Stereoselective (3+3)-Carbocyclization of Enamines with Nitroallylating Reagents

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Abstract: The enamines from open-chain (3-pentanone) and cyclic (cyclopentanone, cyclohexanones, β-tetralone) ketones and the amines pyrrolidine, morpholine or (*S*)-2-methoxymethyl-pyrrolidine combine with *E*-3-phenyl-2-nitro-2-propen-1-yl or *E*-2-nitro-2-hepten-1-yl pivalate (NPP derivatives **6**) to form six-membered rings. Monocyclic (**7**, **8**) and bicyclic (**9**–**14**) products containing four new asymmetric carbon atoms are obtained stereoselectively. The diastereoselectivity observed with the chiral, proline-derived enamines of cyclohexanones is generally higher, and they furnish enantiomerically pure products (cf. the (+)-2-butyl-7-*tert*-butyl-3-nitro-bicyclo[3.3.1]nonan-9-one **14**, formed in 37% yield as one of sixteen stereoisomers!).

There are several methods of carbocyclization leading to six-membered rings from a C_4- and a C_2-component, see Scheme 1. The most important ones are the Diels-Alder reaction[5] (a) and the Robinson anellation[6] (b). In both, simple starting materials can be used and common functional groups are required, both can also be applied to multifunctional reactands, and both can be carried out regio- and stereoselectively. There is a lack of similarly attractive methods by which six-membered rings are formed from two C_3-components[7–9]; *Lawton*'s α-bromomethyl-acrylate[7] and *Büchi*'s allylidene-phosphorane[8] methods are notable exceptions[9].

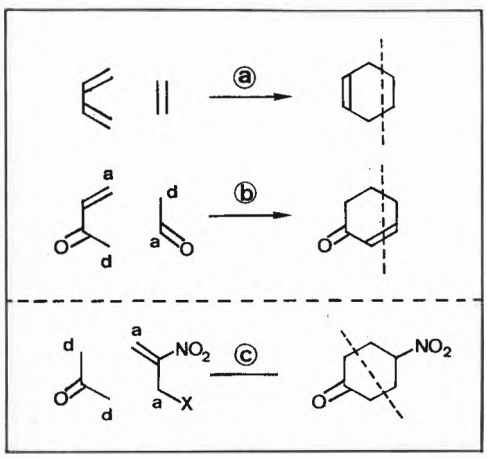
We have now found that enamines and 2-nitro-allylic esters[10] combine to form 4-nitro-cyclohexanones (c) in what appears to be a most valuable synthetic transformation. It follows the same scheme as *Lawton*'s reaction (NO_2 vs. COOR) and is especially promising due to the stereoselectivity observed with substituted reactands.

As characteristic examples of enamines, the morpholino and pyrrolidino derivatives (**1**–**5** in Scheme 2) of 3-pentanone, cyclopentanone, cyclohexanones, and β-tetralone were enabled to react with two typical, readily available NPP[11] derivatives (**6**) of *E*-configuration[12], see procedure below. The products **7**–**14** of cyclization (Scheme 3) were usually obtained in modest yields (not optimized) as single diastereomers, and with the (*S*)-2-methoxymethyl-pyrrolidino enamines[13] **3b**, **4b**, and **5b** the corresponding optically active products (**10**–**14**) were formed in enantiomeric excesses (*ee*) above 90%, see Table 1. The configuration, conformation[14,15], and enantiomeric ratios of the products **7**–**14** were established unambiguously by elaborate high-field NMR techniques. The sense of chirality of the products from (*S*)-2-methoxymethyl-pyrrolidino enamines follows from the known (*Re, Re*) topicities with which they add to simple Michael acceptors[13], see **15**, **16** in Scheme 4 and the bonds marked by dotted lines in the formulae of Scheme 3. For yields and characteristic data of the products see Table 1. Except for the monocyclic case, the intermediates present before hydrolysis were not isolated or identified. Only the monocyclic product of type **17** can possibly be stabilized by proton transfer from the α-NR_2 to the α-NO_2 position to form a nitroenamine (**8**), hydrolysed to **7a** and deuterolysed to **7b**, so that two of the four new asymmetric carbon atoms originate in selective deprotonation/protonation[16] steps. Two mechanistic features are probably most important for the observed stereoselectivity of the reaction: (a) The high reactivity of nitroolefins as Michael acceptors secures that the first step of combination with the enamine occurs at low temperature and is kinetically controlled[15]; (b) both, the NO_2 group in nitroolefins and the NR_2 group in enamines provide a strong preference for a single, namely the *E*-configuration of the double bonds, a prerequisite for selectivity[17].

