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Chirality transfer in the ene-reactions of 3-{2-(2*S*)-[2-(substituted)vinyl]pyrrolidin-1-yl}-2-(substituted)acrolein derivatives

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Abstract

Ene-reactions of 3-{2-(2*S*)-[2-(substituted)vinyl]pyrrolidin-1-yl}-2-(substituted)acrolein derivatives **5**, **8**, **13**, and **16** have been described. Carbonyl-ene reaction of **5** and **16** and imine-ene reaction of **8** proceeded in a highly selective manner to lead to azepine derivatives **6** and **17**, and **9**, respectively. The chirality of the starting acroleins was transferred almost perfectly to the azepine-ring through the ene reactions.

Keywords: ene reactions; cyclization; enantioselection; azepines.

Construction of new strategies for the stereoselective synthesis of azepines continues to attract interest in heterocyclic chemistry, and various methods have been proposed toward this goal.[1] We have also reported that ene reactions of 3-[(*E*)-alk-2-enyl]amino-2-cyano- and 3-[(*E*)-alk-2-enyl]amino-2-(methoxycarbonyl)-acroleins and their imines and vinyl substrates have been revealed to be a powerful and effective tool for mono-cyclic 4,5-dihydro-1*H*-azepine derivatives.[2] Therein, we proposed that this azepine ring formation from acyclic systems constitutes of two consecutive orbital-allowed reactions: the [1,6] sigmatropic shift of the allylic hydrogen (**TS 1**) generating a conjugated azomethine ylide (**Intermediate**) and its [1,7] electrocyclic ring closure (**TS 2**). This means that the azepine ring formation is expected to proceed in a highly selective manner. In continuation of our study, we examined the ene reaction of the titled acrolein derivatives bearing a chiral center at the alkenylamino moiety and their imines and vinyl compounds, so as to develop further utility of these ene reactions.

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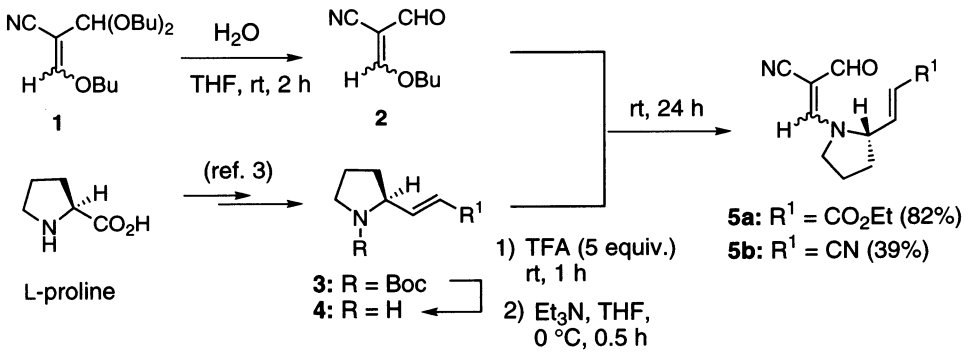
At first, 3-{2-(2*S*)-[2-(*E*)-(ethoxycarbonyl)vinyl]pyrrolidin-1-yl}-2-cyanoacrolein **5a** and {2-(2*S*)-[2-(*E*)-cyanovinyl]pyrrolidinyl} substrate **5b** were prepared by the reaction of 3-butoxy-2-cyanoacrolein **2** and pyrrolidine **4a** and **4b**[3] in moderate to poor yields, respectively. These acrolein derivatives **5a** and **5b** were obtained as ca. 4:1 inseparable mixtures of two geometric isomers, and the mixtures were utilized for the ene reaction without further purification due to their low instability (Scheme 1).



Scheme 1.

