The asymmetric aza-silyl-Prins reaction: synthesis of enantiopure piperidines.

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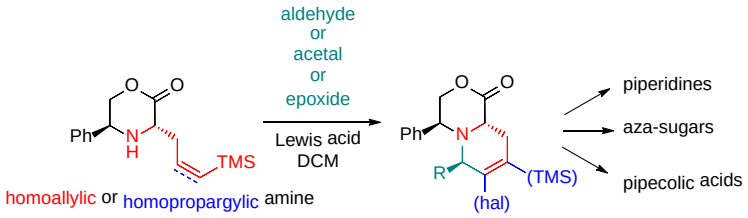
Supporting Information

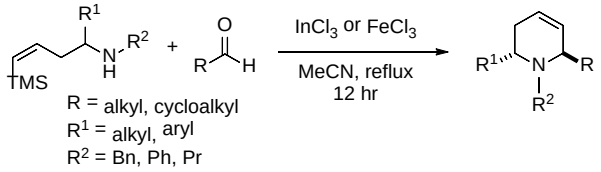


ABSTRACT: The design and development of the first asymmetric aza-silyl-Prins reaction is reported, giving rise to valuable and diverse piperidines and pipecolic acid derivatives in both high yields and as single enantiomers. The creation of a novel chiral auxiliary-homoallylic amine for the aza-silyl-Prins reaction is essential to its success.

Chiral functionalized piperidine heterocycles are distributed widely in nature and as scaffolds for the pharmaceutical industry, being the most common nitrogen-containing heterocycle in marketed drugs.[1] Methods for their synthesis are wide ranging and have recently been reviewed.[2]

The aza-silyl-Prins (ASP) reaction is a highly efficient and high yielding synthesis of tetrahydropyridines, starting from a vinylsilane-containing homoallylic amine, aldehyde and Lewis acid (Scheme 1).[3-10] The reaction proceeds via an iminium ion intermediate and silicon β-stabilised secondary carbocation. After elimination, the resultant alkene serves as a convenient handle for further functionalization. The methodology has been utilized in a number of total syntheses.[11] Methods for the asymmetric synthesis of heterocycles via chiral iminium ion cyclisations have been reviewed.[12] However, while the ASP reaction is highly diastereoselective for the 2,6-*trans* isomer, the one significant drawback of the method to date has been the lack of an asymmetric version. In 2016, List reported a catalytic asymmetric Prins reaction to produce pyrans using a novel class of highly confined imino-imidodiphosphate Brønsted acids, in high yields and up to 95.5:4.5 *e.r.*[13,14] However there remains no general asymmetric variant of the aza-Prins reaction to yield enantiopure piperidines. Herein we report the first examples of an asymmetric aza-Prins reaction, giving rapid access to six-membered nitrogen heterocycles as a single enantiomer.

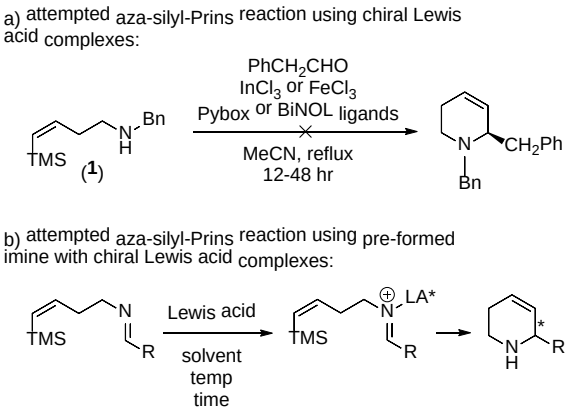
Scheme 1. The aza-silyl-Prins reaction.[3,4]



It is possible to envisage several approaches to the development of an asymmetric ASP reaction, including the use of chiral Lewis acid/ligand complexes or employing auxiliaries in the starting material(s).

