, J = 11 Hz, J' = 5.5 Hz), 2.30 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 1.78 (d, 3 H, CH_3, J = 6.9 Hz). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 69.96; H, 6.21; N, 8.45.

***cis,anti*-4-(α-Methylstyryl)-1-(4-methoxyphenyl)-3-(1-nitroethyl)azetidin-2-one (29c).** Following the general procedure starting from **25c** (3.64 g, 10 mmol), the title compound was obtained: yield 3.29 g (90%); mp 144–146 °C (EtOH); IR ($CHCl_3$) ν 1736, 1551, 1511, 1442, 1355, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.24 (m, Ar, 7 H), 6.85 (d, Ar, 2 H), 6.62 (s, 1 H, =CH), 4.88 (qd, 1 H, $CHNO_2$, J = 6.6 Hz, J' = 9 Hz), 4.78 (d, 1 H, H-4, J = 6 Hz), 3.97 (dd, 1 H, H-3, J = 6 Hz, J' = 9 Hz), 3.77 (s, 3 H, OCH_3), 1.95 (s, 3 H, CH_3), 1.66 (d, 3 H, CH_3, J = 6.6 Hz). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.64. Found: C, 68.25; H, 6.13; N, 7.58.

***cis,syn*-4-(α-Methylstyryl)-1-(4-methoxyphenyl)-3-(1-nitroethyl)azetidin-2-one (29c).** The compound *anti*-**29c** (0.73 g, 2 mmol) was dissolved in methylene chloride (10 mL) and triethylamine was added (cat.). After the solution was stirred for 24 h at room temperature, the mixture was evaporated, and the title compound was obtained as the only reaction product: yield 0.71 g (97%); mp 164–166 °C (EtOH); IR (KBr) ν 1735, 1550, 1510, 1355, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.2 (m, Ar, 7 H), 6.87 (d, 2 H, Ar, J = 9 Hz), 6.53 (s, 1 H, =CH), 4.96 (qd, 1 H, $CHNO_2$, J = 6.9 Hz, J' = 11.7 Hz), 4.73 (d, 1 H, H-4, J = 5.4 Hz), 4.19 (dd, 1 H, H-3, J = 5.4 Hz, J' = 11.7 Hz), 3.79 (s, 3 H, OCH_3), 1.86 (d, 3 H, CH_3, J = 6.9 Hz), 1.85 (s, 3 H, CH_3).

1-(4-Methoxyphenyl)-3-(1-nitroethyl)-4-styrylazetidin-2-one (29d). Following the general procedure starting from **25d** (3.5 g, 10 mmol), the title compound was obtained: yield 2.64 g (75%); IR (KBr) ν 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.26 (m, 7 H, Ar), 6.86 (d, 2 H, Ar, J = 9 Hz); syn,cis diastereoisomer 6.71 (d, 1 H, =CH, J = 15.9 Hz), 6.12 (dd, 1 H, =CH, J = 6.9 Hz, J' = 15.9 Hz), 4.87 (m, 1 H, $CHNO_2$), 4.86 (dd, 1 H, H-4, J = 5.7 Hz, J' = 6.9 Hz), 4.08 (dd, 1 H, H-3, J = 5.7 Hz, J' = 12 Hz), 3.77 (s, 3 H, OCH_3), 1.85 (d, 3 H, CH_3, J = 6.8 Hz); anti,cis diastereoisomer 6.16 (dd, 1 H, =CH, J = 8.4 Hz, J' = 16.2 Hz), 4.87 (m, 2 H, H-4, $CHNO_2$), 3.97 (dd, 1 H, H-3, J = 6 Hz, J' = 8.4 Hz), 1.67 (d, 3 H, CH_3, J = 6.6 Hz); anti,trans diastereoisomer 6.81 (d, 1 H, =CH, J = 15.9 Hz), 6.26 (dd, 1 H, =CH, J = 8.0 Hz, J' = 15.9 Hz), 4.87 (m, 1 H, $CHNO_2$), 4.60 (dd, 1 H, H-4, J = 2.4 Hz, J' = 8.0 Hz), 3.76 (s, 3 H, OCH_3), 3.52 (dd, 1 H, H-3, J = 2.4 Hz, J' = 10.8 Hz), 1.82 (d, 3 H, CH_3, J = 6.63 Hz); syn,trans diastereoisomers 6.27 (dd, 1 H, =CH, J = 7.8 Hz, J' = 15.9 Hz), 5.03 (m, 1 H, $CHNO_2$, J = 6 Hz, J' = 6.9 Hz), 4.66 (dd, 1 H, H-4, J = 2.1 Hz, J' = 8.1 Hz), 3.70 (s, 3 H, OCH_3), 1.74 (d, 3 H, CH_3, J = 6.9 Hz). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.51; H, 5.75; N, 7.82.