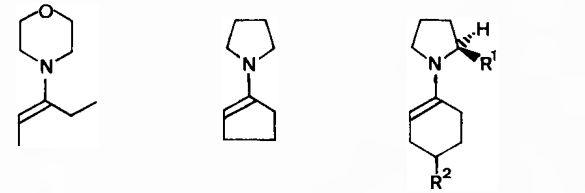
Optimizations, including the use of other NPP derivatives[12] and of other chiral enamines, as well as applications of the method are currently under investigation.

Typical procedure: The nitroolefin (**6**, 3–20 mmol in ca. 30 mL dry CH_2Cl_2) and

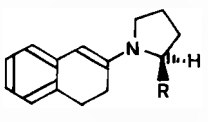
Scheme 1



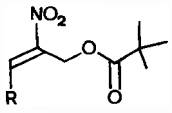
Scheme 2



1 **2** **3a**: $R^1=R^2=H$; **3b**: $R^1=CH_2OCH_3$, $R^2=H$; **4a**: $R^1=H$, $R^2=t$-Bu; **4b**: $R^1=CH_2OCH_3$, $R^2=t$-Bu



5a: R = H
5b: $R=CH_2OCH_3$



6a: $R=C_6H_5$
6b: $R=C_4H_9$

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Scheme 3

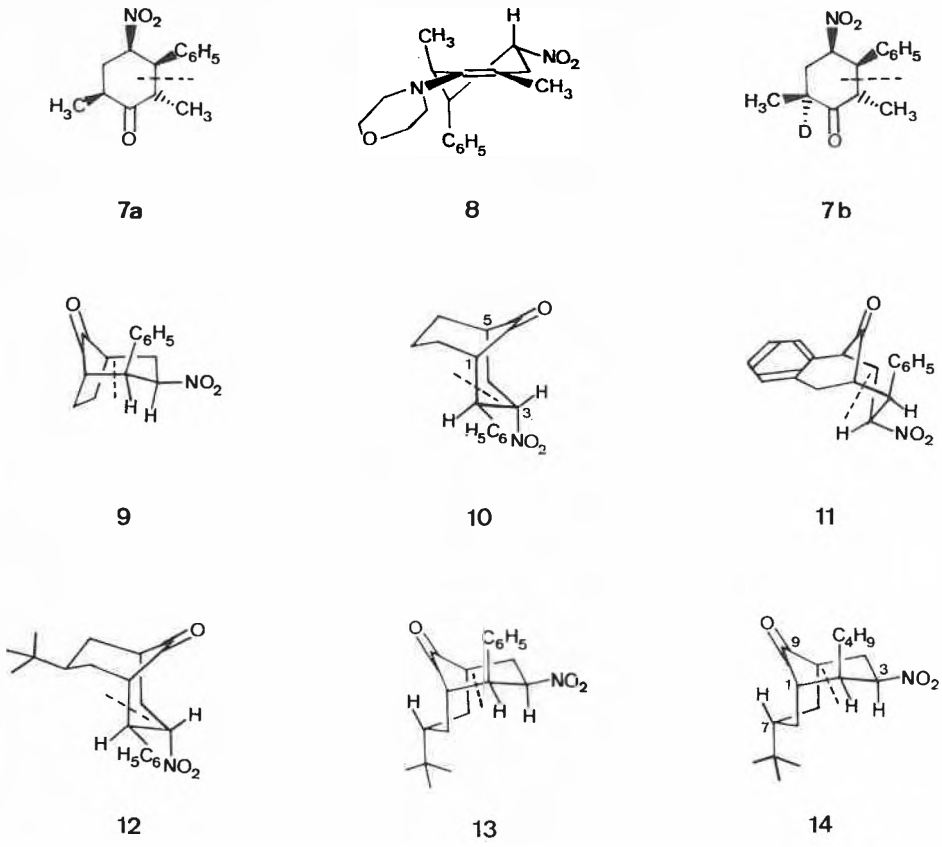
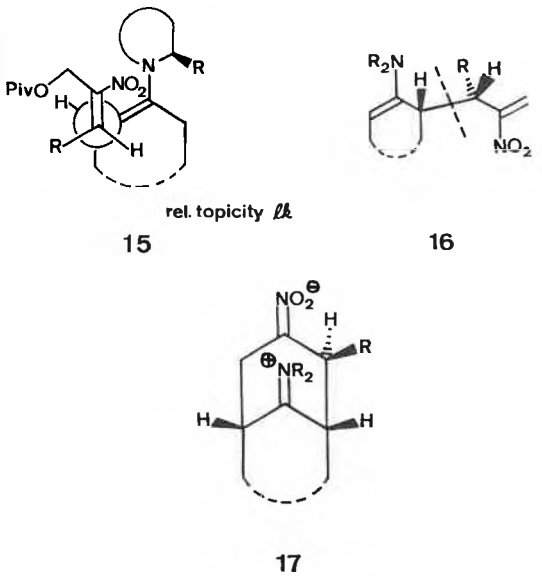


