

Asymmetric Electrophilic α -Amidoalkylation, 9:¹ Highly Stereoselective Syntheses of 2-Substituted Piperidines

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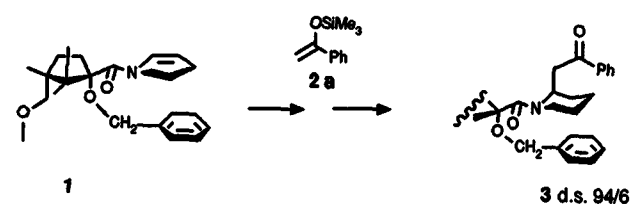
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Dedicated to Prof. Herbert Oelschläger on the occasion of his 70th birthday

Abstract: Enantiomerically pure 2-substituted piperidines **8** are synthesized by diastereoselective addition of various nucleophiles **2** to a chiral *N*-acyliminium ion with an *N*-acyl group as chiral auxiliary generated in situ from enamide **5** (1-((1*S*,3*R*)-3-methoxymethyl-2,2,3-trimethyl-1-triphenylsilyloxycyclopentyl)carbonyl)-1,2,3,4-tetrahydropyridine).

One of the most versatile and general principles for the preparation of α -substituted amines includes the reaction of *N*-acyliminium ions with nucleophiles which is termed electrophilic α -amidoalkylation^{3,4}. According to the concept presented by us some time ago⁵ this method may be utilized for asymmetric synthesis in general by employing *N*-acyliminium ions having a chiral *N*-acyl group which serves as chiral auxiliary^{6,7}.

Meanwhile we have successfully implemented this concept which we have named Asymmetric Electrophilic α -Amidoalkylation (AE α A) also for the synthesis of pyrrolidines, piperidines and 1,2,3,4-tetrahydroisoquinolines.

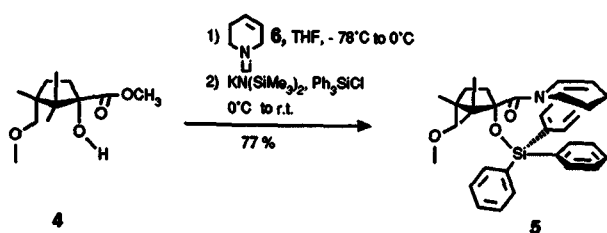


Scheme 1

In the case of the piperidines, enamides have proven to be useful *N*-acyliminium ion precursors and the optimization of the chiral auxiliary with respect to the asymmetric induction led to **1** which exhibits a d.s. of 94/6 in the addition of **2a**⁸.

However, due to the steric hindrance by the benzyl group of **1** (this benzyl group is essential for a high asymmetric induction) the cleavage of the amide bond turned out to be difficult. For example, attempts to hydrolyze an amidoalcohol derived from **3** under alkaline conditions were unsuccessful.

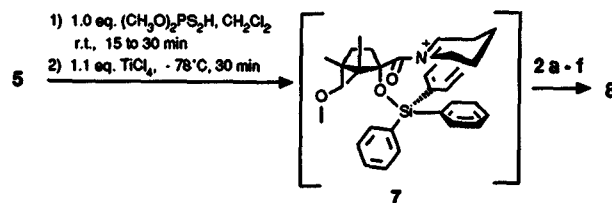
We finally solved this problem by first removing the benzyl group by hydrogenolysis and then reductively cleaving the amide bond⁸ (similar to the transformation of **9a** to **13** in Scheme 6).



Scheme 2

As many functional groups are incompatible with our procedure we developed the asymmetric α -amidoalkylation reagent **5** with a triphenylsilyl moiety. Starting from **4**⁹ enamide **5** may be obtained in high yield through a simple one-pot reaction. On treatment of **4** with an excess of **6** at -78°C the corresponding amide was formed which upon warming to 0°C underwent a base catalyzed rearrangement to afford an enamide which after transmetalation of the hydroxy group with $\text{KN}(\text{SiMe}_3)_2$ and treatment with Ph_3SiCl afforded **5**.

We have found amidoalkylation reactions with **5** to proceed smoothly and to result in high chemical yield and excellent diastereoselectivity when the enamide **5** is activated by sequential addition of *O,O*-dimethyldithiophosphoric acid and TiCl_4 . Thus the scavenging reaction of the *N*-acyliminium ion **7** with the silyl enol ether **2a-f** at -78°C yielded a diastereoselectivity which was even higher than that of **1** (d.s. 97/3, see Table 1).