We first studied the use of chiral Lewis acid complexes (Scheme 2). We have previously reported extensive Lewis acid screening to promote the ASP reaction, finding that $InCl_3$ and $FeCl_3$ were the most efficient and high yielding.[3,4,11] Therefore we investigated the use of chiral ligands around these Lewis acids. Disappointingly, no combination gave any enantiomeric excess, although yields of the racemic mixture were consistent with those obtained in the absence of the ligand (Scheme 2a).[15]

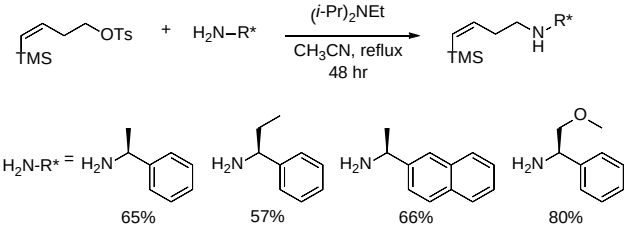
Scheme 2. Attempted asymmetric ASP reactions using chiral Lewis acid complexes.



The underlying principle of using chiral Lewis acid complexes relies on forming a chiral iminium ion intermediate. These results suggest that the Lewis acid is only involved in promoting iminium ion formation and does not provide a chiral intermediate during the cyclisation process. In order to furnish such a chiral complex, we investigated pre-forming an imine and activating this by the addition of a Lewis acid. In this way, the chiral complex would still be present during the cyclisation (Scheme 2b). Reaction optimization was first conducted in the racemic series.[15] Only three compounds, $InCl_3$, $In(OTf)_3$ and $Sc(OTf)_3$, gave reasonable yields of tetrahydropyridines, but requiring lengthy reaction times at high temperature. For purification purposes, it was easier to trap the tetrahydropyridine as its CBz-derivative. Four ligands were next prepared and employed in the proposed chiral Lewis acid-mediated imine-vinylsilane cyclisation: (*S*)-(*i*-Pr)-PYBOX, (*S*)-(*i*-Pr)-$(Ph)_4$-PYBOX,[6] (*R*)-BINOL and (*S*)-BINOL, all based on their ability to coordinate to In- and Sc-based halides and triflates.[16-32] Initially, the imine derived from 2-naphthaldehyde was used, as the product CBz-derivative was the easiest to follow by chiral hplc. None of the indium complexes gave any product; all the scandium triflate complexes gave product in low to modest yields, the best combination being $Sc(OTf)_3$/(*S*)-(*i*-Pr)-PYBOX/acetonitrile/reflux/120 hours, but only as a racemic mixture. The same outcomes were observed using the imines derived from benzaldehdye or cyclohexanecarboxaldehyde. In summary, while chiral scandium-based Lewis acids are capable of promoting vinylsilane-imine cyclisations, there is no observed enantiomeric excess.

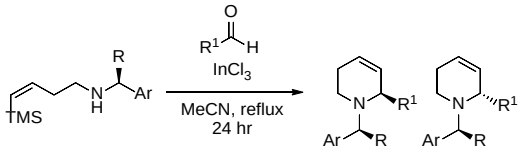
Therefore the second approach, employing a chiral auxiliary was investigated. Racemic and optically active auxiliaries have been employed in iminium ion-type cyclisations, with modest success.[33-36] Our original studies on the ASP reaction employed the N-benzyl secondary amine (**1**, Scheme 1 and 2a). A number of chiral amines are commercially available, and four were specifically prepared (Scheme 3).

Scheme 3. Preparation of a variety of chiral secondary amines.



These were screened in a number of ASP reactions (Table 1). Modest yields and low %*d.e.* were observed with the α-methyl and α-ethyl derivatives (Table 1 entries 1-4), with an improvement observed when benzyl was changed to naphthyl (entry 5). The best diastereoselectivity (60%*d.e.*) was observed employing the amine with the additional chelating oxygen (Table 1, entry 6).