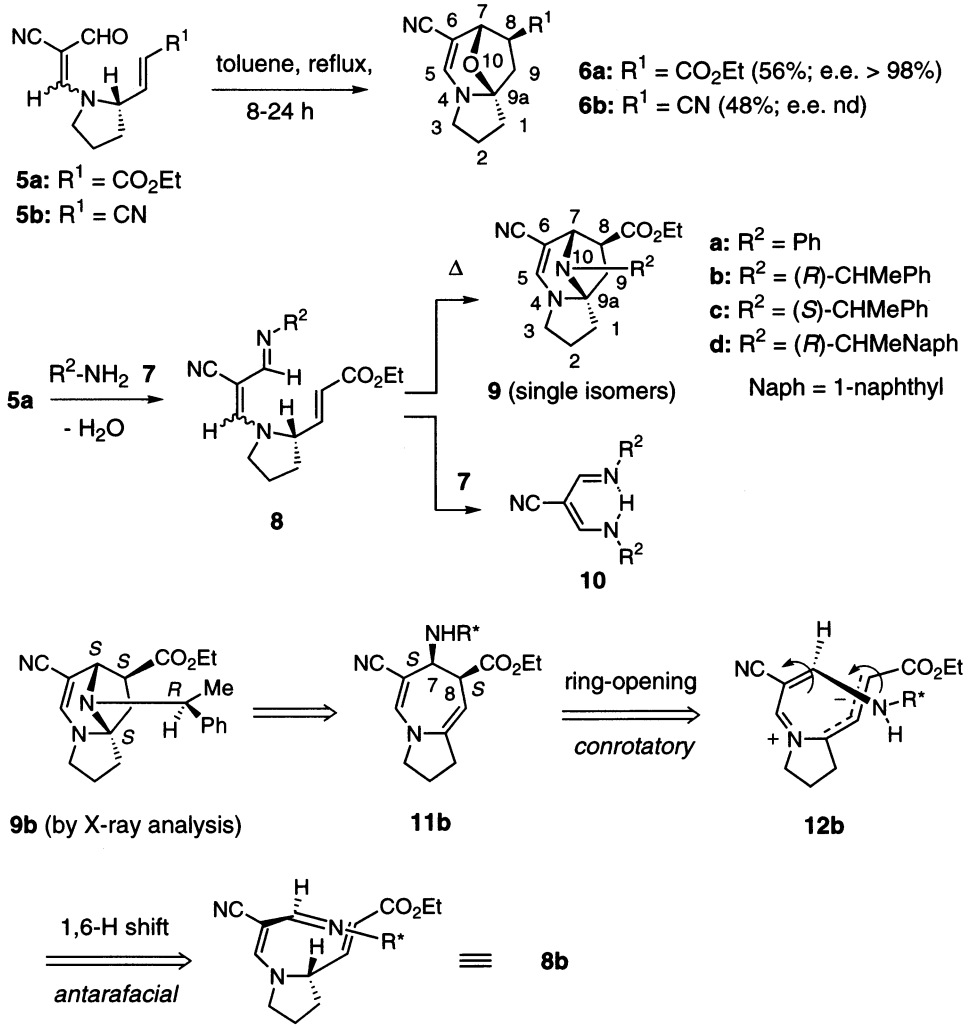
Heating **5a** and **5b** in refluxing toluene gave 7,9a-oxapyrrolo[1,2-*a*]azepines **6a** and **6b** in moderate to good yields as single isomers, together with unidentified polymeric products. The reaction of acrolein **5a** and aniline (**7a**) in refluxing xylene in the presence of toluene-*p*-sulfonic acid (PTSA) gave 7,9a-iminopyrrolo[1,2-*a*]azepine **9a**, via the corresponding imine ene reaction of **8a**, and vinamidine **10a**[4] in 68 and 20% yield, respectively. Further reaction of **5a** with chiral primary amines **7b–d** also gave iminopyrroloazepines **9b–d** and vinamidines **10b–d** in good total yields (Table 1). Iminopyrroloazepines **9b–d** obtained were revealed to be single isomers (d.e: >99%) from the ^{1}H NMR spectra and/or HPLC of the crude reaction mixtures. This means that the imine-ene reaction from acroleins **5a** and **7b–d** proceeds with perfect induction of the chirality in acrolein **5a** on the resulting three chiral centers of the iminopyrroloazepine nuclei of **9b–d**. To elucidate the efficiency of the chirality transfer of these ene reactions, we performed similar carbonyl- and imine-ene reactions using a racemic substrate (***rac***)-**5a** from (***rac***)-**3a** as a reference. High enantioselectivity of the reactions utilizing chiral substrates was attained by a chiral HPLC method; the e.e. of carbonyl-ene product **6a** was 98% from the starting L-proline,[5] while that of imine-ene product **9a** was 93%; therefore, the enantioselectivity of the ene reaction process was more than 98 and 93%, respectively. In order to obtain a more precise understand-

Table 1
Reaction of chiral aldehyde **5a** and primary amines **7**

Run	Amine	Solvent	Additive	Time/h	Iminopyrroloazepine/yield (%);[a] selectivity	Vinamidine/yield (%)[a]
1	**7a**	Xylene	PTSA (cat.)	2.5	**9a**/68; e.e.: >93	**10a**/20
2	**7b**	Toluene	MS (4 Å)	6	**9b**/66; d.e.: >99	**10b**/25
3	**7c**	Xylene	MS (4 Å)	1	**9c**/63; d.e.: >99	**10c**/21
4	**7d**	Xylene	MS (4 Å)	1	**9d**/34; d.e.: >99	**10d**/45

[a] Based on isolated product.

