Enzyme and Gold Catalysis: A New Enantioselective Entry into Functionalized 4-Hydroxy-2-pyrrolines

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Abstract: A new route toward functionalized pyrrolines starting from acetylenic aldehydes was developed. Key steps involved a hydroxynitrile lyase catalyzed asymmetric hydrocyanation of acetylenic aldehydes and a gold-catalyzed cyclization of substituted acetylene-containing amino alcohols.

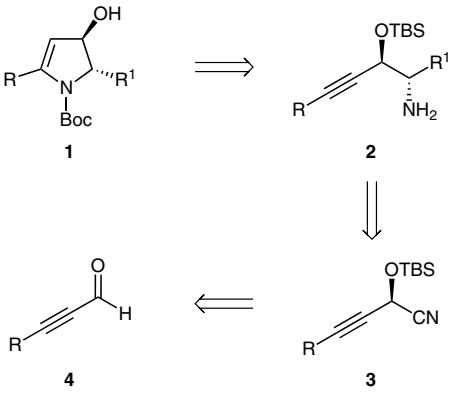
Key words: gold catalysis, cyanohydrins, hydroxynitrile lyases, pyrrolines, pyrrolidines

Functionalized pyrrolidines and pyrrolines are important structural motifs in a wide array of natural products[1] and pharmaceutically relevant molecules.[2] Besides the relevant biological activity, these heterocyclic moieties have been extensively used as organocatalysts[3] and chiral auxiliaries[4] or chiral ligands[5] for asymmetric synthesis.

Over the past decades, a plethora of synthetic methods to construct functionalized nitrogen heterocycles have been developed and the search for new synthetic methodologies is still ongoing.[6] In the past years, increasing attention has been drawn to the use of gold catalysis to create nitrogen-containing ring systems,[7] taking advantage of the ability of gold to act as a soft Lewis acid toward unsaturated carbon–carbon bonds. An example is provided by the group of Uriac, who reported a convenient route for synthesizing substituted pyrrolin-4-ones via catalysis with gold.[8]

Recently, we reported novel strategies for the synthesis of functionalized aziridines[9] and morpholines[10] starting from enantiopure cyanohydrins obtained from the corresponding aldehydes via hydroxynitrile lyase (HNL)-mediated asymmetric hydrogen cyanide addition. We anticipated that the latter chemoenzymatic reaction in combination with gold catalysis should also provide a basis for efficient entries into a variety of functionalized hydroxylated pyrrolines **1**.

Retrosynthetic analysis of the target 4-hydroxy-2-pyrrolines **1**, which can be considered as key precursors for the synthesis of various pyrrolidines,[8,11] might be synthesized via gold-catalyzed 5-*endo*-dig cyclization of the acetylenic amino alcohols **2** (Scheme 1). Installation of the homopropargylic stereogenic center may occur by performing Grignard additions onto cyanohydrins **3**, followed by stereocontrolled imine reduction. The cyanohydrins **3**, in turn, could arise from HNL-mediated enantioselective addition of hydrogen cyanide onto the functionalized acetylenic aldehydes **4**.



Scheme 1

We commenced by making key intermediate **3** from commercially available 3-(trimethylsilyl)-2-propynal (**5**) via HNL-mediated asymmetric hydrogen cyanide addition.[12] We reasoned that the anticipated cyanohydrin **6** would hold considerable potential since facile removal of the TMS group would offer the possibility to introduce a range of aromatic and aliphatic groups via palladium-catalyzed cross-coupling reactions. Therefore, we were pleased to find that the TMS-protected acetylenic aldehyde **5** was well accepted by (*S*)-HNL providing the desired product **6**, after TBS protection, in good yield (83%, over two steps) and an excellent enantiomeric excess of 99% (Table 1, entry 1). The immediate O-protection (TBSCl, DMAP, imidazole) was required in order to prevent racemization due to the intrinsic instability of the free cyanohydrins **7** toward basic conditions. Unfortunately, however, standard TMS deprotection attempts to liberate the terminal alkyne failed, even after more extensive screening, mostly leading to decomposition of the starting compound.

