Highly Stereoselective Conjugate Addition of (*R*)- or (*S*)-4-Phenyl-2-oxazolidinone to Nitroalkenes

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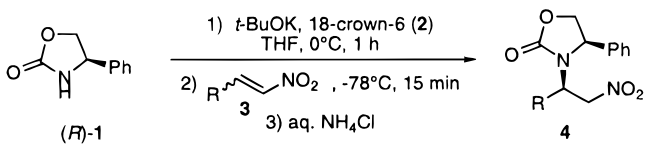
The conjugate addition of chiral, nitrogen nucleophiles to nitroalkenes could provide access to chiral compounds having nitrogen functionalities on vicinal carbon atoms. Various natural products belong to this class, such as biotin, penicillin, and several amino acids that are components of the peptide antibiotics bleomycins,[1] lavendomycin,[2] and edeines[3] *inter alia*. Chiral vicinal diamines have also been used as platinum ligands in antitumoral compounds.[4]

While the aza-analogous Michael addition to α,*β*-unsaturated esters has found numerous applications in organic synthesis,[5] few examples of the corresponding reaction to nitroalkenes have been described.[6,7] However, Enders *et al*. recently published a study on this subject, using a hydrazine obtained from D-mannitol as the nucleophile, which was applied to the diastereo- and enantioselective synthesis of several vicinal diamines.[6c] In this paper, we describe the highly diastereoselective conjugate addition of an anion derived from (*R*)- or (*S*)-4-phenyl-2-oxazolidinone on monosubstituted nitroalkenes.

It appears from several reports that *β*-aminonitroalkanes are unstable compounds,[8] which is understandable since they contain both a basic nitrogen atom and acidic protons and are thus prone to *β*-elimination. We reasoned that the product of a conjugate addition would be more stable if an attracting group had been bound to the nitrogen atom of the nucleophile. Several experiments using derivatives of α-methylbenzylamine as nucleophiles led only to low amounts of addition products, probably because of the bulkiness of the corresponding anions. We then decided to study the anions derived from either (*R*)- or (*S*)-4-phenyl-2-oxazolidinone (**1**), both of which are commercially available, or may be readily prepared.[9] Moreover, it was also expected from the work of other authors that the heterocycle could then be easily cleaved from the conjugate addition adduct to generate an amino group.[9,10]

Table 1. Conjugate Addition of (*R*)-4-Phenyl-2-oxazolidinone Potassium Salt on Nitroalkenes



entry	R	*E*/*Z* ratio in **3**[a]	**3**/**1** ratio	product	% yield	% de[b]
1	propyl	>99/1	1	**4a**	59[c]	>98
2	isopropyl	90/10	1	**4b**	87	>98
3	cyclohexyl	83/17	1	**4c**	78	>98
4	*tert*-butyl	>99/1	1	**4d**	87	>98
5	phenyl	>99/1	5	**4e**	43	>98

[a] Determined by ^{1}H NMR spectroscopy. [b] Evaluated by ^{13}C NMR spectroscopy; only one diastereomer was seen in the ^{1}H NMR and ^{13}C NMR spectra of the crude product **4**. [c] A byproduct resulting from the addition of the nitronate derived from **4a** to another molecule **3a** was also isolated, in 21% yield.

Potassium *tert*-butylate was used as the base; at first, the reactions were performed in DMF, but since stirring of the reaction mixtures tends to become difficult after the addition of the electrophile and since the temperature could not be lower than −45 °C, THF was then used as the solvent, and crown ether 18-crown-6 was also added. The results obtained from (*R*)-**1** and several nitroalkenes **3a**−**e**[11] (containing 0−17% *Z*-isomers) are summarized in Table 1.

All of the nitroalkenes reacted rapidly at −78 °C with the potassium salt of (*R*)-**1** in the presence of 1 equiv of 18-crown-6, leading to the corresponding conjugate addition products **4a**−**e**.[12] In some cases, byproducts arising from the addition of the nitronate on other molecules of nitroalkene were also observed. Oligomerization products formed in the reaction of the very reactive *β*-nitrostyrene **3e**; hence, it was necessary to use a large excess of this nitroalkene in order to isolate compound **4e**, albeit in moderate yield (Table 1, entry 5).

The major feature of these reactions is that in each case the addition product was obtained *as a single isomer*, on the basis of the ^{1}H NMR and ^{13}C NMR spectra of the crude product. The absolute configuration of the newly

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(12) **Experimental Procedure.** THF (5 mL) was added to a mixture of (*R*)-4-phenyl-2-oxazolidinone (100 mg, 0.61 mmol), potassium *tert*-butylate (68.8 mg, 0.61 mmol), and 18-crown-6 (162 mg, 0.61 mmol), cooled at 0 °C, under argon. After 1 h at 0 °C, the resulting solution (in several cases, a white solid had precipitated) was cooled at −78 °C, and a solution of (*E*)-3,3-dimethyl-1-nitrobut-1-ene (**3d**) (78.4 mg, 0.61 mmol) in THF (2 mL) was added *via* syringe. After 15 min, saturated aqueous NH_4Cl (2.5 mL) was added, and after being warmed to room temperature, the mixture was extracted with ether (2 × 10 mL). The combined organic phases were then washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by chromatography (silica gel, 30/70 AcOEt/pentane) to yield compound **4d** (154.8 mg, 0.53 mmol, 87%).