Preparation of Ketones. General Procedure. The corresponding methylene chloride solution of the α-substituted tin nitronate prepared as above was diluted with the same solvent (30 mL) and the solution was cooled to −78 °C. A stream of ozone was passed through the reaction mixture until a pale blue coloration was observed and then the solution was purged with nitrogen. A solution of Me_2S (4 mL) in methylene chloride (10 mL) was added dropwise at −78 °C. When the addition was completed, the bath was removed and the solution was stirred until it reached room temperature. The reaction mixture was washed with H_2O (25 mL) and NaCl (3 × 30 mL, saturated solution). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave a residue, which was diluted with methanol and treated with a solution of H_2F_2 in methanol, and the resulting precipitate tin compounds were filtered off and the residue was subjected to column chromatography. In other cases the residue was directly crystallized from ethanol to give the corresponding ketone.

***cis*-4-Acetonyl-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (19a).** Following the general procedure starting from **15a** (2.13 g, 6 mmol), an oil was obtained that was treated with ethanol and further crystallized from the same solvent: yield 1.37 g (70%); mp 127–129 °C; IR (KBr) ν 1761, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–6.87 (m, 9 H, Ar), 5.39 (d, 1 H, J = 5.0 Hz, H-3), 5.0 (m, 1 H, H-4), 3.80 (s, 3 H, OCH_3), 3.10 (dd, 1 H, J = 18.1 Hz, J' = 8.0 Hz, CH_AH_BCO), 3.01 (dd, 1 H, J = 18.1 Hz, J' = 4.4 Hz, CH_AH_BCO), 2.12 (s, 3 H, CH_3CO). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.54; H, 5.90; N, 4.29.

***cis*-4-Acetonyl-1-[(methoxycarbonyl)methyl]-3-phthalimidoazetidin-2-one (19b).** Following the general procedure starting from **15b** (1.87 g, 5 mmol), an oil was obtained that was treated with ethanol and further crystallized from the same solvent: yield 1.22 g (71%); mp 160–162 °C; IR (KBr) ν 1780, 1762, 1744, 1715, 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.79–7.90 (m, 4 H, Ar), 5.54 (d, 1 H, J = 5.4 Hz, H-3), 4.52–4.57 (m, 1 H, H-4), 4.25 (d, 1 H, J = 18 Hz, CH_2COOCH_3), 4.04 (d, 1 H, J = 18 Hz, CH_2COOCH_3), 3.77 (s, 3 H, $COOCH_3$), 3.07 (dd, 1 H, J = 9.7 Hz, J' = 18.6 Hz, CH_2COCH_3), 2.72 (dd, 1 H, J = 3 Hz, J' = 18.6 Hz, CH_2COCH_3), 2.09 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.29; H, 4.69; N, 8.14. Found: C, 58.14; H, 4.73; N, 8.06.

