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Cycloadditions of 2-Nitro 1,3-Dienes to Enamines. Asymmetric Induction and Synthesis of Unsaturated Nitroketones and Diels-Alder Adducts via [4+2] Heterocycloadditions

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Abstract. 2-Nitro 1,3-dienes, generated *in situ* from the corresponding nitroseleno compounds, react with enamines affording [4+2] heterocycloadducts of different stability. With chiral enamines a high asymmetric induction was observed in some cases. Some of the adducts were readily hydrolyzed to unsaturated γ-nitroketones whereas others spontaneously rearranged to Diels-Alder-type carbocycloadducts.

Over the last several years, the chemistry of electron-deficient dienes has attracted increasing interest.[1,2] We recently reported the synthesis of 2-nitro 1,3-dienes from the corresponding conjugated dienes via a nitroselenation-elimination sequence.[2] These dienes are of synthetic interest for further reaction with electron-rich olefins like enol ethers.[2] We now report the cycloaddition reaction between 2-nitro 1,3-dienes and enamines, and the transformation of the cycloadducts to synthetically useful unsaturated nitroketones.[3]

The 2-nitro 1,3-dienes were generated *in situ* from the corresponding nitroseleno compounds[4] via base-catalyzed elimination of PhSeH.[2] In this case the enamine catalyzes the latter elimination and no extra base is needed. Once obtained, the highly reactive nitroolefin reacts readily with the enamine as a 4π electron component giving products of [4+2] heterocycloaddition, most likely via a two-step reaction.[5]

When compound **2** (see Scheme 1), obtained by nitroselenation of 1,3-cyclohexadiene,[4] was allowed to react with the morpholino-enamine **A**,[6] nitrodiene **3** was generated and readily cyclized with

Scheme 1

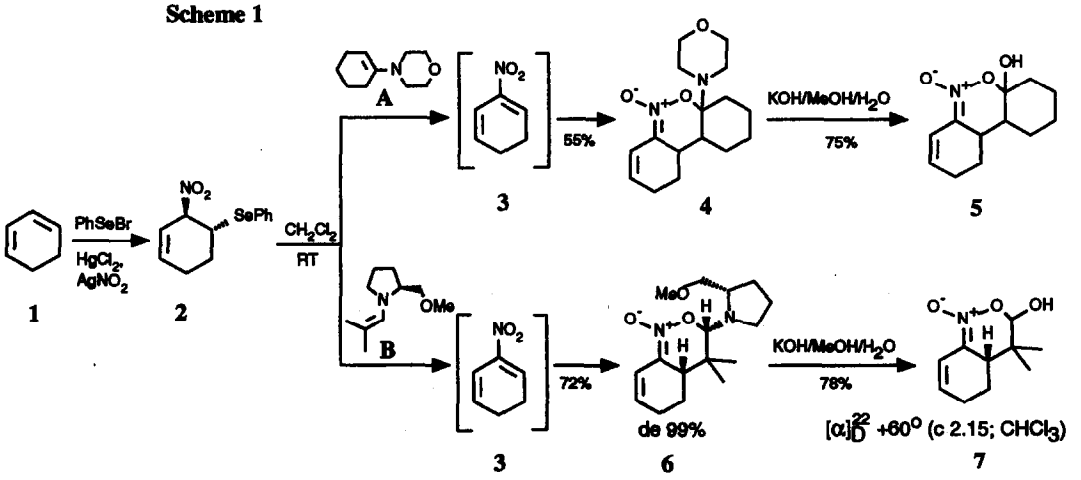
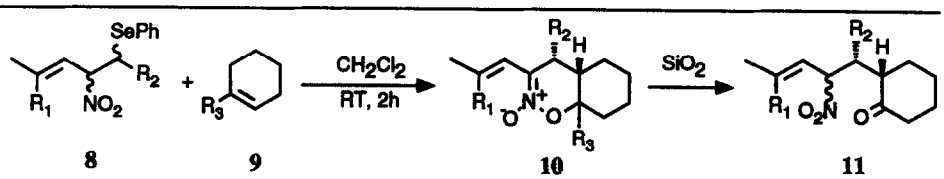
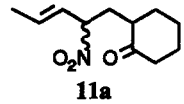
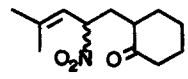
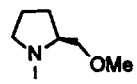
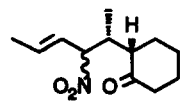


Table 1. Preparation of unsaturated nitroketones



8 9 10 11

Entry	diene precursor no.	R_1	R_2	enamine R_3	nitroketone[a]	% yield[b]	% ee[c]
1	**8a**	H	H		 **11a**	40	-
2	**8b**	Me	H		 **11b**	72	-
3						69	-
4						70	45
5	**8c**[d]	H	Me		 **11c**	51	-

a. Mixture of two diastereoisomers ca 1/1. b. Isolated yield after flash chromatography. c. Determined by ^{1}H NMR using $Eu(hfc)_3$. d. Erythro and threo isomers gave the same results.

the electron-rich species affording cycloadduct **4**. The analogous reaction employing chiral (*S*)-2-methoxymethylpyrrolidino-enamine **B**[7] afforded **6**. The latter reaction occurred with high asymmetric induction and only one isomer could be detected with the absolute stereochemistry indicated (determined by NOE experiments). Unexpectedly, these adducts were stable after treatment with different solvents,[8] and a series of attempted hydrolytic procedures afforded mainly complex mixtures or tars except for basic hydrolysis which gave oxazine N-oxide derivatives **5** and **7**.[9] The rather high stability of these cycloadducts could be due to conjugation of the nitronate function with the olefinic bond or to the cyclohexene structure itself.

