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Stereodivergent Diversity Oriented Synthesis of Piperidine Alkaloids[‡]

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Dedicated to Dr Stuart Warren on the occasion of his retirement

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Alkylidenetitanium reagents enable the reagent-controlled high throughput asymmetric synthesis of 2-substituted piperidines and rapid access to multiple cyclic imines using solid phase synthesis (SPS). The Schrock carbenes, generated by reduction of thioacetals, convert resin-bound esters into enol ethers. Treatment with acid releases amino ketones that are cyclized with TMSCl to give iminium salts. Reduction introduces a chiral centre at C-2, whose absolute stereochemistry is determined by a phenethylamine (PEA) chiral auxiliary.

Introduction

The generation of libraries of pure structurally-diverse compounds is key to the discovery of new medicines and to the elucidation of biological pathways through chemical genetics.[1] While relatively simple molecules can interact well with enzymes and receptors a degree of complexity is often required for selectivity, and so it is important to construct three dimensional chiral structures. This requires the generation of stereodiverse libraries where the relative and absolute configuration of stereocentres is controlled, so that mixtures of compounds are avoided and detecting the biodiscrimination of enantiomers is straightforward. Since chemical space is so large, the inclusion of structural motifs that are known to interact with biological systems is important. A good way of identifying such privileged structures[2] is from natural products,[3] as by their very nature these must interact with biological machinery. The piperidine alkaloids[4] have excellent pedigree in this respect with compounds such as γ-coniceine **1a** and (*S*)-coniine (**S**)-**2a** responsible for the effects of hemlock used to execute the ancient Greek philosopher Socrates (Figure 1). The drug Ritalin®[5] that treats attention-deficit-hyperactivity-disorder and the insect repellent Bayrepel®[6] also contain a 2-substituted piperidine core.

1a
γ-Coniceine

(*S*)-**2a**
(*S*)-Coniine

Figure 1. Piperidine alkaloids from hemlock.

Results and Discussion

We envisaged two approaches for the sterodivergent synthesis of 2-substituted piperidines. In the first approach, we would develop a route to cyclic imines[7] that could serve as useful substrates for asymmetric reactions. There has been a great deal of interest in the asymmetric reduction of imines,[8,9] particularly using organocatalysis,[10] and easy access to libraries of substrates would be useful to such methods. In the second approach, we would use a chiral auxiliary to control the absolute stereochemistry and so prepare both enantiomeric series of piperidines having one chiral centre. We would also control the diastereomer formed when more than one chiral centre was present.

We had shown that alkylidenetitanium compounds bearing an internal nucleophile can be generated from thioacetals and used on solid phase to prepare indoles,[11] benzofurans,[11,12] benzothiophenes[13] and quinolines[14] in high purity. We decided to follow a similar strategy for accessing piperidines and so prepared thioacetals **4** and **5** from dihydrofuran **3** by ring opening,[15] oxidation and then reductive amination (Scheme 1). Treating each of these substrates with 4 equiv. of low valent titanocene complex[16] **6** gave effective alkylidenating agents, presumably having the Schrock carbene structures **7** and **8**.[17] The bulky benzylic