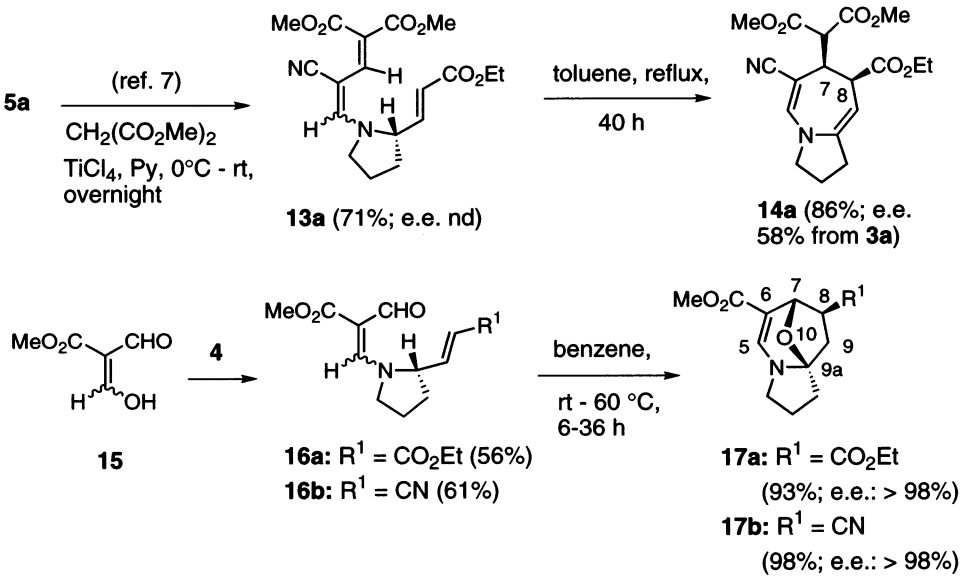
ing of the reaction pathway, we examined the absolute structure of 7,9a-iminopyrrolo[1,2-*a*]azepines **9**; the structure of **9b**, obtained from acrolein **5a** and (*R*)-1-phenylethylamine (**7b**), was unambigiously established by X-ray single-crystal analysis.[6] Therefore, the stereochemistry of azepine derivative **11b**, the precursor of **9b**, was deduced to be (7*S*,8*S*) based on the absolute *R* configuration derived from the 1-phenylethylamino moiety. The structure of the azomethine ylide intermediate **12b** was deduced by the conrotatory ring-opening of azepine **11b**. The formation of intermediate **12b** was ascribed to the antarafacial [1,6]hydrogen shift of the chiral imine **8b** (Scheme 2).



Scheme 2.

Stimulated by these results, we further examined chiral transfer of the olefin-ene reaction of the related system; condensation[7] of acrolein **5a** with dimethyl malonate gave conjugated diene compound **13a**. Thermal reaction of **13a** in refluxing toluene proceeded in a highly stereoselective manner to afford pyrroloazepine derivative **14a** (chemical yield: 86%; e.e.: 58% from **3a**). As regards the lowered e.e. of azepine **14a**, it occurred to us that the condensation conditions from

acrolein **5a** and dimethyl malonate would cause a racemization of conjugated diene **13a**. To check this possibility, we examined the e.e. of the starting conjugated diene **13a**. Unfortunately, we have not succeeded in finding the optimal HPLC conditions to separate the two enantiomers of (***rac***)-**11a**. Our next concern was focussed on the reaction of 3-{2-(2*S*)-[2-(*E*)-(ethoxycarbonyl)vinyl]pyrrolidin-1-yl}-2-(methoxycarbonyl)acrolein **16a** and {2-(2*S*)-[2-(*E*)-cyanovinyl]-pyrrolidinyl} substrate **16b**; they were expected to have higher reactivity toward these ene reactions than the 2-cyano derivatives **5** due to the restriction of configurational and/or conformational flexibility of the substrates.[2] The desired **16a** and **16b** were prepared from 2-(methoxycarbonyl)malonaldehyde (**15**)[8] in moderate yield, similarly to the method for acroleins **5**. Interestingly, acroleins **16** were not so stable and cyclized spontaneously at room temperature to afford oxapyrroloazepines **17a** and **17b** in almost quantitative yields. The efficiency of the chirality transfer in the carbonyl-ene reaction was almost perfect (e.e.: more than 98%). Unfortunately, the preparation of imines from acrolein **14a** failed due to its too-high reactivity toward the carbonyl-ene reaction; the reactions of **14a** with aniline and *N*-(triphenylphosphoranylidene)aniline under several conditions gave only oxapyrroloazepine **17a** and vinamidine **10a** (Scheme 3).



Scheme 3.

In conclusion, an almost perfect chirality transfer has been accomplished in the carbonyl- and imine-ene reactions of the titled systems leading to enantiopure functionalized pyrroloazepines and related compounds. These findings should lead to a useful application of the ene reactions to further chiral induction, and employment of the resulting products as asymmetric building blocks.

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