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Enantioselective Chemoenzymatic Synthesis of *trans*-Aziridines

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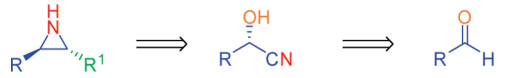

A straightforward, five-step procedure for the synthesis of enantiomerically pure 2,3-disubstituted *trans*-aziridines has been developed starting from commercially available aldehydes. Hydroxynitrile lyase-mediated cyanohydrin formation provided cyanohydrins in excellent enantioselectivities and good yields. Subsequent formation of diastereomerically pure *anti*-amino alcohols via a one-pot Grignard addition−reduction sequence, Cu^{II}-catalyzed diazotransfer, and triphenylphosphine-mediated reductive cyclization provided the corresponding *trans*-aziridines in good yields and excellent diastereoselectivities.

Since the first synthesis by Gabriel in 1888,[1] aziridines have gained increasing interest in organic synthesis and medicinal chemistry.[2−4] Aziridines are highly reactive but, nevertheless, occur in several natural products exhibiting potent biological activity. For instance, mitomycins A−C, together with porfiromycin and mitiromycin, represent an important class of naturally occurring mitosanes, first isolated from soil extracts of *Streptomyces versticillatus*.[5] These mitosanes[6] display both antibiotic and antitumor activity, the latter resulting from their ability to cross-link DNA. Structure−activity relationships[7,8] have identified the aziridine ring as being essential for such antitumor activity and extensive research has concentrated on synthesizing derivatives of these natural products with increased potency.[9,10]

The ability of aziridines to undergo regio- and stereoselective ring-opening reactions, as well as ring expansions, provides direct access to structural motifs and renders them attractive building blocks in organic synthesis. They have been applied in the total synthesis of natural products including alkaloids,[11] amino sugars,[12] amino acids,[13] and lactam antibiotics, such as (+)-thienamycin.[14] Other applications are found in asymmetric synthesis, where chiral aziridines have been utilized both as ligands and auxiliaries. Among these reactions are the asymmetric dihydroxylation of alkenes[15] and the enantioselective addition of dialkylzinc to various aliphatic and aromatic aldehydes.[16]

As a consequence, the development of efficient synthetic routes to aziridines has been an important subject of investigation over the past decades. Two of the most fundamental pathways involve the metal-catalyzed addition of nitrenes to alkenes[17] and the addition of ylides to imines.[18] Although frequently applied in the past, both methods lack full stereocontrol over the outcome of the reaction and often require harsh conditions or the use of expensive catalysts. Other known methods for the synthesis of aziridines include addition of metal carbenoids to imines,[19,20] addition across azirines[21] and addition of carbenes to imines.[22] Furthermore, alkenes can readily be transformed into aziridines via cyclic sulfates, obtained from asymmetric dihydroxylation products and via epoxides, generated by application of the Sharpless asymmetric epoxidation.[23] However, the oldest and conceptually perhaps most obvious synthesis of aziridines utilizes 1,2-amino alcohols as precursors. In 1935, Wenker already demonstrated that addition of sulfuric acid to amino alcohols at elevated temperatures can yield enantiopure aziridines.[24] Direct ring closure of amino alcohols to provide aziridines is known to be difficult, and previous reports show only moderate yields.[25] Better results are obtained when the hydroxyl group is converted into a

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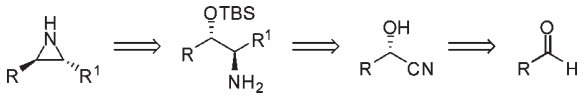
SCHEME 1. Retrosynthetic Route to Aziridines



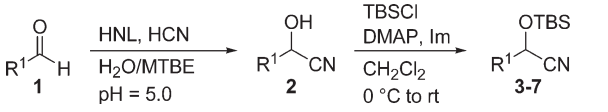
powerful leaving group, thus inducing an intramolecular displacement reaction. Several methods are described and extensive investigations of this reaction showed that aziridines can be isolated in high yield and stereoselectivity.[26,27]

Inspired by these results and the relevance of these molecules we set out to investigate a new and readily applicable catalytic pathway for the synthesis of enantiomerically pure *trans*-aziridines. Our approach is outlined retrosynthetically in Scheme 1. We envisioned that the aziridine skeleton could arise via a direct closure of the aforementioned 1,2-amino alcohols, which would occur in a stereoselective manner. Furthermore, we hypothesized that optically active cyanohydrins could be used as strategic synthons for the synthesis of the amino alcohols, exploiting the electrophilicity of the cyano group toward stereoselective addition of organometallic reagents. Finally, chemoenzymatic cyanohydrin formation was envisioned to provide these precursors in high ee using aldehydes as substrates.

