Highly Enantioenriched Tetrahydropyridines from Chiral Organosilanes: Application to the Synthesis of Quinolizidine Alkaloid (−)-217A

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Functionalized tetrahydropyridine and piperidine ring systems are widely found in biologically active natural products and pharmaceuticals.[1] While considerable progress has been achieved in the asymmetric synthesis of substituted piperidines,[2] there are few reports concerning the preparation of tetrahydropyridines with high levels of enantiopurity.[3] Vinylsilane-terminated annulation of iminium ions is a useful approach to the synthesis of nitrogen-containing heterocycles.[4] However, in cases involving the synthesis of 2,6-substituted tetrahydropyridines, the use of allyl- and vinyl-silanes as π-nucleophiles shows limitations as a competitive aza-Cope rearrangement often compromises reaction diastereoselectivities.[3,5]

In this communication we report a highly stereoselective approach to both 2,6-*cis*- and 2,6-*trans*-3-*trans*-trisubstituted tetrahydropyridines, which relies on a mild intramolecular imine croty-lation. This reaction is based on previously reported experiments leading to [4 + 2] dihydropyran annulation and underscores the important role of a silicon-bearing center as a dominant stereocontrol element leading to highly selective annulations (Scheme 1).[6] The utility of this methodology was further demonstrated in the first asymmetric synthesis of quinolizidine alkaloid (−)-217A.

In considering methods to promote this annulation, we were initially interested in the use of lanthanide triflates due to their unique reactivity in the presence of water. On the basis of literature precedent, we hoped that Yb(OTf)$_3$ could activate imines, generated in situ, and catalyze an intramolecular crotylation to provide tetrahydropyridines in a one-pot operation.[7] Although the reaction proceeded under mild conditions, the diastereoselectivity of the reaction was disappointingly low. After several attempts to increase the reaction diastereoselectivity, we discovered that the vinylglycine-like moiety embedded in the annulation product was prone to epimerization. Moreover, *syn*-**1b** was unreactive under the same reaction conditions.[8]

Treatment of the preformed imine with a Lewis acid at low temperature provided the desired product with good-to-excellent diastereoselectivity.[9] Among Lewis acids screened, TiCl$_4$ was identified as the most general and effective in promoting the annulation (Scheme 2).[10] Thus, complexation of the imine with 2.0 equiv of TiCl$_4$ (CH$_2$Cl$_2$, −78 °C) followed by slow warming to room temperature and then quenching the reaction mixture at −78 °C (saturated aqueous NaHCO$_3$) provided efficient conversion to the tetrahydropyridines, which were protected as trifluoroacetamides before chromatography. The protected tetrahydropyridines could be isolated as single stereoisomers in 90% purified yield (Table 1).
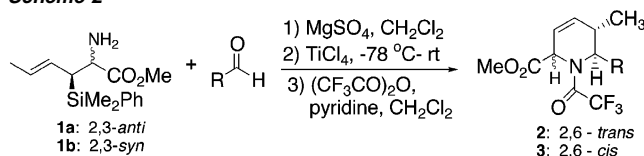
Scheme 1
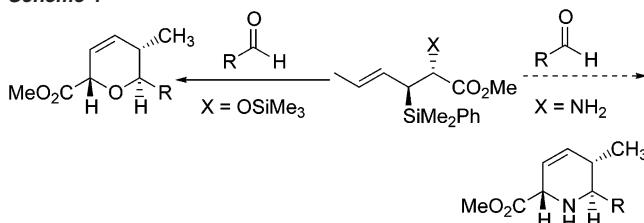
Scheme 2

Table 1. Asymmetric Synthesis of 1,2,5,6-Tetrahydropyridines

| entry	R =	chiral silanes	products	yield %[a]	dr C2,C6-*cis*/*trans*[b]
1	*i*-Pr	**1a**	**2a**	73	1:13
2	*m*-NO$_2$Ph	**1a**	**2b**	90	<1:30
3	2-furyl	**1a**	**2c**	89	1:12
4	(*trans*)PhCHCH	**1a**	**2d**	64	1:9
5	C$_6$H$_{12}$	**1b**	**3a**	78	10:1
6	4-BrPh	**1b**	**3b**	82	>30:1
7	2-furyl	**1b**	**3c**	75	8:1

[a] All yields are based on pure materials isolated by chromatography on SiO$_2$. [b] Stereochemistry assigned by NOE experiments. Ratios of diastereomers were determined by ^{1}H NMR (400 MHz) on the crude reaction mixture before TFA protection.

Results from these experiments demonstrate that the relative configuration of the silane reagent is the dominant stereocontrol element and dictates the stereochemical course of the annulation. The reactivity and selectivity may be attributed to the ability of silyl group to stabilize the emerging carbocation at the β-position.[11] These experiments have shown that aromatic aldehydes were generally more efficient than aliphatic counterparts. Complete conversion was achieved within 12 h for aromatic aldehydes, while longer reaction times were required for aliphatic aldehydes. Both *cis*- and *trans*-2,6-trisubstituted tetrahydropyridines can be prepared with high diastereoselectivity. More importantly, the annulation proceeded with complete transfer of chirality from the chiral silane reagents to the pyridine products. For instance, starting from enantioenriched chiral silanes (95% ee), tetrahydropyridines were obtained with high enantiopurity (95 ± 1% ee) for all substrates studied.[12]

As an added dimension, the reaction products can be efficiently converted to isomeric 1,4,5,6-tetrahydropyridines by treating the