Table 1. Selectivity in the chiral auxilliary-ASP reaction

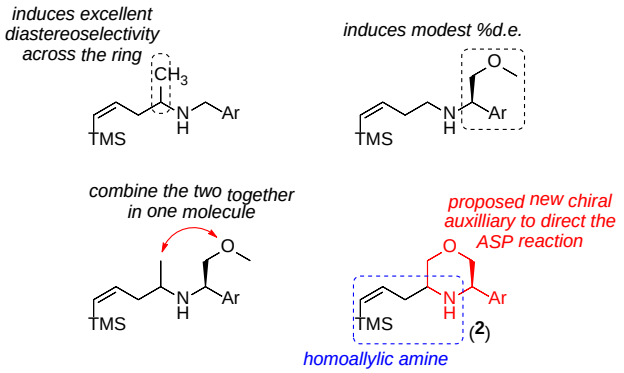


entry[]	R	Ar	R^1	% yield[a]	%*d.e.*
1	Me	Ph	n-Pn	36	26
2	Me	Ph	Bn	53	12
3	Me	Ph	Ph	45	31
4	Et	Ph	Ph	23	18
5	Me	Naphth	Ph	40	50
6	CH_2OMe	Ph	CO_2Et	62	60

[a] isolated and purified yields

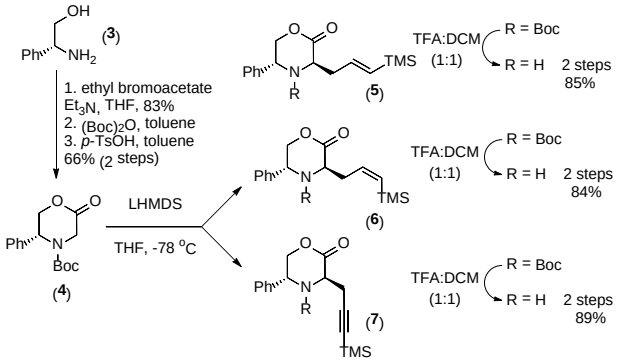
The observation with the $–CH_2OCH_3$ auxiliary presented the opportunity of a new approach, designing a novel chiral auxiliary based on the cross-nitrogen diastereoselectivity observed in Scheme 1, and tethering this to the α-benzyl chiral auxiliary (Scheme 4). Thus compounds of the generic structure **2** were targeted.

Scheme 4. Rational design of novel chiral auxiliary for ASP reaction.



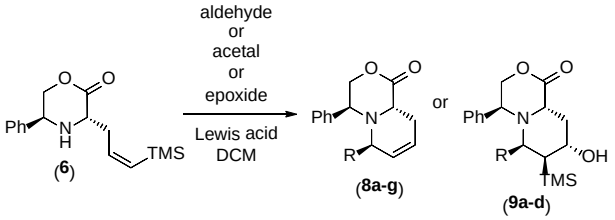
The new cyclic chiral auxiliary was prepared in 3 steps starting from either (*R*)- or (*S*)-phenylglycinol (**3**, Scheme 3).[37] Both series of enantio-complementary starting materials were prepared and utilized throughout the study. *N*-alkylation, Boc-protection and acid-catalysed cyclisation gave enantiopure phenyl-substituted morpholinone (**4**). Deprotonation with LHMDS followed by various allylic or propargylic halides gave the *cis*- or *trans*- vinyl- (**5** and **6**) or alkynyl- (**7**) silanes as single enantiomers after TFA-promoted Boc deprotection.

Scheme 5. Preparation of a variety chiral secondary amines (performed on both (*S*)-3 and (*R*)-3).



Vinylsilane (**6**, R=H) was used in a broad screening of Lewis acids.[15] Only $ZnCl_2$ and $InCl_3$ gave cyclisation products. Zinc chloride was particularly efficient at promoting the ASP reaction, giving bicyclic compounds in high yields and as single diastereomers and enantiomers (Table 2 entries 1-5). The reaction also proceeded well when employing acetals or epoxides in place of the aldehyde, albeit in slightly lower yields (Table 2 entries 6-7). Utilising indium trichloride tetrahydrate also gave a single diastereomer and enantiomeric product, but this was different from the product obtained with zinc chloride. Rather than elimination of the silane, water trapping of the intermediate carbocation was observed (Table 2 entries 8-9). Indium trichloride tetrahydrate did not promote the reaction with epoxides (Table 2 entry 11) and in lower yields with acetals (entry 10). The unusual structure of (**9a**, Table 2, entry 8) was confirmed by x-ray crystallography.[38] In all examples, the use of the opposite enantiomer of phenylglycinol the opposite enantiomeric product, in identical yields.