In response to these results, the initial strategy to the target molecules **1** was redesigned. Instead of starting from TMS-protected aldehyde **5**, which would be diversified after the enzymatic step, we now chose to start from functionalized acetylenic aldehydes which were all subjected to the HNL-catalyzed hydrocyanation. It is interesting to note that among the numerous examples of HNL-catalyzed hydrocyanations of aldehydes, additions onto such α,β-acetylenic aldehydes have only been reported once.[13]

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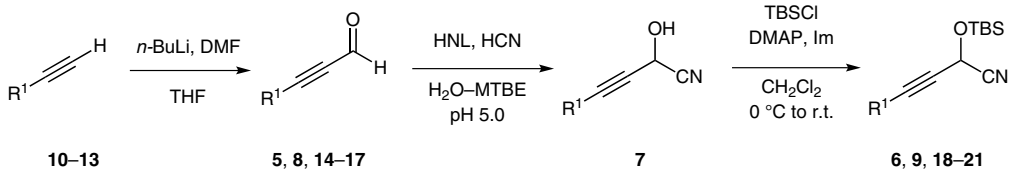
Table 1 HNL-Mediated Cyanohydrin Formation and Protection



10–13 **5**, **8**, **14–17** **7** **6**, **9**, **18–21**

Entry	Substrate	R^1	Aldehyde	Yield (%)[a]	Enzyme	Product	Yield (%)[a]	ee (%)[b]	Config.
1	–	TMS	**5**[c]	–	(*S*)-HNL	**6**	83	>99	*S*
2	–	Ph	**8**[c]	–	(*R*)-HNL	**9**	86	>95	*R*
3	**10**	4-$MeOC_6H_4$	**14**	71	(*S*)-HNL	**18**	81	>99	*S*
4	**11**	3-$MeOC_6H_4$	**15**	61	(*S*)-HNL	**19**	80	>99	*S*
5	**12**	4-FC_6H_4	**16**	73	(*S*)-HNL	**20**	22	93	*S*
6	**13**[d]	3-piperonyl	**17**	68	(*S*)-HNL	**21**	92	>99	*S*

[a] Isolated yield after column chromatography.
[b] Determined by chiral HPLC analysis.
[c] Commercially available.
[d] Obtained via Corey–Fuchs reaction on piperonal.[15]

Since substituted α,β-acetylenic aldehydes are not commercially available [except for **5** and 3-phenyl-2-propynal (**8**)], we turned to a method described by Journet et al. starting from terminal alkynes and using DMF as the formylating reagent.[14]

We were pleased to find that with this methodology aldehydes **14**–**17** were readily obtained in acceptable yields of 61–73% (Table 1, entries 3–6).

As can be seen from Table 1, subjection of aldehydes **8** and **14**–**17** to the chemoenzymatic reaction conditions with both *R*- and *S*-selective hydroxynitrile lyases, followed by TBS protection, provided the corresponding products **9** and **18**–**21** in generally excellent enantiomeric purities and chemical yields. Only in case of the fluorinated aldehyde **16** substantial background addition of cyanide, most likely due to the more reactive nature of the aldehyde, led to a reduction of the enantiomeric excess of product **20**. To optimize the enantioselectivity, the reaction was stopped in a preliminary stage before reaching full conversion, resulting in a lower isolated yield of 22%, but a rather good enantiomeric excess of 93%. Addition of larger amounts of the enzyme also did not lead to an improvement of the yield or enantiopurity.

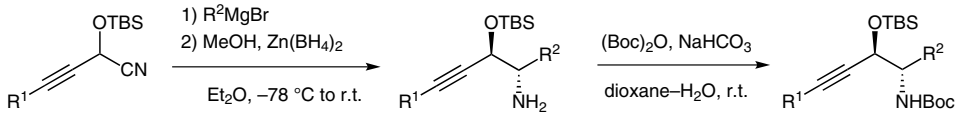
With the availability of a suitable procedure for the synthesis of the acetylenic cyanohydrins **6**, **9**, and **18**–**21**, the stage was set for performing the Grignard addition. Much to our satisfaction, when submitted to phenylmagnesium bromide, TLC and mass analysis of the crude reaction mixture revealed that cyanohydrin **9** underwent a successful transformation into the corresponding imine. Subsequent immediate chelation-controlled diastereoselective imine reduction to the acetylenic amino alcohols was best achieved using $Zn(BH_4)_2$ at low temperature providing the corresponding amino alcohol **22** in an acceptable yield of 58% as an inseparable mixture of diastereoisomers with a good *syn*/*anti* ratio of 1:8 (Table 2, entry 1).