Inspired by previous work from the group of Effenberger[28−30] and due to our own general interest in the synthesis and application of chiral cyanohydrins,[31] the first step in our envisioned route was realized via hydroxynitrile lyase (HNL)-mediated cyanohydrin formation. Hydroxynitrile lyases are designed by nature to convert cyanohydrins into the corresponding aldehydes and hydrogen cyanide, which are used by some plants as a defense mechanism. By using a two-phase system of water and methyl *tert*-butyl ether (MTBE) and a large excess of HCN, however, the equilibria can be directed to the cyanohydrins.[32] Starting from five different aldehydes and using (*R*)-selective HNL from *Prunus amygdalus* (*Pa*HNL) and (*S*)-selective HNL from *Hevea brasiliensis* (*Hb*HNL) as catalysts yielded the corresponding hydroxynitriles **2** as the crude products. Subsequent protection of the hydroxyl group (TBSCl, DMAP, imidazole) to prevent racemization and regeneration of the aldehyde, provided cyanohydrins **3**−**7** in high yield, and excellent enantiomeric excess (Table 1).

For the introduction of the second stereogenic center we used an elegant method developed by Brussee et al.,[33] which relied on a tandem Grignard addition−$NaBH_4$ reduction sequence providing the desired compounds in high yield and excellent diastereoselectivity. Thus, addition of phenylmagnesium bromide to cyanohydrin **3** in diethyl ether at 0 °C

TABLE 1. HNL-Mediated Cyanohydrin Formation and Protection



entry	R^1	enzyme	product	yield (%)[a]	ee (%)	config.
1	Ph	(*S*)-HNL	**3**	90	>99[b]	(*S*)
2	4-BrC_6H_4	(*R*)-HNL	**4**	79	>99[c]	(*R*)
3	3-piperonyl	(*R*)-HNL	**5**	81	>99[b]	(*R*)
4	2-furanyl	(*R*)-HNL	**6**	70	>99[c]	(*S*)[e]
5	4-butenyl	(*R*)-HNL	**7**	67	>99[d]	(*R*)

[a]Isolated yield after chromatography. [b]Determined by GC analysis. [c]Determined by HPLC analysis. [d]Determined by derivatization with Mosher's acid chloride and comparison with the diastereomeric esters prepared from their racemic counterparts. [e]The stereochemical arrangement is as expected for the (*R*)-HNL; however, due to priority changes following the Cahn-Ingold-Prelog rules, the product has the (*S*)-configuration.

smoothly afforded the metallo imine, as was monitored by mass analysis. Dry methanol was added to destroy the excess of Grignard reagent and to protonate the primary imine anion intermediate. In situ reduction by adding an excess of $NaBH_4$ took place in a diastereoselective fashion according to Cram's chelation model, affording **8** in 92% yield with excellent diastereoselectivity of 99% (entry 1, Table 2). Pleased with these results, we applied the one-pot reaction sequence on cyanohydrins **3**−**7** by using various Grignard reagents. Gratifyingly, the desired *anti*-amino alcohols **9**−**17** could be isolated in reasonable to good yields. In the case of entry 3, the addition of 3-chlorophenylmagnesium bromide proceeded much slower and produced only 21% of alcohol **10**. Prolonged stirring or other attempts to improve the yield led to considerable side product formation. It seems conceivable that steric interactions play a more decisive role in this reaction. Additionally, we were pleased to find that in all cases the dr of the reaction sequence was >95%, except for entry 10, which showed a significantly lower dr of 72% as compared to the aromatic cyanohydrins. This discrepancy is presumably caused by the decreased size of the butenyl side chain of the cyanohydrin, resulting in a smaller difference between both diastereofaces. Synthetic efforts to react cyanohydrin **7** with aliphatic Grignard reagents provided the desired amino alcohols in rather poor dr. For this reason we decided to focus on the synthesis of the aromatic amino alcohols.