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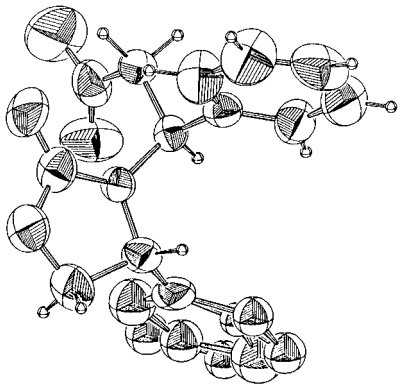
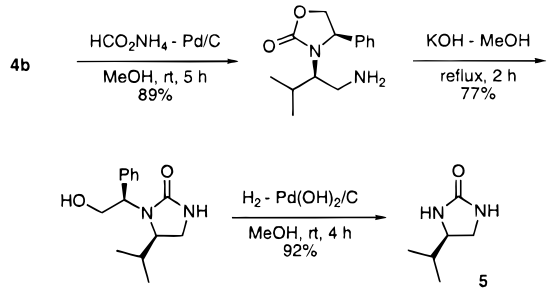
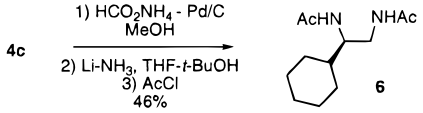


Figure 1. X-ray structure of adduct **4e**.

Scheme 1



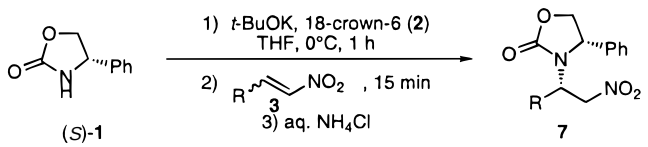
Scheme 2



created stereogenic center in the adducts **4b**,**c**,**e** was established to be *R*. Thus, compound **4b** led to the known (*R*)-4-isopropyl-2-imidazolidinone **5**[13] using the chemical sequence described in Scheme 1, and compound **4c** was converted into the diacetamide **6** (Scheme 2), the enantiomer of which has been described.[14] Lastly, the structure of compound **4e** was determined by single-crystal X-ray analysis (Figure 1).[15] We assume that the diastereoselectivity occurred in the same way in the reactions involving the nitroalkenes **3a** and **3d**.

Conjugate additions of (*S*)-4-phenyl-2-oxazolidinone potassium salt on several nitroalkenes were also performed, and the importance of some parameters was also evaluated (Table 2). As is apparent from entries 1 and 2 (Table 2), under conditions similar to those described above (−78 °C, 1 equiv of crown ether), nitro compounds **7**, enantiomers of **4**, were obtained as single isomers. On the other hand, higher reaction temperatures (Table 2, entries 3 and 4) resulted in lowering the diastereomeric excess of the product, although it was still 80% at room temperature. Lastly, we also ran an experiment at −78 °C using only 0.1 equiv of 18-crown-6 (Table 2, entry 5). This reaction was a bit slower than the previous ones, needing 30 min to get to completion, but, to our delight, it worked very well, affording nitro compound **7c** in 85% yield and with complete diastereoselectivity.

Table 2. Conjugate Addition of (*S*)-4-Phenyl-2-oxazolidinone Potassium Salt on Nitroalkenes



entry	R	**1**/**3**/**2** ratio	*T* (°C)	product	% yield	% de
1	*tert*-butyl	1/1/1	−78	**7d**	89	>98[a]
2	phenyl	1/5/1	−78	**7e**	54	>98[a]
3	cyclohexyl	1/1/1	0	**7c**	72	92[b]
4	cyclohexyl	1/1.1/1.1	25	**7c**	91	80[b]
5	cyclohexyl	1/1/0.1	−78	**7c**	85	>98[a]

[a] Evaluated by ^{13}C NMR spectroscopy; only one diastereomer was seen in the ^{1}H NMR and ^{13}C NMR spectra of the crude product **7**. [b] Determined by ^{1}H NMR spectroscopy (**7c**: major diastereomer; **7′c**: minor diastereomer).

It is not known whether the crown ether merely activates the anion or also plays a role in determining the stereochemical outcome of the reaction.[16] An intriguing observation is that nitroalkenes containing a mixture of *E*- and *Z*-stereomers nevertheless afforded single adducts; this observation is in good agreement with previous reports that show that a reversal of product configuration was not obtained when enolates or enamines were added to *Z*-nitroalkenes instead of *E*-nitroalkenes.[17]

In conclusion, we have shown that conjugate additions of (*R*)- or (*S*)-4-phenyl-2-oxazolidinone potassium salt to nitroalkenes proceed rapidly and with complete stereoselectivity, using a procedure very easy to carry out. One of the products has been conveniently transformed into an optically pure 4-substituted imidazolidinone. We are currently studying the access to other classes of compounds from these products, taking advantage of the versatility of the nitro group as precursor of other functions.[18]

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Supporting Information Available: Analytical data for compounds **4**−**7** and experimental procedures for the synthesis of imidazolidinone **5** and diacetamide **6** (5 pages).

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(15) The X-ray data have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, U.K.

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