Table 2. The aza-silyl-Prins reaction

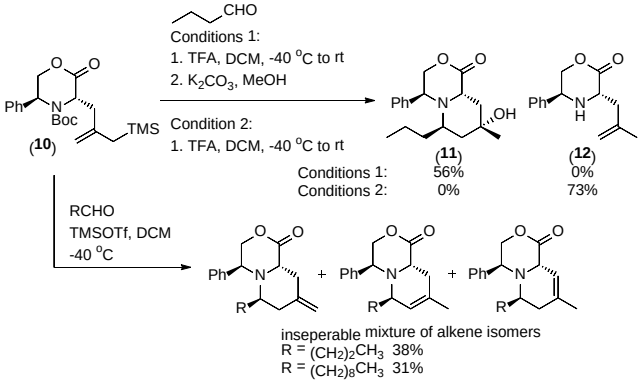


entry	aldehyde[a]	Lewis acid	time /hr	product[b]	%yield[c]
1	Butanal	$ZnCl_2$	12	8a	83[d]
2	Decanal	$ZnCl_2$	12	8b	81
3	Propanal	$ZnCl_2$	12	8c	80
4	Phenylacetaldehyde	$ZnCl_2$	12	8d	82
5	Ethyl glyoxalate	$ZnCl_2$	12	8e	85
6	Cinnamaldehyde	$ZnCl_2$	12	8f	0[d]
7	$CH_3(CH_2)_2CH(OEt)_2$	$ZnCl_2$	12	8a	65
8	Styrene oxide	$ZnCl_2$	24	8d	57
9	Butanal	$InCl_3.4H_2O$	12	9a	81
10	Propanal	$InCl_3.4H_2O$	12	9b	80
11	$CH_3(CH_2)_2CH(OEt)_2$	$InCl_3.4H_2O$	36	9c	43
12	Styrene oxide	$InCl_3.4H_2O$	36	9d	0[e]

[a] Typical procedure: aldehyde (or acetal or epoxide, 1 mmol); amine (1 equiv.), Lewis acid (1 equiv.) in dichloromethane (20 ml). [b] all products isolated as a single enantiomer (chiral shift NMR and chiral hplc) and in the case of **9a-d** >99% single diastereomer. [c] isolated and purified yield; all compounds gave satisfactory spectroscopic data. [d] comparable yields (±5%) and single enantiomer/diatereomers obtained in opposite enantiomeric series. [d] rapid decomposition. [e] no reaction.

To expand the scope of the asymmetric ASP reaction, we have also investigated the use of allylsilanes in the reaction (Scheme 4).[39]

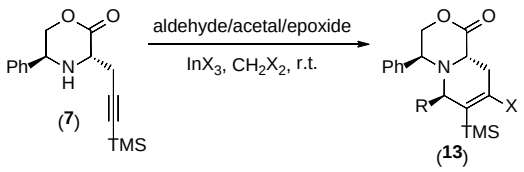
Scheme 6. Use of allylsilanes in the asymmetric ASP reaction.



Although the Boc-protected compound (**10**) was stable, the corresponding secondary amine was highly unstable; attempted deprotection using TFA gave both the deprotected and de-silylated compound in 73% yield. Therefore a simultaneous deprotection-cyclisation protocol was attempted using TFA (Scheme 4, conditions 1) and butanal. An unexpected tertiary alcohol product (**11**) was obtained as the only characterisable product in 56% yield. Again the instability of the allylsilane under the reaction conditions is believed to be responsible, with desilylation occurring prior to Prins cyclisation, meaning –OH trapping of the tertiary carbocation becomes a facile process. Neither $Sc(OTf)_3$ nor $BF_3.OEt_2$ were capable of performing the first Boc-deprotection step. TMSOTf was found to be more efficient at promoting the simultaneous deprotection/ASP reaction sequence. Although very slow at -78 ºC, warming to -40 ºC proved more fruitful with the asymmetric ASP reaction occurring to give an inseparable mixture of three alkene isomers in modest yield, but as single diastereisomers in each case, and consistent with the previous observed results (Table 2).