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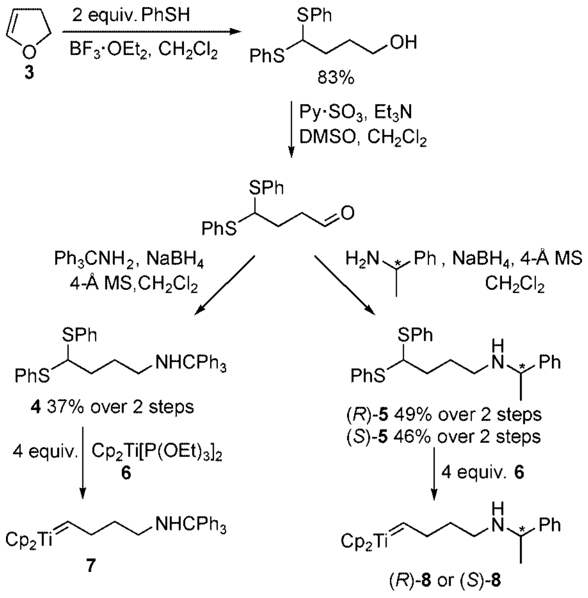
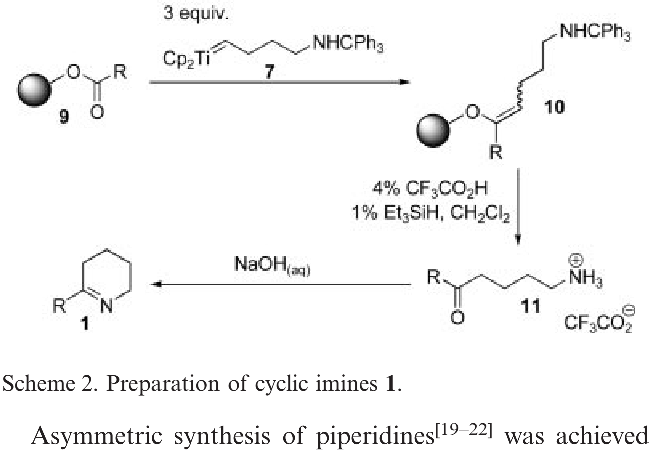
protecting groups do not allow the nitrogen atom to interfere with alkylidene formation, and they are more stable than the *N*-silyl Boc group that we used when preparing indoles.[11]



Scheme 1. Synthesis of alkylidenetitanium reagents.

To access imines, Merrifield resin-bound esters **9** were treated with 3 equiv. of the alkylidenetitanium compound **7**. The resulting enol ethers **10** were cleaved with mild acid in the presence of Et_3SiH and the solvent removed to give ammonium salts **11** (Scheme 2). The Et_3SiH reduced the trityl cation during cleavage so that the only side product was Ph_3CH which was easily removed by washing the ammonium salts with hexane.[18] Treatment with NaOH then generated the selected imines **1a**–**f** in the yields shown based on the original loading of Merrifield resin (Figure 2). No chromatography was necessary as any unreacted resin-bound ester is unaffected by the mild conditions used in the cleavage. Only imine **1e** contained significant impurities, in this case due to some unavoidable elimination of the diethylamino group.



Scheme 2. Preparation of cyclic imines **1**.

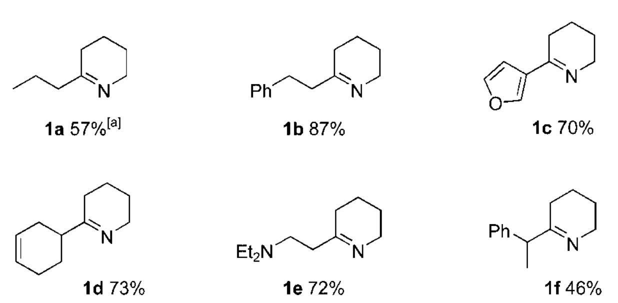
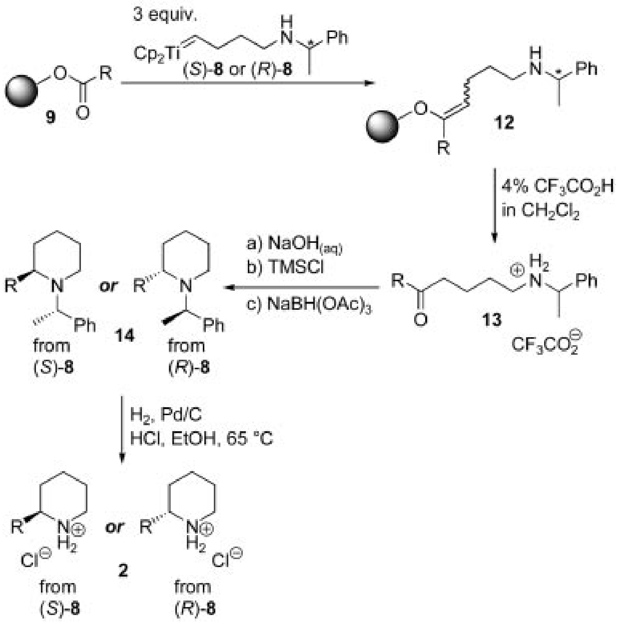


