Synthesis of Functionalised Piperidines Through a [3+3] Cycloaddition Strategy

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Abstract: A novel approach to functionalised piperidines is described through a [3+3] cycloaddition reaction of aziridines with Pd-trimethylenemethane complexes. Importantly, the employment of enantiomerically pure aziridines (prepared in three steps from the appropriate amino acids) allows the corresponding piperidines to be furnished in enantiomerically pure form. Additionally, the application of this technique in the total synthesis of (–)-pseudoconhydrine is described.

Key Words: cycloadditions, aziridines, piperidines, palladium-trimethylenemethane

Cycloaddition reactions are amongst the most effective methods for the rapid synthesis of functionalised cyclic systems in a stereocontrolled manner.[1] Additionally, the application of transition metal catalysts in these processes provides added opportunity to exert further control over the efficiency and selectivity of these reactions. In the context of six membered ring formation, the Diels–Alder reaction holds a uniquely prominent position and formally comprises a [4+2] assembly strategy.[2] In contrast, the employment of a [3+3] cycloaddition approach has been much less widely studied.[3] In this context, the employment of Pd-catalysis has led to techniques for the assembly of pyran derivatives[4] whereas piperidine systems have been prepared by a formal [3+3] cycloaddition reaction of 1,3-cyclic sulfates with *C*,*N*-dianions,[5] vinylogous amides with α,β-unsaturated iminiums,[6] α,α'-dimethoxylated amides with allyltrimethylsilane[7] and Pd-trimethylenemethane (Pd-TMM) complexes with aziridines.[8] We anticipated that the latter approach represented a potentially efficient technique for the synthesis of enantiomerically pure nitrogen and oxygen containing heterocyclic products through the employment of readily available enantiomerically pure aziridines and epoxides (Figure). Despite the attractiveness of this approach, only a single reaction of this type is known in the literature whereby racemic *N*-tosyl and *N*-acyl 2-methylaziridines have been transformed to the corresponding piperidines.[8] We decided to undertake a study of the generality of this [3+3] cycloaddition process, particularly with a view to preparing enantiomerically pure piperidines. Accordingly, we report herein our initial results on the reaction scope and its use in a short enantioselective synthesis of (–)-pseudoconhydrine.

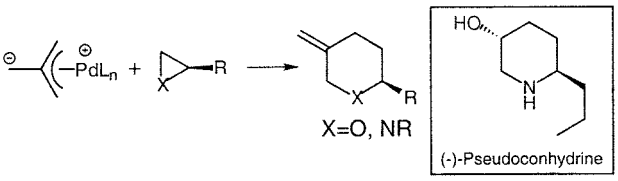
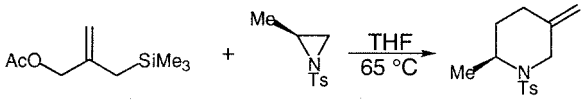


Figure [3+3] Cycloaddition strategy to 6-membered heterocycles

Enantiomerically pure aziridines were prepared in 3 steps from the appropriate amino acids by the method of Craig.[9] We decided to employ the commercially available conjunctive reagent 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate as a convenient source for the in situ generation of the Pd-TMM complex, since it has been applied successfully in the presence of a range of palladium catalysts and has been shown to be an efficient partner for other cycloaddition processes.[10] With the requisite substrates in hand, we began our studies by investigating the effects of catalyst system on the efficiency of the [3+3] cycloaddition reaction. In our hands, the use of $Pd(PPh_3)_4$ following the procedure of Kemmitt *et al.* [8] was ineffective in promoting piperidine formation. Notably, Trost has reported that the utilisation of non-basic phosphite ligands enhances the reactivity of Pd-TMM complexes in [3+2] and [4+3] cycloaddition processes.[10] Accordingly, we found that the use of $Pd(OAc)_2$ and $P(OiPr)_3$ in a 1:6 ratio with *n*-BuLi as reductant provided the desired piperidine smoothly and in high yield (Scheme 1).[11]



Scheme 1

We subsequently decided to investigate the scope of the [3+3] cycloaddition process and our results are outlined in the Table. As outlined in entries 1, 2, 4 and 7, the use of tosyl protected 2-substituted aziridines provided the corresponding piperidines in good to excellent yields.