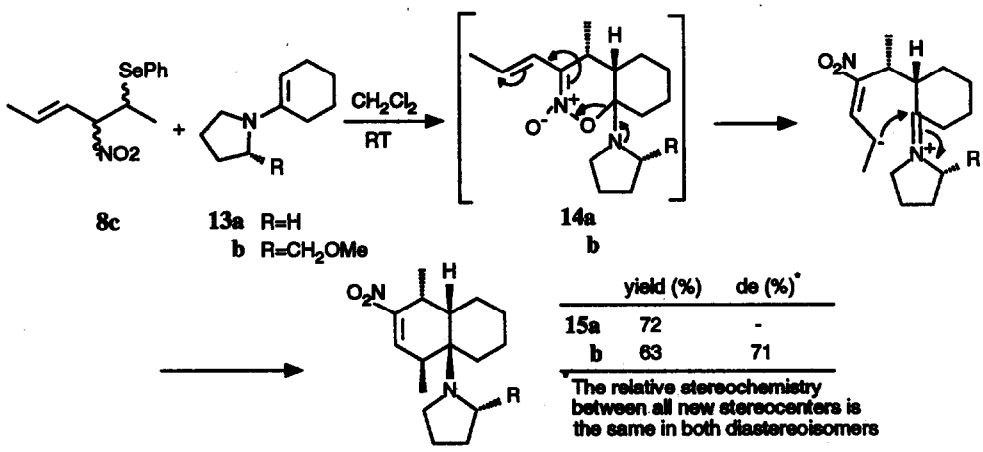
Reaction of acyclic nitrodienes, obtained *in situ* from reaction of the corresponding nitroseleno compounds **8** (see Table 1), with the appropriate enamines **9** afforded cycloadducts **10**. The adducts were identified in the crude reaction mixtures by ^{1}H NMR, and were readily hydrolyzed using mild acidic conditions (silica gel) to the δ,ε-unsaturated γ-nitroketones **11**.[10] With the use of the chiral enamine 1-cyclohexenyl-(2*S*)-methoxymethyl-pyrrolidine (entry 4), both diastereoisomers afforded 45% ee (analysis of the corresponding heterocyclic intermediate **10b** indicated an asymmetric induction of 50% and apparently a slight loss of stereospecificity occurs during workup). High diastereoselectivity was also observed in these heterocyclizations[8] when R_2=Me (entry 5). Thus, **11c** was obtained with total relative stereocontrol between the α and β stereocenters and only two of the four possible diastereoisomers were formed in a 1/1 ratio.

When the reaction was performed with the nitroseleno adduct **8c**[11] and 1-cyclohexenyl-pyrrolidine **13a** (Scheme 2), the reaction pathway was apparently different and the isolated compound was the Diels-Alder-type carbocycloadduct **15a** instead of the expected γ-nitroketone, as in the reaction with the 1-cyclohexenyl-morpholine (Table 1, entry 5). This cycloadduct was obtained with complete and predictable regiospecificity as one diastereoisomer and with a relative stereochemistry determined by NOE experiments. When chiral enamine **13b** was used, the cycloaddition compound **15b** was obtained with 71% de.[12]

In order to elucidate the mechanism of the formation of these Diels-Alder cycloadducts, the reaction was performed in the NMR tube and followed until completion. In this way it was possible to detect the presence of the 1,2-oxazine N-oxide **14** as the kinetic product. Compound **14** is unstable under the reaction conditions and rearranges to **15** by cleavage of the carbon-oxygen bond and subsequent C-C bond formation. Moreover, hydrolysis of **14** in the crude reaction mixture before completion of the reaction afforded nitroketone **11c** in low yield (15%) due to the rapid transformation of the intermediate to carbocycloadduct **15**. All these experiments confirm that this type of cycloaddition does not occur through a concerted mechanism.

It is remarkable that such different products **11c** or **15** can be obtained under the same reaction conditions with the only difference in the enamine being exchange of a morpholino by a pyrrolidino system. The different fate of the heterocycloadduct intermediate **14** in the reaction medium is possibly due to a higher electron-releasing capacity of the nitrogen in the pyrrolidino system. This would allow cleavage of the kinetic product and its further carbocyclization.