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Scheme 3. Asymmetric Synthesis of 1,4,5,6-Tetrahydropyridines

Scheme 4 ^{a}
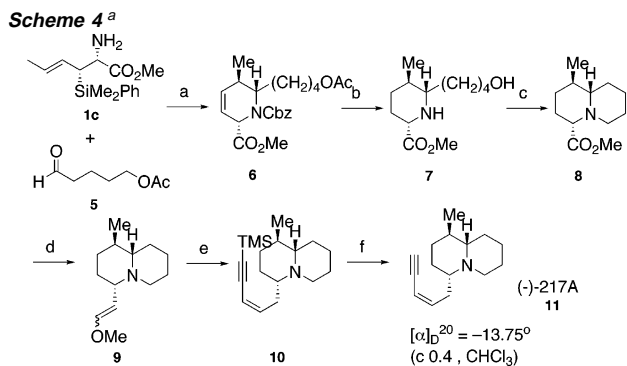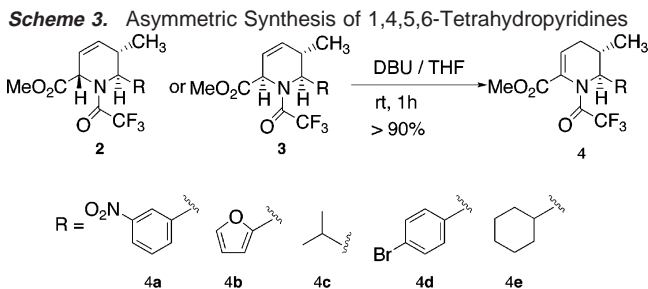
^{a} Reaction conditions: (a) i. MgSO$_4$, CH$_2$Cl$_2$; ii. TiCl$_4$, CH$_2$Cl$_2$; iii. CbzCl, Na$_2$CO$_3$, CH$_2$Cl$_2$, 60% (three steps). b) i. H$_2$, PtO$_2$, MeOH; ii. H$_2$, Pd/C, K$_2$CO$_3$, MeOH, 90% (two steps). (c) CBr$_4$, NEt$_3$, PPh$_3$, CH$_2$Cl$_2$, rt, 93% (d) i. DIBAL-H, Et$_2$O; ii. Ph$_3$P=CHOMe, THF, 67% (two steps). (e) i. 6 N HCl, Et$_2$O; ii. Me$_3$SiCCCH$_2$TBS, t-BuLi, Ti(OiPr)$_4$, THF, Z/E 5:1, 60% (two steps). (f) K$_2$CO$_3$, MeOH, 95%.

annulation products with DBU (1 equiv) in THF (rt, 2 h, Scheme 3). Accordingly, both *trans*-**2** and *cis*-**3** isomers were cleanly converted to **4a**−**e** (>90% yield).

As an application of this methodology, a concise enantioselective route to quinolizidine alkaloids has been developed. Using this approach, quinolizidine ring system (and presumably indolizidine) can be obtained in enantioenriched form from 1,2,5,6-tetrahydropyridines. While the structures of the inferior homologs 1,9-disubstituted quinolizadines are well-known, the 1,4-disubstituted quinolizidines are a relatively new class of alkloids isolated from amphibians.[13] Due to their limited availability from natural sources, the structure elucidation of this alkaloid class was primarily based on GC−FTIR and GC−MS analysis. Quinolizidine 217A, isolated from the Madagascan frog *Mantella baroni*, is the only 1,4-disubstituted quinolizidine that has been isolated in sufficient quantities to allow structure elucidation by ^{1}H NMR spectroscopy.[14] To date, a racemic synthesis from the Pearson group has confirmed the relative stereochemistry.[15] To resolve the absolute configuration, an asymmetric synthesis of quinolizidine 217A was initiated by reaction of silane **1c** and aldehyde **5** to provide Cbz-protected tetrahydropyridine **6** in 60% yield as a single diastereomer. A short sequence of functional group conversions (**6** → **9**) afforded the intermediate enol−ether, which after conversion to the aldehyde was subjected to Yamamoto's olefination to provide enyne **10** in 70−80% yield (*Z/E*, 5:1).[16] Deprotection of the terminal alkyne provided quinolizidine 217A in quantitative yield (Scheme 4). The spectroscopic data are in full agreement with those published for the natural product.[14,15] Earlier work has shown synthetic racemic 217A can be resolved into two enantiomers by a chiral GC

column.[15] The most highly retained enantiomer coeluted with natural 217A. Assignment of absolute stereochemistry of synthetic (−)-217A was confirmed when the synthetic material coeluted with the isolated natural product.[17] Thus, it was established that the natural 217A has the same configuration as synthetic (−) − 217A.

In summary, we have described an enantioselective [4 + 2] annulation, which leads to the assembly of functionalized trisubstituted tetrahydropyridines. The methodology has been used as a key step in a stereocontrolled synthesis of quinolizidine 217A. Further development and application of this process will be reported in due course.

Supporting Information Available: General experimental procedures including spectroscopic and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Imines are readily prepared as single isomer in quantitative yield by the condensation of silanes **1** with a variety of aldehydes in the presence of MgSO$_4$ (CH$_2$Cl$_2$, rt, 0.5 h).
(10) Among Lewis acids that were evaluated, SnCl$_4$, ZnI$_2$, ZrCl$_4$, HfCl$_4$, and BF$_3$·Et$_2$O either gave low conversion or were less general in terms of aldehydes employed.
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