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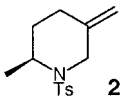
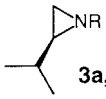
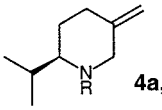
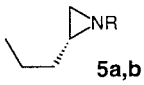
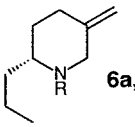
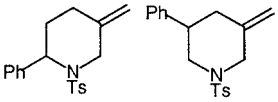
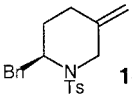
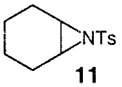
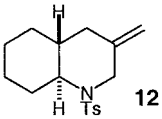
Notably, these aziridines underwent regioselective addition of the Pd-TMM complex at the less hindered site and furnished the products in enantiomerically pure form which confirmed that the cycloaddition process did not cause unwanted epimerisation at the remote stereogenic centre.[12] In contrast, the use of 2-phenylaziridine **7** (entry 6) resulted in an almost equal mixture of regioisomeric products **8a** and **8b**. This observation was unsurprising as the tendency for a phenyl substituent to promote aziridine cleavage at the benzylic site is well documented.[14] Finally, we have also found that the methodology is applicable to the synthesis of bicyclic piperidines **12** (entry 8). Unfortunately however, aziridine **11** was found to be rather sluggish towards the cycloaddition reaction and **12** was furnished in low yield. We have also discovered that the *N*-substituent can have a profound effect on the efficiency of aziridine cleavage in this reaction process. Indeed, whilst we have found that *p*-toluenesulfonyl (Ts) and *p*-methoxybenzenesulfonyl (PMBS) groups permit smooth cycloaddition to take place (entries 3 and 5), the *p*-nitrobenzenesulfonyl unit furnished a complex mixture of products whereas carbamate (Boc, Cbz) and diphenyl phosphinoyl moieties failed to provide the corresponding piperidines and starting materials were returned (>95%) in all cases.

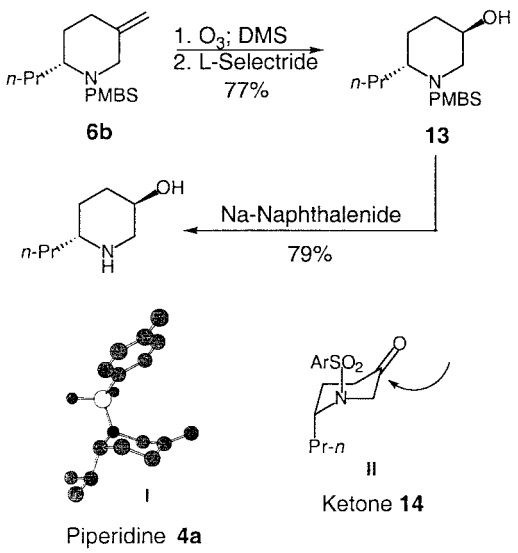
With a rapid and reliable method for enantiomerically pure piperidine synthesis in hand, we turned our attention to the application of this methodology to the synthesis of (–)-pseudoconhydrine. Pseudoconhydrine has been isolated from Poison Hemlock, *Conium maculatum* and is a member of a class of biologically active piperidine alkaloids.[15] We were able to readily convert PMBS protected piperidine **6b** to the natural product in a three pot process. Ozonolysis of **6b** followed by reduction with L-selectride® provided **13** as a single diastereoisomer (Scheme 2). In considering the stereoselectivity of this reaction, an X-ray crystal structure of piperidine **4a** proved enlightening (represented as a Chemdraw 3D™ picture **I**, H-atoms omitted for clarity), and showed the expected 2-axial alkyl conformation.[16] Assuming that this conformation is maintained in the ketone **14** derived from ozonolysis of **6b**, the stereoselectivity of the reduction likely arises from attack of the bulky reducing agent to the less hindered face of the carbonyl moiety as depicted in **II**. Finally, removal of the PMBS group provided (–)-pseudoconhydrine in 61% overall yield from **6b**, mp 103-105 °C, $[\alpha]^{25}_{D}$ -11.4° (c 0.99, CH_2Cl_2), (lit. data for the (+)-enantiomer,[17] mp 102-103 °C, $[\alpha]^{29}_{D}$+11.1° (c 1.0, EtOH).

In conclusion, we have demonstrated that a [3+3] cycloaddition strategy provides an effective entry into a variety of functionalised piperidine systems. Additionally, the employment of readily available enantiomerically pure aziridines provides an attractive means for the preparation of the corresponding heterocycles in enantiomerically pure form. The employment of this technique in the

Table Scope of the [3+3] Cycloaddition Reaction.[13]

Entry	Aziridine	Products	Yield
1	 **1**	 **2**	82%
2; R = Ts **3a** 3; R = PMBS **3b**	 **3a,b**	 **4a,b**	72% 69%
4; R = Ts **5a** 5; R = PMBS **5b**	 **5a,b**	 **6a,b**	44% 63%
6	 **7**	 **8a** (1: 1.6) **8b**	68%[a]
7	 **9**	 **10**	79%
8	 **11**	 **12**	31%

[a] Reaction carried out on racemic aziridine.



Scheme 2

synthesis of alternative heterocyclic compounds is currently underway in our labs and will be reported in due course.

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(11) All new compounds showed satisfactory spectral and analytical data.
(12) Enantiomeric purities of piperidines shown in entries 2 and 7, Table were established by HPLC analysis, the enantiomeric purity of the product from entry 5, Table was confirmed by its conversion to (–)-pseudoconhydrine. The enantiomeric purity of compounds in entries 1, 3 and 4 is inferred from this data.
(13) Reaction Conditions: A solution of 2-[(trimethylsilyl)-methyl]-2-propen-1-yl acetate, aziridine (1.5 equiv) and 10 mol% of catalyst solution [generated from a solution of $Pd(OAc)_2$ (50 mg, 0.225 mmol), $P(OPr\text{-}i)_3$ (39 mg,1.35 mmol) and 2.5 M *n*-BuLi (0.18 mL) in 1.6 mL dry toluene] in THF heated at reflux for 16–48 h under N_2.
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