Figure 2. Cyclic imines prepared. [a]Volatile: yield calculated on ketone precursor.

Asymmetric synthesis of piperidines[19–22] was achieved using the enantiopure alkylidenetitanium compounds (*S*)-**8** and (*R*)-**8**. The 1-phenethyl auxiliary was chosen as both enantiomers of 1-phenethylamine are readily available,[23] and it had been used to prepare (*S*)-coniine and (2*S*)-phenylpiperidine with high *ee* values through reduction of an iminium salt generated by intramolecular *N*-alkylation of a chiral imine[24] or from a diol using iridium catalysis,[25] respectively. Alkylidenation of the resin-bound esters **9**, and acid-induced cleavage of the resulting enol ethers **12** gave the ketones **13**, which were cyclized and reduced stereoselectively to give the piperidines **14** (Scheme 3). Cyclization to the iminium salt using trimethylsilyl chloride (TMSCl) provided a chloride counterion and gave only volatile side products. A range of reducing agents and temperatures were tested, but a weak bulky reducing agent at room temperature proved best. Removal of the auxiliary[23] gave (*R*)- and (*S*)-2-substituted piperidines **2a**,**b**,**g** as hydrochloride salts with high *ee* values (Figure 3).[26] All were obtained in excellent purity following a wash with EtOAc and without chromatography or recrystallization at any stage.



Scheme 3. Synthesis of enantiomerically enriched piperidines.

Reagent-controlled diastereoselective synthesis was also demonstrated using enantiopure resin-bound esters derived from (*S*)-(+)-2-methylbutyric acid and (*R*)-(+)-citronellic acid. The diastereomers **2h** and **2i** were produced in higher

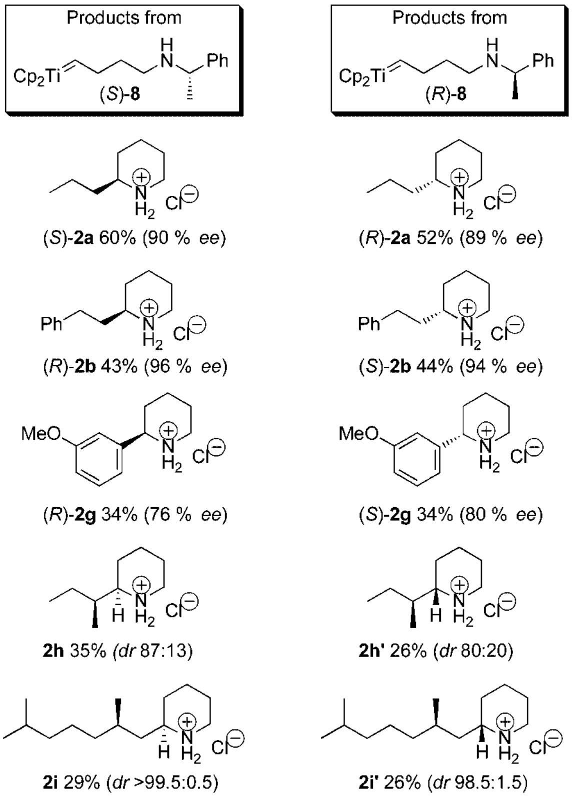


Figure 3. Chiral piperidines prepared,[26] yields based on resin loading.

diastereomeric purity as the directing effects of the auxiliary and chiral centre are matched. As with piperidine **2g**, a branch adjacent to the iminium ion reduces selectivity by decreasing the steric difference between the two faces.