Fairly similar results were obtained upon subjection of cyanohydrin **9** to 4-fluorophenylmagnesium bromide (Table 2, entry 2). Encouraged by these results, we set out to also apply this one-pot methodology to the substituted cyanohydrins **18**–**21** using various Grignard reagents (Table 2, entries 3–8). This resulted in the predominant formation of *anti*-amino alcohols in generally satisfactory yields. To prevent tedious and lengthy chromatographic purification, we decided to separate the *syn*/*anti* isomers in a later stage of the synthesis.

Having the desired acetylenic amino alcohols in hand, subsequent Boc protection smoothly furnished the corresponding carbamate analogues **30**–**37** in 70–85% yield. In this stage, the diastereomeric ratio of most of the substrates could be readily improved through chromatographic purification (Table 2).

Completion of the synthetic route required gold-catalyzed 5-*endo*-dig cyclization. We decided to explore the strategy developed by Uriac[8] in which Au_2O_3 was used as the catalyst (THF, 60 °C) as a basis for the construction of the targeted 4-hydroxy-2-pyrroline systems **1**. Initially, we observed complete formation of the aromatic pyrrole when carbamate **30** was subjected to these conditions. This might be caused by complexation of the gold(III) catalyst to the protected hydroxyl substituent, which is then sufficiently activated to act as a leaving group. In an attempt to circumvent pyrrole formation, we deprotected the hydroxyl group of **30** prior to cyclization, however, this again only afforded the undesired pyrrole after column chromatography. Pretreatment of silica gel with Et_3N

Table 2 Grignard Addition, Reduction, and Boc Protection



17–21 22–29 30–37

Entry	Substrate	R^1	R^2	Amino alcohol	Yield (%)[a]	Ratio *syn*/*anti*[b]	Product	Yield (%)[a]	Ratio *syn*/*anti*[b,c]	Config.
1	**9**	Ph	Ph	**22**	58	1:8	**30**	73	1:17	*R*,*S*
2	**9**	Ph	4-FC_6H_4	**23**	57	1:7	**31**	72	1:10	*R*,*S*
3	**18**	4-$MeOC_6H_4$	4-FC_6H_4	**24**	42	1:30	**32**	70	1:60	*S*,*R*
4	**19**	3-$MeOC_6H_4$	Ph	**25**	53	1:6	**33**	75	1:6	*S*,*R*
5	**19**	3-$MeOC_6H_4$	4-FC_6H_4	**26**	73	1:7	**34**	80	1:12	*S*,*R*
6	**19**	3-$MeOC_6H_4$	4-ClC_6H_4	**27**	66	1:6	**35**	85	1:7	*S*,*R*
7	**20**	4-FC_6H_4	4-ClC_6H_4	**28**	56	1:5	**36**	79	1:5	*S*,*R*
8	**21**	3-piperonyl	Ph	**29**	69	1:7	**37**	74	1:8	*S*,*R*

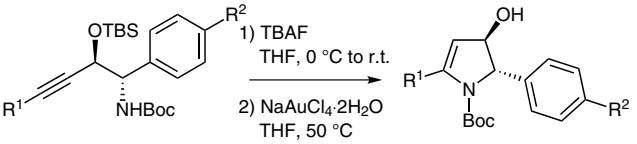
[a] Isolated yield after column chromatography.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] After separation by column chromatography.

(1% v/v) solved the latter problem providing the desired pyrroline **38** in a rather low yield. Consequently, we set out to investigate the cyclization of substrate **30** with a series of gold catalysts in order to identify the optimal conditions. In our hands, $NaAuCl_4 \cdot 2H_2O$ turned out to be a superior catalyst (10 mol%, THF, 50 °C) affording pyrroline **38** in 87% yield.[16]

Encouraged by the successful 5-*endo*-dig cyclization of **30**, we deprotected the amino alcohols **31**–**37** as well prior to the gold-catalysis step (Table 3). Clean conversions were observed for all compounds rendering further column chromatographic purification redundant. Instead, a simple extraction was sufficient so that the resulting deprotected amino alcohols were directly used for the next step. To our delight, subjection of all precursors to $NaAuCl_4 \cdot 2H_2O$ in THF at 50 °C furnished the desired pyrrolines **38**–**45** in good yields of 76–91% over two steps. An unexpected bonus was that at this point we were successful in fully separating both diastereoisomers via column chromatography.

In conclusion, we have developed a new and facile enantio- and diastereoselective route to aryl-substituted 4-hydroxy-2-pyrrolines proceeding via 5-*endo*-dig gold-catalyzed cyclization of acetylene-containing amino alcohols in excellent yield. It has also been demonstrated that these amino alcohols are readily accessible using a one-pot Grignard addition–$Zn(BH_4)_2$ reduction sequence starting from the corresponding acetylenic cyanohydrins in reasonable yield and good diastereomeric ratio. Extension of this methodology to other heterocyclic ring systems is currently under investigation in our group.