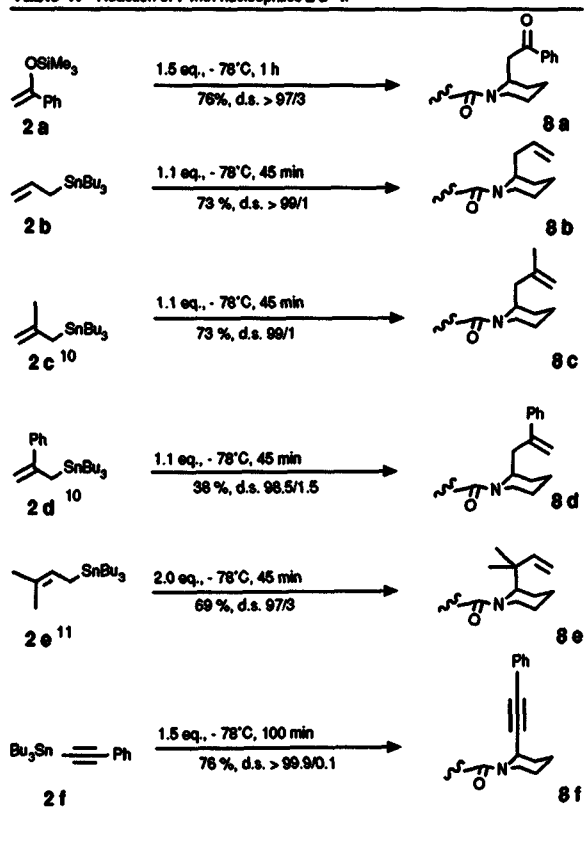
Scheme 3

Encouraged by the above findings, we investigated the addition of allyl metal compounds to **7**.

However, when allyltrimethylsilane was used a complex reaction mixture resulted and only minor amounts of the desired product could be detected.

We, therefore, directed our attention to the more reactive allylstannanes which have proven to be useful reagents in related reactions¹². Indeed, when **2b** was employed at -78°C a clean reaction occurred and **8b** was formed with an exceptionally high stereoselectivity (>99/1) and an isolated yield of 73%. In addition to **2b** the substituted allylstannanes **2c-e** were employed in this type of asymmetric synthesis. As can be seen from Table 1 the results obtained with these nucleophiles were also very satisfactory.

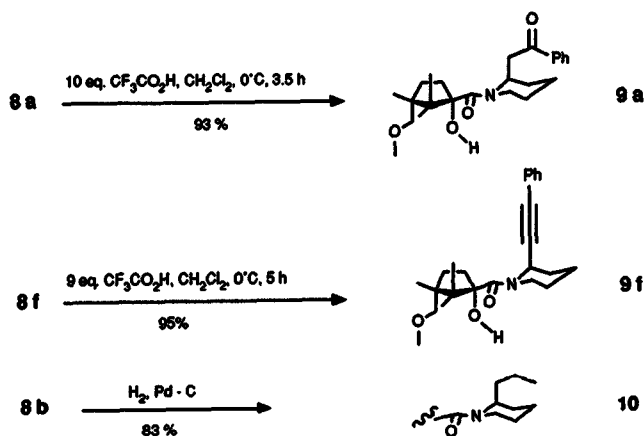
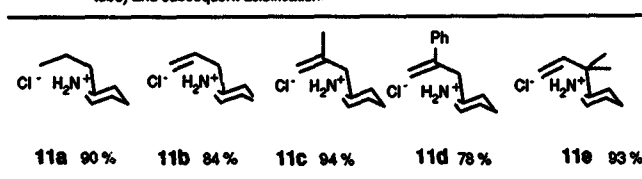
In order to test the feasibility of a stereoselective alkylation reaction, **7** was treated with the alkylstannane **2f**¹³. Again a clean reaction occurred and a very impressive diastereoselectivity (>99.9/0.1) was observed (see Table 1). Most likely this increase in diastereoselectivity is to be attributed to the bulkiness of the reaction center in **2f**.

Table 1. Reaction of **7** with nucleophiles **2 a - f**.^a

^a) Yields refer to the pure major diastereomer after flash chromatography. Diastereoselectivities were determined by HPLC.