Scheme 2



8c **13a** R=H, **b** R=CH_2OMe **14a** **b**

	yield (%)	de (%)*
15a	72	-
b	63	71

*The relative stereochemistry between all new stereocenters is the same in both diastereoisomers

A *typical procedure* for the cycloaddition is as follows. To a solution of 1 mmol of nitroseleno compound[4] in 2 mL of dry methylene chloride was added 1.2 mmol of enamine and the mixture was stirred for 2 h at room temperature. 1,2-Oxazine N-oxides **4** and **6** were isolated by flash chromatography (CH_2Cl_2/EtOH, 98/2). The other cycloadducts **10** were hydrolyzed by the addition of 2 g of silica gel to the reaction mixture. The solvent was evaporated at reduced pressure and the dry silica gel was chromatographed (pentane/ether, 9/1) affording the nitroketones.[13]

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1. For recent examples see: (a) Plobeck, N.; Bäckvall, J.E. *J. Org. Chem.* **1991**, *56*, 4508. (b) Barco, A.; Benetti, S.; Pollini, G.P.; Spalluto, G.; Zarinato, V. *Tetrahedron Lett.* **1991**, *32*, 2517. (c) Padwa, A.; Gareau, Y.; Harrison, B.; Norman, B.H. *J. Org. Chem.* **1991**, *56*, 2713. (d) Bäckvall, J.E.; Plobeck, N. *J. Org. Chem.* **1990**, *55*, 4528. (e) Back, T.G.; Lai, E.K.Y.; Muralidharan, K.R. *J. Org. Chem.* **1990**, *55*, 4595. (f) Posner, G.H.; Kinter, C.M. *J. Org. Chem.* **1990**, *55*, 3967. (g) Chou, S.S.P.; Wey, S.J. *J. Org. Chem.* **1990**, *55*, 1270. (h) Weichert, A.; Hoffmann, H.M.R. *J. Chem. Soc., Chem. Commun.* **1990**, 2154. (i) Bäckvall, J.E.; Löfström, C.; Maffei, M.; Langer, V. *Tetrahedron Lett.* **1992**, *33*, 2417.

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11. Erythro or threo isomers gave the same results.

12. The diastereomeric excess was determined by ^{1}H NMR spectroscopy by integration over the vinylic resonances.

13. All compounds have been characterized by spectroscopic methods As an example, the spectral data of compounds **6**, **11c** and **15a** are given (^{1}H and ^{13}C NMR, 300 and 75.4 MHz respectively, $CDCl_3$ as solvent). **6**: ^{1}H NMR δ 6.64 (1H, dd, J=10.1, 3.0Hz), 6.14 (1H, m), 5.08 (1H, s), 3.57 (1H, m), 3.35-3.17 (3H, m), 3.29 (3H, s), 2.95 (1H, m), 2.34 (2H, m), 2.23 (1H, m), 1.93-1.72 (4H, m), 1.47 (2H, m), 1.07 (3H, s), 1.04 (3H, s); ^{13}C NMR δ 134.9, 122.6, 120.3, 101.4, 76.6, 61.6, 58.7, 46.3, 45.6, 35.1, 28.0, 25.9, 25.6, 22.5, 22.4, 15.9. **11c** isomer 1: ^{1}H NMR δ 5.81 (1H, dc, J=15.1, 6.8Hz), 5.62 (1H, ddc, J=15.1, 9.3, 1.5Hz), 4.86 (1H, t, J=9.3Hz), 2.90 (1H, m), 2.40-1.85 (5H, m), 1.77 (3H, dd, J=6.8, 1.5), 1.70-1.45 (4H, m), 0.83 (3H, d, J=6.8 Hz); ^{13}C NMR δ 210.6, 135.3, 124.2, 92.3, 51.2, 42.3, 35.0, 27.9, 27.6, 24.9, 18.0, 12.0; isomer 2: ^{1}H NMR δ 5.91 (1H, dc, J=15.1, 6.8Hz), 5.62 (1H, ddc, J=15.1, 9.3, 1.5Hz), 4.80 (1H, t, J=9.3Hz), 2.78 (1H, m), 2.40-1.85 (5H, m), 1.77 (3H, dd, J=6.8, 1.5Hz), 1.70-1.45 (4H, m), 0.90 (3H, d, J=6.8Hz); ^{13}C NMR δ 210.6, 134.9, 125.1, 94.0, 50.9, 42.3, 35.0, 27.4, 27.2, 25.1, 18.1, 12.3. **15a:** ^{1}H NMR δ 6.78 (1H, m), 2.97 (2H, m), 2.82 (4H, m), 1.90 (1H, m), 1.75 (4H, m), 1.70-1.40 (8H, m), 1.14 (3H, d, J=6.5Hz), 1.10 (3H, d, J=7.4Hz); ^{13}C NMR δ 151.7, 139.4, 57.6, 44.3, 41.8, 34.4, 30.5, 24.7, 24.4, 22.6, 21.2, 19.8, 18.8, 16.2.

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