In a first attempt to cyclize the amino alcohols to the corresponding aziridines, simultaneous nosylation of both the alcohol and amino functionality was investigated. Various reaction conditions were explored but unfortunately this approach afforded only mixtures of *N*-sulfonylated product with small amounts of the desired precursor. With this precursor in hand, however, we continued with the base-catalyzed cyclization. Much to our surprise, all efforts to cyclize this precursor failed, even after prolonged reaction times. Heating of the reaction mixture up to 50 °C to force any cyclization merely led to formation of side products. Considering these results, we concluded that direct ring closure of the free amino alcohol using Mitsunobu-type conditions might be more successful. Subjection of the amino alcohol to PPh_3 in combination with either DEAD or DIAD in various solvents, however, did not result in any reaction

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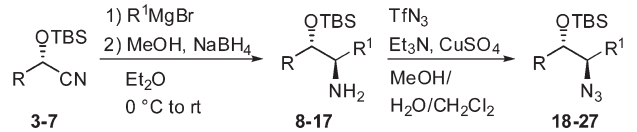
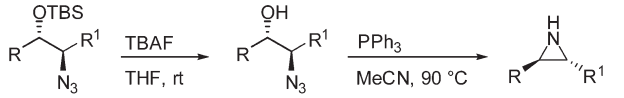
TABLE 2. Grignard Addition, Reduction, and Diazotransfer



entry	s.m.	R^1	amino alcohol	yield[a] (%)/ dr[b] (%)	azido alcohol	yield[a] (%)	config.
1	**3**	Ph	**8**	92/99	**18**	99	(*S*,*R*)
2	**3**	4-FC_6H_4	**9**	70/99	**19**	93	(*S*,*R*)
3	**3**	3-ClC_6H_4	**10**	21/99	**20**	99	(*S*,*R*)
4	**3**	allyl	**11**	64/95	**21**	91	(*S*,*R*)
5	**4**	4-FC_6H_4	**12**	51/99	**22**	87	(*R*,*S*)
6	**4**	4-$MeOC_6H_4$	**13**	49/99	**23**	76	(*R*,*S*)
7	**6**	4-FC_6H_4	**14**	52/99	**24**	66	(*S*,*S*)
8	**6**	4-$MeOC_6H_4$	**15**	53/99	**25**	64	(*S*,*S*)
9	**5**	4-$MeOC_6H_4$	**16**	91/99	**26**	90	(*R*,*S*)
10	**7**	Ph	**17**	52/72	**27**	76	(*R*,*S*)

[a]Isolated yield after chromatography. [b]Determined by ^1H NMR analysis of the crude product.

TABLE 3. Desilylation and Ring Closure



entry	s.m.	R	R^1	product	yield[a] (%)/ dr[b] (%)	config.
1	**18**	Ph	Ph	**29**	60/99	(*R*,*R*)
2	**19**	Ph	4-FC_6H_4	**30**	47/99	(*R*,*R*)
3	**20**	Ph	3-ClC_6H_4	**31**	89/99	(*R*,*R*)
4	**21**	Ph	Allyl	**32**	51/99	(*R*,*R*)
5	**22**	4-BrC_6H_4	4-FC_6H_4	**33**	73/99	(*S*,*S*)
6	**23**	4-BrC_6H_4	4-$MeOC_6H_4$	**34**	53/99	(*S*,*S*)
7	**24**	2-furanyl	4-FC_6H_4	**35**	[c]	
8	**25**	2-furanyl	4-$MeOC_6H_4$	**36**	[c]	
9	**26**	3-piperonyl	4-$MeOC_6H_4$	**37**	54/99	(*S*,*S*)
10	**27**	4-butenyl	Ph	**38**	46/99	(*S*,*S*)

[a]Isolated yield after chromatography. [b]Determined by ^1H NMR analysis of the crude product. [c]Product decomposed during reaction.

despite literature precedent on similar substrates.[26,34] A modified synthetic route involving protection of the nitrogen atom to enhance the Mitsunobu reaction would be less attractive since this requires an additional deprotection step to afford the unprotected aziridine. Consequently, an alternative approach was conceptualized involving the introduction of an azide functionality. The conditions for the Cu^{II}-catalyzed diazotransfer reaction were based on a comparison between two different literature procedures, namely, with imidazole-1-sulfonyl azide[35] and triflic azide[36,37] as reagents. Because the latter reaction gave the highest yield (near quantitative) for the conversion of **8** to the corresponding azido alcohol **18**, we decided to conduct all diazotransfer reactions under these conditions. Thus, subjection of the amino alcohols **9**−**17** under the aforementioned conditions, afforded the azido alcohols **19**−**27** in good yields (64−99%).