Table 1. Preparation of racemic (±) and of enantiomerically pure products **7**–**14** (all $[\alpha]_D^{25}$ in CH_2Cl_2, c = 1–2) from enamines **1**, **2**, **3a**, **4a**, **5a** and **3b**, **4b**, **5b**, respectively, and phenyl or butyl NPP (**6a**, **6b**). % *ds*: content of the diastereomer (formulae **7**–**14**) before crystallization. %: yield after recrystallization. All products gave correct (±0.3%) elemental analyses.

(±)-**7a**:	60% from **1** and **6a**, > 95% *ds*, *m.p.* 93–94°C.
(±)-**7b**:	80% from **8** and DCl/CH_3OD/D_2O, > 95% *ds*, *m.p.* 93°C.
(±)-**8**:	50% from **1** and **6a**, work-up without acidic hydrolysis, > 95% *ds*, *m.p.* 119–121°C.
(±)-**9**:	8% from **2** and **6a**, 85% *ds*, *m.p.* 151–152°C.
(+)-**10**:	from **3a** and **6a**, the crude product (65% yield) contained two diastereomers (ratio up to 4:1) which were separated by fractional crystallization; major product **10** (28%), *m.p.* 117–119°C.; minor product, *m.p.* 144°C (10% yield).
(±)-**10**:	41% from **3b** and **6a**, > 95% *ds*, > 95% *ee*, m.p. 101–102°C, $[\alpha]_D$ = +59.
(±)-**11**:	20% from **5a** and **6a**, > 90% *ds*, *m.p.* 186–187°C.
(−)-**11**:	44% from **5b** and **6a**, > 90% *ds*, > 95% *ee*, *m.p.* 188–190°C, mixed *m.p.* with (±)-**11** 178–181°C, $[\alpha]_D$ = − 100.
(±)-**12**:	65% of a mixture of (±)-**12** and (±)-**13** (7:3) from **4a** and **6a**; (±)-**12**: 38%, *m.p.* 169–171°C.
(±)-**13**:	(from the mixture with (±)-**12**, see above), 15%, *m.p.* 216°C.
(+)-**12**:	55% of a mixture of (+)-**12** and (+)-**13** (17:3) from **4b** and **6a**; (+)-**12**: 39%, *m.p.* 206–207°C, > 95% *ee*, $[\alpha]_D$ = +31.
(+)-**13**:	(from the mixture with (+)-**12**, see above), 8%, *m.p.* 206°C, mixed *m.p.* with (+)-**12** 166–173°C, $[\alpha]_D$ = +66.
(+)-**14**:	37% from **4b** and **6b**, > 90% *ds*, > 90% *ee*, *m.p.* 124°C, $[\alpha]_D$ = +47.

an equivalent amount of the enamine (**1**–**5**, in 10 mL CH_2Cl_2) were combined at dry ice temperature (dropwise addition of the latter by syringe). After allowing to warm to room temperature overnight, 5–20 mL 1N HCl and 5–10 mL H_2O were added, and the mixture was heated at reflux for 1 h. Extraction of the aqueous phase with CH_2Cl_2, washing and drying the combined organic layers, evaporation of the solvent, and flash-chromatography gave the products (**7a**, **9**–**14**) which were recrystallized from ether or ether/CH_2Cl_2. Careful optimization of these conditions may be necessary for any given case. For the hydrolysis step in the preparation of the monocycle **7a** see procedure in[17b].

Scheme 4



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