***cis*-4-Acetonyl-1-(2-hydroxy-2-phenylethyl)-3-phenoxyazetidin-2-one (19e).** Following the general procedure starting from **15d** (2.67 g, 6 mmol), and after column chromatography (silica gel 70–230 mesh, eluent CH_2Cl_2/hexane 1:2), *cis*-4-acetonyl-1-[2-(chloroacetoxy)-2-phenylethyl]-3-phenoxyazetidin-2-one (**19d**) was obtained as an oil. To a solution of this oil in MeOH (15 mL) were added thiourea (0.45 g, 6 mmol) and triethylamine (0.83 mL, 6 mmol).[26] The resulting mixture was stirred for 40 min, and a white precipitate appeared after few minutes of stirring at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (25 mL), 1 N HCl (2 × 25 mL), and $NaHCO_3$ (25 mL, saturated solution). After drying over $MgSO_4$, the solution was evaporated at reduced pressure to give the title compound as an equimolar mixture of diastereoisomers: overall yield 1.42 g (70%); syrup; IR (KBr) ν 3378, 1743, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ (one diastereomer) 7.38–6.96 (m, 10 H, Ar), 5.23 (d, 1 H, J = 4.9 Hz, H-3), 5.16 (dd, 1 H, J = 7.5 Hz, J' = 3.1 Hz, HCO), 4.41 (m, 1 H, H-4), 4.10 (m, 1 H, OH), 3.53 (dd, 1 H, J = 14.4 Hz, J' = 7.4 Hz, CH_AH_BCO), 3.43 (dd, 1 H, J = 14.4 Hz, J' = 2.5 Hz, CH_AH_BCO), 2.76 (dd, 1 H, J = 18.7 Hz, J' = 4.6 Hz, $CH_AH_BCNO_2$), 2.56 (dd, 1 H, J = 18.7 Hz, J' = 7.9 Hz, $CH_AH_BCNO_2$), 2.06 (s, 3 H, CH_3CO); (other diastereomer) 7.39–6.97 (m, 10 H, Ar), 5.73 (d, 1 H, J = 4.9 Hz, H-3), 4.96 (dd, 1 H, J = 8.2 Hz, J' = 2.5 Hz, HCO), 4.50 (m, 1 H, H-4), 3.96 (m, 1 H, OH), 3.62 (dd, 1 H, J = 14.5 Hz, J' = 3.5 Hz, CH_AH_BCO), 3.30 (dd, 1 H, J = 14.9 Hz, J' = 8.8 Hz, CH_AH_BCO), 2.94 (dd, 1 H, J = 18.3 Hz, J' = 5.1 Hz, $CH_AH_BCNO_2$), 2.82 (dd, 1 H, J = 18.3 Hz, J' = 7.2 Hz, $CH_AH_BCNO_2$), 2.16 (s, 3 H, CH_3CO). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.40; H, 5.98; N, 3.98.

***cis*-Methyl 4-[1-(4-Methoxyphenyl)-2-oxo-3-phthalimidoazetidin-4-yl]acetoacetate (20f).** To a solution of the α-substituted nitroalkene **16f** (2.33 g, 5 mmol) in methylene chloride (50 mL) was added tributyltin hydride (2.64 mL, 10 mmol), and the mixture was refluxed for 48 h. Following the general procedure for preparation of ketones, the resulting residue, after filtration of tin compounds, was subjected to column chromatography (silica gel, 70–230 mesh, eluent methylene chloride/hexane 3:1) to give the title compound: yield 1.09 g (50%); mp 140–143 °C (EtOH);

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IR (KBr) ν 1787, 1765, 1758, 1731, 1718 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 6.92-7.93 (m, 8 H, Ar), 5.61 (d, 1 H, J = Hz, H-3), 4.79-4.96 (m, 1 H, H-4), 3.82 (s, 3 H, p-CH_3OPh), 3.62 (s, 3 H, $COCH_2COOCH_3$), 3.35 (s, 2 H, $COCH_2COOCH_3$), 3.07 (dd, 1 H, J = 8.7 Hz, J' = 17.4 Hz, CH_AH_BCO), 2.66 (dd, 1 H, J = 5.1 Hz, J' = 17.4 Hz, CH_AH_BCO). Anal. Calcd for $C_{23}H_{20}N_2O_7$: C, 63.29; H, 4.63; N, 6.42. Found: C, 63.58; H, 4.75; N, 6.73.

***trans*-3-Acetyl-1,4-phenylazetidin-2-one (30a).** Following the general procedure starting from **25a** (1.76 g, 6 mmol), the title compound was obtained: yield 1.18 g (78%); mp 90-93 °C ($CHCl_3$/hexane); IR (KBr) ν 1740, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.06 (m, 10 H, Ar), 5.48 (d, 1 H, CH, J = 2.55 Hz), 4.14 (d, 1 H, CH, J = 2.55 Hz), 2.39 (s, 3 H, CH_3). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70; N, 5.28. Found: C, 76.90; H, 5.69; N, 5.00.