The triphenylsilyl ether moieties in **5** and **8a-f** exhibited a remarkable stability under the reaction conditions employed, as evidenced by the only minute amounts of detected desilylated compounds in the crude product. On the other hand, a complete desilylation could be effected by the conversion of **8a** and **8f** to **9a** and **9f**, respectively. This is an important finding, as the amide bond in α -hydroxyamides¹⁴ can be easily cleaved by reduction (see Scheme 5).

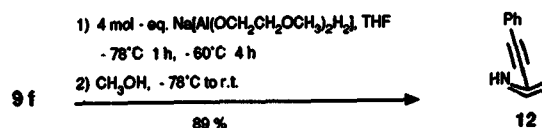
For the synthesis of the alkaloid S-(+)-coniin (**11a**) amide **8b** was subjected to hydrogenation using Pd on carbon as catalyst to yield the appropriate precursor **10**.

**Scheme 4****Table 2.** Piperidine hydrochlorides **11 a - e** obtained from **8 b - f** and **10** by hydrolysis (30 eq. LiOH · H₂O, CH₃OCH₂CH₂OH, 3 d, sealed pressure tube) and subsequent acidification.

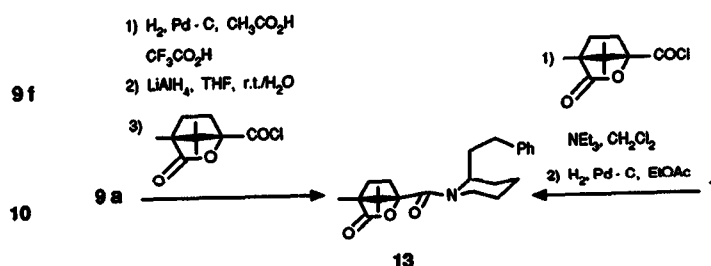
The simplest way of removing the chiral auxiliary that we have found is by heating the corresponding compounds with LiOH/CH₃OCH₂CH₂OH to 160°C in a sealed tube. Thereby high amine yields were obtained from **8b-e** and **10** (see Table 2).

It should be noted that according to TLC the first step in this reaction is the cleavage of the silyl ether moiety.

However, the conditions described above were not applicable to **8f** due to the base sensitivity of the alkyne moiety. In this case the presence of the α -hydroxy group in **9f**, which is the product of desilylation of **8f**, allowed to reduce the amide bond in a highly selective manner to an N,O-acetal which after quenching the reaction with MeOH and aqueous workup gave **12** in 89% yield (see Scheme 5). This further highlights the versatility of the present chiral auxiliary.

**Scheme 5**

In order to determine the configuration of the newly created stereocenter of **9a** and **12**, these compounds were correlated with **13**⁸ (as illustrated in Scheme 6) and were found to possess (R)-stereochemistry. The same sense of chirality was found for the alkaloid **11a** by comparison of its optical rotation ($[\alpha]_D^{25} = +4.9^\circ$) with literature data ($[\alpha]_D^{25} = +5.2^\circ$ ¹⁵). Its precursor **8b** must be of (R)-configuration, therefore, and because of typical similarities in the chemical shift values and coupling constants in the ¹H-NMR-spectra (400-MHz) of **8b-8e** it seems reasonable to assume that this is the case for all of the major isomers.

**Scheme 6**

Based on the reasons already set forth for the N-acyliminium ion of **1**⁸ we propose stereomodel **7** (Scheme 3) as a rationale for the sense of asymmetric induction.

General Procedure: To a stirred solution of **5** (1 mmol in 4 ml CH₂Cl₂) O,O-dimethyldithiophosphoric acid (1 eq.) is added and the resulting mixture is kept at room temperature for 30 min. Then it is cooled down to -78°C and TiCl₄ (1.1 eq.) is added, followed after 30 min by the addition of the desired nucleophile **2** (1.1 to 2.0 eq.). The reaction mixture is stirred for 45 min and then quenched by pouring it into an aqueous solution of NaHCO₃ cooled with ice. The aqueous layer is extracted twice with CH₂Cl₂ and the combined organic layers are dried (MgSO₄) and concentrated. Pure diastereomers are obtained by flash chromatography or MPLC.

Acknowledgements

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References and Notes

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