Martin *et al* have recently reported the alkyne-Prins and alkyne-aza-Prins reactions.[40-45] Therefore we have extended the methodology to the asymmetric alkyne-ASP reaction (Table 3).

Table 3. The alkyne aza-silyl-Prins reaction



entry	aldehyde	Lewis acid	solvent	time /hr	product	X=[b]	%yield [b,c]
1	Butanal	$InCl_3$	DCM	12	13a	Cl	80[d]
2	Decanal	$InCl_3$	DCM	12	13b	Cl	78
3	$Ph(CH_2)_2CHO$	$InCl_3$	DCM	12	13c	Cl	81
4	$PhCH_2CHO$	$InCl_3$	DCM	12	13d	Cl	83
5	$CH_3(CH_2)_2CH(OEt)_2$	$InCl_3$	DCM	24	13a	Cl	78
6	Styrene oxide	$InCl_3$	DCM	24	13d	Cl	57
7	Butanal	$InBr_3$	DBM	12	13e	Br	85
8	$Ph(CH_2)_2CHO$	$InBr_3$	DBM	12	13f	Br	86
9	$PhCH_2CHO$	$InBr_3$	DBM	12	13g	Br	83
10	$CH_3(CH_2)_2CH(OEt)_2$	$InBr_3$	DBM	24	13e	Br	80
11	Styrene oxide	$InBr_3$	DBM	24	13g	Br	62

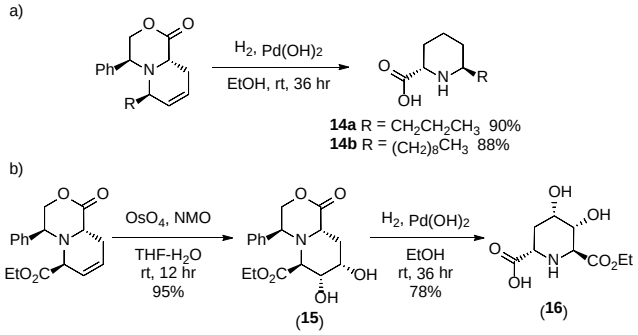
a] Typical procedure: aldehyde (or acetal or epoxide, 1 mmol); amine (1 equiv.), Lewis acid (1 equiv.) in dichloromethane (20 ml). [b] all products isolated as a single enantiomer (chiral shift NMR). [c] isolated and purified yield; all compounds gave satisfactory spectroscopic data. [d] comparable yields (±5%) and single enantiomer/diastereomers obtained in opposite enantiomeric series.

The optimized conditions from the ASP reaction were initially applied to the alkyne-APR reaction employing butanal and gave the chloro-alkene TMS-substituted product in an excellent 80% and as a single enantiomer (Table 3 entry 1). It was also possible to prepare the corresponding bromo-substituted (Table 3 entry 7) product using indium tribromide and dibromomethane as the solvent (to avoid mixed halogen products).[43] The scope of the cyclisation was further demonstrated by employing additional aldehyde (entries 2-4, 8 & 9), and also acetals (entries 5 & 10) and epoxides (entries 6 & 11), although again the overall yields with acetals and epoxides were slightly lower. The reaction surprisingly did not work with benzaldehyde with either Lewis acid, but did proceed well with aromatic functions on a distal position relative to the carbonyl group. The structure and stereochemistry was again confirmed by x-ray crystallography (entry 7).[46]

