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New applications of chiral *N*-acyliminium precursors

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Abstract - The optically pure *cis* and *trans* iron-carbonyl complexes of the chiral C-5 isopropoxy enelactam **6** react with allyltrimethylsilane under influence of $\text{BF}_3 \cdot \text{OEt}_2$ through a *N*-acyliminium intermediate to yield enantiocontrolled substitution products.

Enantioselective introduction of substituents at C-2 of pyrrolidine **1** (fig. 1) is nowadays possible by making use of asymmetric deprotonation.¹ The electrophilic counterpart, i.e. the direct substitution at C-5 of a chiral alkoxylactam **2** so far has never indicated the formation of optically active lactams.² Only in case of the nitrogen carrying chiral substituents asymmetric induction was established.³

Fig. 1

Numerous studies have been connected with the use of appropriate *N*-acyliminium intermediates derived from chiral pool materials, such as tartaric acid⁴ threonine⁵ and malic acid.⁶ In the latter cases it is to be noted that diastereoselective reactions are occurring, the results depending on the degree of control exerted by the ring substituent. Thus in case of malic acid the outcome will be determined by the type of OX present in **3** (fig. 2), while also the structure and nucleophilic character of the incoming substituent have a distinct influence. Conversely if the precursor **4** could be synthesized in a chiral manner from **3**, the type of stereocontrol then would originate from the C-5 oxy substituent in nucleophilic additions to the enelactam resulting in different types of *N*-acyliminium precursors. Finally the direct treatment of **4** under acid conditions would result in a structure which due to its pancake format would not be expected to lead to

Fig. 2

optically pure enantiomers. The effect of the size of the nucleophile is convincingly demonstrated in fig. 3. Upon reaction of the PMB substituted diacetate **5** with a series of closely related silyl enol ethers the results show a complete *anti* addition with the trisubstituted derivatives while the less hindered trimethylsilyloxystyrene affords a 12:88 *cis/trans* mixture.⁷

Fig. 3

As a chiral precursor for direct introduction of the nucleophile we have selected the enelactam **6**, the synthesis of which is outlined in fig. 4. Of high value herein is the synthesis of the enantiopure trichloroacetate which can be used as the starting material for a number of differently N-substituted enelactam derivatives.⁸

Fig. 4

The enelactam **6** has been applied in 2+4 cycloadditions⁹ while also the conjugate addition of amines and thiols has been studied.¹⁰ Of particular interest is the application as a chiral dienophile in the construction of a precursor for the total synthesis of the alkaloid gelsemine.¹¹ While the approaches outlined do give rise to novel applications of chiral N-acyliminium ions in practice one problem still exists.

Fig. 5

Direct substitution (fig. 5) of the chiral enelactam **7** has to proceed through the intermediacy of achiral **8** and it would be therefore expected that a net control of *retention* or *inversion* at C-5 will be impossible. A second obstacle is inherent to the structure of **7** which formally can be considered as a N, N diacylamine. Since generation of the cationic intermediate requires the participation of the nitrogen lone pair, one of the acyl substituents has to be removed. Although chemically this can be done by treatment with an amine the resulting N-H enelactam is not suitable to study the desired transformation. Due to instability of the corresponding cation only

polymer formation is observed upon treatment with acid. In search for other possibilities to eliminate the electronic influence of the second carbonyl substituent we considered the possible complex formation with an appropriate metal. (Fig. 6)

Fig. 6

Such a process would obviate the negative influence of a second carbonyl without making the system inherently unstable. Although a metal atom would be expected to draw electron density out of the ring the overall process could still be beneficial in terms of backdonation. This type of metal complex has been studied before¹² and it has been established that iron-carbonyl complexes show photoelectron spectra¹³ which clearly indicate a net charge flow into the ring through metal-to-ligand backdonation. Upon acid treatment the system then might form a chiral complex which after reaction with an appropriate nucleophile and removal of the metal would lead to the desired substitution. Of added interest is the fact that the introduction of the nucleophile would take place under stereocontrol of the metal ligand moiety, ML_n , thus effectively promoting the approach from the least hindered side. Formation of the $Fe(CO)_4$ complex of **6** by treatment with $Fe_2(CO)_9$ in ether proceeded smoothly and afforded a mixture of *cis* and *trans* complexes in the ratio indicated (fig. 7).

Fig. 7

Interestingly, while the *cis* isomer appeared to be the kinetically preferred product a slow isomerization to a 67:33 *cis/trans* mixture was observed upon standing.¹⁴ Both isomers were readily separated by flash chromatography thus allowing each isomer to be investigated. Although we have no definite proof on the mechanism of the $Fe_2(CO)_9$ addition it seems likely that the preferred *cis* addition is the result of a weak coordinative influence of the isopropoxy function. Having available both $Fe(CO)_4$ complexes separate nucleophilic substitutions could be studied. For the *cis*-isomer *inversion* at C-5 would be expected since the approach from the least hindered side of the intermediate will be determined by the position of the $Fe(CO)_4$ group. By the same reasoning the *trans*-isomer is expected to show *retention* at C-5.

Fig. 8

(Fig. 8) In practice the latter phenomenon was indeed observed upon reaction with allyltrimethylsilane in presence of $BF_3 \cdot OEt_2$. In a rather fast reaction a 51% yield of the substitution product **9** was obtained after oxidative removal of the iron substituent. According to 1H -NMR chiral shift measurements the ee was determined as $>95\%$. On the contrary the *cis* isomer reacted much slower to produce **10** with an ee of 55%. Since we were not able to

improve on these results by variation of the reaction parameters other N-substituents were examined. Therefore the N-tosyl derivative **11** was prepared (fig. 9) in a manner already described.

Fig. 9

Quite unexpectedly almost all of the material obtained proved to possess the *cis*-structure of the complex and could be easily purified by crystallization. Most remarkably, however, the *cis*-N-tosyl complex **11** reacted rapidly with allyltrimethylsilane to produce a quantitative yield of the *inverted* (fig. 10) substitution product which after work-up and purification afforded the enantiopure enelactam **12** in 72% yield. Investigations on the precise role of the N-substituent as well as the influence of different types of metal complexes are currently being carried out.

Fig. 10

Also the nature of the nucleophile is varied to gain a better insight in this transformation. Results on these experiments will be reported elsewhere.¹⁵

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