***trans*-3-Acetyl-4-(2,5-dimethylphenyl)-1-phenylazetidin-2-one (30b).** Following the general procedure starting from **25b** (1.86 g, 6 mmol), the title compound was obtained: yield 1.32 g (75%); mp 86-87 °C ($CHCl_3$/hexane); IR (KBr) ν 1764, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27-7.00 (m, 8 H, Ar), 5.66 (d, 1 H, CH, J = 2.63 Hz), 4.07 (d, 1 H, CH, J = 2.63 Hz), 2.39 (s, 6 H, CH_3, CH_3NO_2), 2.21 (s, 3 H, CH_3). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.54; H, 6.59; N, 4.67.

***trans*-3-Acetyl-4-(α-methylstyryl)-1-(4-methoxyphenyl)-azetidin-2-one (30c).** To a solution of *anti*-**29c** (1 mmol, 0.36 g) in methylene chloride (3 mL) and *N,O*-bis(trimethylsilyl)-acetamide (BSA) (1.5 mmol, 0.37 mL) cooled to 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 drop). After 15 min of stirring at the same temperature, the resulting solution was added to a cooled (0 °C) solution of MCPBA (1.2 mmol, 0.26 g) in methylene chloride (3 mL) and stirred at room temperature for 1 h. The mixture was then washed with 1 N Na_2SO_3, 1 N HCl, and aqueous $NaHCO_3$ (saturated solution). The organic layer was separated and dried ($MgSO_4$) and evaporation of solvent gave a mixture of *cis,syn*-**29c** and *trans*-**30c** in a ratio of 30:70. Compound **30c** was isolated by column chromatography as an oil[25]: yield 50%; IR ($CHCl_3$) ν 1749, 17151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38-7.25 (m, 7 H, Ar), 6.85 (d, 2 H, Ar, J = 9 Hz), 6.74 (s, 1 H, =CH), 5.01 (d, 1 H, H-4, J = 2.4 Hz), 4.13 (d, 1 H, H-3, J = 2.4 Hz), 3.77 (s, 3 H, OCH_3), 2.33 (s, 3 H, CH_3), 1.86 (d, 3 H, CH_3, J = 1.5 Hz).

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New Methodologies: Fluorodemetalation of Organogermanium, -tin, and -lead Compounds. Applications with Organometallic Sulfides To Produce Highly Active Anions and Spectroscopic Evidence for Pentavalent Intermediates in Substitution at Tin

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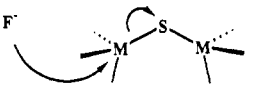
The general concept of fluorodemetalation is illustrated with three novel methodologies. Fluoride ion smoothly demetalates organogermanium, -tin, and -lead sulfides under mild and neutral conditions to liberate active nucleophilic sulfur species. Eight different sulfur transfer agents derived from group IV are used to demonstrate fluorodemetalation. The reactions of fluorodeplumbylation and fluorodegermanylation are presented for the first time along with a discussion of their potential uses in chemistry. The study of fluoride sources as demetalating agents, solvents, substituents and substrates variation is reported. Mechanistic and kinetic aspects of fluorodemetalation are also discussed. We propose that a metal proximate to an anion will increase the nucleophilicity of the latter. In addition, we present spectroscopic evidence for a pentacoordinated intermediate involved in the mechanism of substitution at tin by the use of low-temperature ^{19}F and ^{119}Sn NMR spectroscopy.

Introduction

While organotins are widely used for industrial applications,[1] in organic synthesis organotin sulfides have not been significantly explored.[2-5] Recently, we reported that bis(trialkyltin) sulfide (**2**) is useful as a general sulfur transfer agent for the high-yield synthesis of thioethers and related derivatives, albeit under forcing conditions.[6] Further, we communicated that fluoride and cyanide ions attack organotin sulfides and smoothly liberate the corresponding sulfur ligand.[7] While several methods are known for making sulfides, fluorodestannylation[8-10] represents a real improvement in methodology because of the neutrality of the medium, the mildness of the conditions, and the high reactivity of the sulfide ion released. This intriguing reactivity has been exploited by two groups using this methodology since classic procedures had failed.[11] The fast rate of these reactions favors the formation of macrocyclic sulfides, and the mild and neutral conditions could open new synthetic routes to other interesting structures.[12-14]

Scheme I. Fluorodemetalation



M = Si, Ge, Sn, Pb

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