In summary, we have developed a method for the diversity-oriented generation of cyclic imines and the stereodiversity-oriented synthesis of piperidine alkaloids in high enantiomeric and diastereomeric purity.

Experimental Section

Preparation of Resin-Bound Enol Ethers 10 and 12: Cp_2TiCl_2 (0.93 g, 12 equiv.), Mg (100 mg, 13.2 equiv., predried at 250 °C overnight) and freshly activated 4-Å molecular sieves (0.25 g) were twice heated, gently, by heat-gun under reduced pressure (0.3 Torr) for about 1 min, shaking the flask between heatings, and then placed under argon. Dry THF (5 mL) was added followed by dry $P(OEt)_3$ (1.3 mL, 24 equiv.). After stirring for 3 h, the thioacetal **4**, (*R*)-**5** or (*S*)-**5** (3 equiv.) in dry THF (5 mL) was added to the mixture and stirring continued for 15 min. Resin-bound ester **9** [0.311 milliequiv./reactor from Merrifield resin with a loading of 1.83 milli-equiv. (chloride) g^{-1}] contained in a porous polypropylene reactor (internal volume 2.4 mL, pore size 74 μM) and prepurged with argon was added. After 17 h the reactor was removed from the flask and washed with THF (5×) then alternately with MeOH and DCM (3×), and finally with MeOH then Et_2O. The reactor containing the resin-bound enol ether **10** or **12** was then dried under vacuum.

Preparation of Cyclic Imines 1: A reactor containing a resin-bound enol ether **10** was shaken with a mixture of trifluoroacetic acid (TFA) (4%) and Et_3SiH (1%) in DCM (5 mL) for 2 h. The solution was removed and the reactor was washed with DCM (3×). Combined organics were concentrated in vacuo. The resulting residue was washed with cold hexane, treated with 4 M NaOH and extracted into DCM. The organics were dried with Na_2SO_4 and the solvent removed to give the imine **1**.

Preparation of Chiral Piperidines 2: A reactor containing a resin-bound enol ether **12** was shaken with TFA (4%) in DCM (5 mL) for 1 h. The solution was removed and the reactor was washed with DCM (3×). The combined organics were concentrated under reduced pressure to give the salt of an amino ketone **13**, which was re-dissolved in DCM and washed (2×) with 1 M NaOH. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. TMSCl (5 equiv.) was added to a solution of the resulting amino ketone (1 equiv.) in dry DCM (1.5 mL) under argon. After stirring at room temp. for 6 h, solvent was removed under vacuum (0.3 Torr). The resulting iminium salt was dissolved in dry DCM (1.5 mL) under argon, cooled to 0 °C and $NaBH(OAc)_3$ (2 equiv.) was added. After stirring for 18 h at room temp. the solution was treated with 1 M NaOH at 0 °C, washed with 1 M NaOH (3×) and then brine, dried with $MgSO_4$, and concentrated in vacuo to give a piperidine **14**. 10% Pd/C (25 mol-%) was added to a solution of the bisubstitued piperidine (1 equiv.) and 6 M HCl (2 equiv.) in ethanol (1.5 mL). The atmosphere was changed to H_2, and the reaction was stirred at 65 °C for 5 h. The reaction mixture was centrifuged and the supernatant liquid was decanted through a filter. Concentration in vacuo gave the piperidine hydrochloride salt **2** as a solid which was then washed with EtOAc.

Supporting Information (see also the footnote on the first page of this article): Spectroscopic data for compounds **1**, and **2** (together with experimental showing how enantiomeric purity was determined), experimental procedures for the preparation of **4** and **5** and scanned ^1H NMR spectra of all imines **1** and piperidines **2** (to show purity).

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