With the *anti*-azido alcohols in hand, the stage was set for the synthesis of the *trans*-aziridines (Table 3). Deprotection with TBAF in THF resulted in clean conversion into the corresponding free azido alcohols, which could be used after a simple extraction, but without further purification in a phosphine-mediated Staudinger-type ring closure.[38−40] Performing the cyclization in THF or DMF at elevated temperatures (70−90 °C) in combination with trimethylphosphine initially led to poor conversion into the desired *trans*-aziridine. A more rewarding result was obtained by stirring the *anti*-azido alcohols in the presence of triphenylphosphine in refluxing acetonitrile. Much to our satisfaction, the aziridines **29**−**34**, **37**, and **38** could be isolated in moderate to good yields (46−89%). In an attempt to avoid the tedious purification of triphenylphosphine oxide, polymer-bound triphenylphosphine was also used. As anticipated, this decreased the reaction rate dramatically but did not improve the yield.

Unfortunately, in the case of entries 7 and 8, no product could be isolated. Although mass spectrometry of the reaction mixture showed formation of the intermediate oxazaphospholidine and a product with the expected mass, we were unable to isolate the desired aziridines. A suitable mechanistic explanation is lacking, although a partial answer may lie in the electron-donating capacity of the furanyl substituent.

Furthermore, we proved by using chiral HPLC analysis of acetylated **29** that no (partial) racemization had taken place during the whole sequence. Optical rotation measurements were compared to literature values and proved the formation of the *trans*-substituted aziridine **29**.[41]

Conclusions

In summary, a novel and straightforward procedure has been developed that allows for the synthesis of unprotected *trans*-aziridines starting from commercially available aldehydes. The key step in this relatively mild sequence involves chemoenzymatic enantioselective HNL-mediated cyanohydrin formation. We also demonstrated that the corresponding *anti*-amino alcohols could be synthesized in good yields and excellent diastereoselectivities. The last two steps in the sequence, diazotransfer and phosphine-mediated ring closure, produced the target aziridines in high yield and enantiomeric purity.

Experimental Section

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylacetonitrile (3). A solution of benzaldehyde (500 mg, 4.71 mmol) in MTBE (40 mL) was added to a cooled (0 °C) solution of KCN (3.07 g, 47.1 mmol, 10 equiv) in citrate buffer (40 mL, pH = 5.0). After addition of (*S*)-HNL (800 μL), the reaction mixture was stirred at 0 °C for 1.5 h and quenched with 5 M HCl (5 mL), causing the enzyme to precipitate. The precipitate was filtrated over a glass funnel filled with cotton. The filtrate was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layers were combined, dried (Na_2SO_4), and

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concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (15 mL) at 0 °C and TBSCl (781 mg, 5.18 mmol, 1.1 equiv), imidazole (641 mg, 9.42 mmol, 2.0 equiv, dissolved in 1 mL CH_2Cl_2), and DMAP (58 mg, 10 mol %) were added successively. The reaction mixture was stirred overnight at 0 °C. After diluting the reaction mixture with H_2O (15 mL) and Et_2O (15 mL), the organic layer was washed with H_2O (2 × 30 mL) and brine (2 × 30 mL). The resulting organic fraction was dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (EtOAc/heptane, 1:7 → 1:1) yielded compound **3** (1.05 g, 90%) as a colorless oil. R_f 0.65 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +16.8 (*c* 1.05, $CHCl_3$), ref 42. $[\alpha]_D^{20}$ +17.5 (*c* 1.00, $CHCl_3$). ee >99% (GC, isothermic, 120 °C); $R_{t,1}$ = 13.90 min (*S*), $R_{t,2}$ = 14.38 min (*R*).^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49−7.38 (m, 5H), 5.53 (s, 1H), 0.95 (s, 9H), 0.24 (s, 3H), 0.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.5, 129.2, 128.9, 126.0, 119.3, 64.0, 25.5, 18.2, −5.1, −5.2. Data are in agreement with literature.[42]