Elaboration and/or deprotection of the product heterocycles from both ASP and alkyne-ASP reactions would provide a facile route to enantiopure pipecolic acids. Pipecolic acid is a non-proteinogenic amino acid, derived from lysine metabolism and found as a secondary metabolite in numerous plants and fungi. Existing methods for the synthesis of pipecolic acid and its derivatives have been reviewed,[47] and it is surprising that there have only been limited approaches to pipecolic acid derivatives via Prins reaction-type approaches.[48-50]

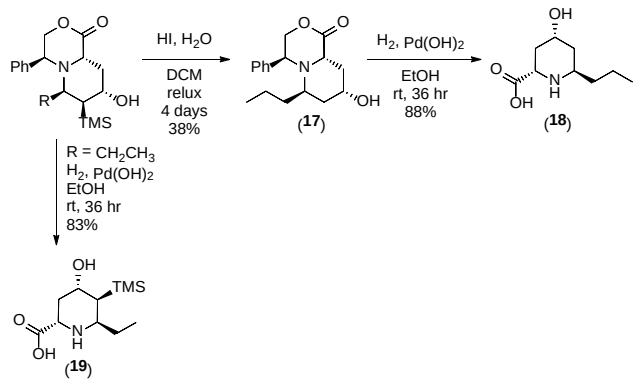
Catalytic hydrogen using Pearlman's catalyst (Scheme 5a) simultaneously removed the chiral auxiliary and reduced the alkene to give enantiopure 6-substituted pipecolic acid derivatives (**14**) in excellent yields. The alkene moiety, however, had been designed into the products to be more useful than for simple reduction. Catalytic dihydroxylation using OsO_4/NMO gave the corresponding diol (**15**), again as a single enantiomer, in 95% yield and >99:1 dr, with the diol on the opposite face to the substituent derived from the aldehyde (Scheme 5b). Without purification, this could be subjected to global hydrogenation to remove the chiral auxiliary and gave the 4,5-dihydroxy-6-substituted pipecolic acid (**16**) derivative as a single enantiomer in 78% yield (75% for the two steps), offering a route to novel aza-sugars.

Scheme 7. Alkene Functionalistion and deprotection.



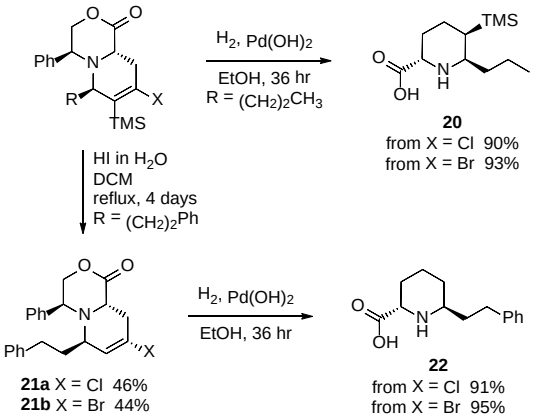
Reaction of the hydroxyl-TMS products from Table 2 with aqueous hydroiodic acid cleaved the TMS group (**17**) and gave 4-hydroxypipecolic acid derivatives after removal of the auxiliary (**18**, Scheme 7). Two alternative de-silylation reagents, HF and TBAF, both gave decomposition. TMS-substituted pipecolic acid derivatives (**19**) could also be obtained from the same starting materials via catalytic hydrogenation.

Scheme 8. Preparation of 4-hydroxypipecolic acid derivatives.



Hydrogenation of the halogenated products from Table 3 simultaneously removed the alkene and halogen, as well as the chiral auxiliary, furnishing novel 5-TMS substituted pipecolic acids (**20**). The same starting materials could also be reduced to the 6-substituted pipecolic acids by a combination of the hydroiodic acid methodology (**21**) followed by catalytic hydrogenation (**22**, Scheme 8).

Scheme 9. Preparation of a variety chiral secondary amines.



In conclusion, we have reported the first examples of an asymmetric aza-silyl-Prins reaction, giving rise to piperidines and pipecolic acid derivatives, in high yields and as a single enantiomer. Applications of the methodology are currently being investigated and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Preparation, screening results, characterization data, NMR spectra.

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NOTES

The authors declare no competing financial interest.

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