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,2-diphenylethanamine (8). A solution of **3** (1.00 g, 4.04 mmol) in dry Et_2O (30 mL) was cooled to 0 °C and phenylmagnesium bromide (4.04 mL of a 3.0 M solution in Et_2O, 12.1 mmol, 3.0 equiv) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h, after which MeOH (30 mL) and $NaBH_4$ (611 mg, 16.2 mmol, 4 equiv) were added. After 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$ (60 mL) and the product was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (EtOAc/ heptane, 1:7→1:1) afforded pure **8** (1.19 g, 90%) as a colorless oil. R_f 0.41 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +31.6 (*c* 1.07, CH_2Cl_2). IR (ATR): 2953, 2926, 2855, 1093, 836, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−7.19 (m, 10H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.02 (d, *J* = 6.5 Hz, 1H), 1.37 (br s, 1H), 0.75 (s, 9H), −0.25 (s, 3H), −0.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.7, 142.0, 127.9, 127.8, 127.4, 127.2, 127.1, 80.2, 62.9, 29.7, 25.7, 18.0, −5.0, −5.7. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{30}NOSi$ $(M + H)^+$, 328.2097; found, 328.2103.

(1*S*,2*R*)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-1,2-diphenylethane (18). To a solution of NaN_3 (261 mg, 4.01 mmol, 6.0 equiv) in a mixture of H_2O/CH_2Cl_2 (4 mL, 1:1 v/v) at 0 °C, was added Tf_2O (337 μL, 2.01 mmol, 3.0 equiv). The reaction mixture was stirred at 0 °C for 2 h. After quenching with saturated aqueous $NaHCO_3$, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 3 mL). The organic layers were combined to afford 5 mL of TfN_3 solution. This TfN_3 was then added to a solution of **8** (219 mg, 0.67 mmol) in MeOH (15 mL), followed by H_2O (5 mL), a solution of $CuSO_4$ (11 mg, 10 mol %) in MeOH (0.5 mL), and Et_3N (297 μL, 2.01 mmol, 3.0 equiv). The reaction mixture was stirred overnight at rt. Then saturated aqueous $NaHCO_3$ (25 mL) was added and the organic solvents were evaporated. The aqueous residue was extracted with EtOAc (3 × 25 mL) and the organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. Purification by column chromatography (EtOAc/heptane, 1:7 → 1:3) afforded **18** (235 mg, 99%). R_f 0.71 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −0.8 (*c* 0.96, CH_2Cl_2). IR (ATR): 2950, 2928, 2855, 2103, 1255, 1099, 838, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−7.21 (m, 10H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 0.74 (s, 9H), −0.22 (s, 3H), −0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.9, 137.0, 128.2, 128.1, 127.9, 127.3, 78.7, 72.2, 25.6, 18.0, −5.0, −5.6.

(2*R*,3*R*)-2,3-Diphenylaziridine (29). To a solution of **18** (142 mg, 0.41 mmol) in THF (4 mL) at 0 °C was added TBAF (480 μL of a 1.0 M solution in THF, 0.48 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 1 h. After quenching with saturated aqueous NH_4Cl (4 mL) the product was extracted with EtOAc (3 × 8 mL). The resulting organic layers were combined, washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Then, the crude product was redissolved in MeCN (4 mL) and PPh_3 (129 mg, 0.48 mmol, 1.2 equiv) was added. After refluxing the reaction mixture for 2 h, the solution was allowed to cool to rt. The solvent was then evaporated and the product was purified by column chromatography (EtOAc/heptane, 1:7 → 1:2) to give pure **29** (36 mg, 60%) as a colorless oil. R_f 0.56 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +331 (*c* 1.27, CH_2Cl_2); ref 43. $[\alpha]_D^{20}$ +328.8 (*c* 1.25, $CHCl_3$). IR (ATR): 3287, 3058, 3023, 1498, 1191 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5−7.2 (m, 10H), 3.3−2.8 (br s, 2H), 1.6−1.2 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.5, 128.6, 127.3, 125.5, 43.7. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}N$ $(M + H)^+$, 196.1126; found, 196.1115. Data are in agreement with literature.[43]

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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