Table 3 Deprotection and Gold-Catalyzed Cyclization



30–37 38–45

Entry	Substrate	R^1	R^2	Product	Yield (%)[a]	Config.
1	**30**	Ph	H	**38**	87	*R*,*S*
2	**31**	Ph	F	**39**	80	*R*,*S*
3	**32**	4-$MeOC_6H_4$	F	**40**	91	*S*,*R*
4	**33**	3-$MeOC_6H_4$	H	**41**	81	*S*,*R*
5	**34**	3-$MeOC_6H_4$	F	**42**	82	*S*,*R*
6	**35**	3-$MeOC_6H_4$	Cl	**43**	79	*S*,*R*
7	**36**	4-FC_6H_4	Cl	**44**	76	*S*,*R*
8	**37**	3-piperonyl	H	**45**	83	*S*,*R*

[a] Isolated yield after column chromatography.

Acknowledgment

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(16) **Representative Procedures**

(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-phenylbut-3-ynenitrile (9)

A solution of 3-phenyl-2-propynal (**8**, 2.42 g, 15.4 mmol) in MTBE (15 mL) was added to a cooled (0 °C) solution of KCN (10.0 g, 154 mmol, 10.0 equiv) in citrate buffer (15 mL, pH 5.0). After addition of a lysate of (*R*)-HNL[17] (4 mL) the reaction mixture was stirred at 0 °C for 4 h and quenched with 5 M HCl (10 mL). The precipitated enzyme was filtered 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 concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (150 mL) at 0 °C, and TBSCl (2.79 g, 1.2 equiv) and imidazole (2.10 g, 2.0 equiv) were added. After stirring overnight at r.t., the mixture was quenched with sat. aq NH_4Cl the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (EtOAc–heptane, 0:1 to 1.5:8.5) afforded **9** (3.60 g, 86% yield) as a yellow oil. R_f = 0.69 (EtOAc–heptane, 1:3). $[\alpha]_D^{20}$ –7.2 (*c* 1.33, CH_2Cl_2); 95% ee [Chiralpak AD-H column: HPLC eluent hexane–*i*-PrOH (85:15), flow 1.0 mL/min]; t_{R1} = 6.12 min (*S*); t_{R1} = 7.01 min (*R*). IR (ATR): 2958, 2928, 2855, 2228, 2202, 1489, 1256, 1091, 836, 780, 759, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2 H), 7.42–7.33 (m, 3 H), 5.50 (s, 1 H), 0.95 (s, 9 H), 0.28 (s, 3 H), 0.26 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0, 129.7, 128.6, 121.0, 116.5, 87.1, 81.9, 52.7, 25.6, 18.3, –4.6. HRMS (EI): *m/z* calcd for $C_{16}H_{21}NOSi$: 271.1392; found: 271.1394.

(1*S*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,4-diphenylbut-3-yn-1-amine (22)

To a solution of **9** (1.00 g, 3.68 mmol) in dry Et_2O (37 mL) was added dropwise PhMgBr (3.68 mL of a 3.0 M solution in Et_2O, 3.0 equiv) at 0 °C. After 5 min the reaction mixture was stirred at r.t. for 2 h. Then dry MeOH (15 mL) was added, and the reaction mixture was cooled to –78 °C followed by dropwise addition of a solution of freshly prepared $Zn(BH_4)_2$ in THF–Et_2O (1:1) in 30 min, and the reaction mixture was stirred overnight. The mixture was quenched with sat. aq $NaHCO_3$ (20 mL) and the product extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (EtOAc–heptane, 0:1 to 3:7) afforded **22** (742 mg, 58% yield) as a yellow oil [inseparable mixture of diastereoisomers (1:8)]. Major diastereoisomer: R_f = 0.34 (EtOAc–heptane, 1:3). $[\alpha]_D^{20}$ –12.4 (*c* 1.71, CH_2Cl_2). IR (ATR): 3031, 2957, 2922, 2850, 1666, 1593, 1493, 1359, 1251, 1091, 836, 788, 758, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.27 (m, 10 H), 4.61 (d, *J* = 5.9 Hz, 1 H), 4.10 (d, *J* = 5.9 Hz, 1 H), 1.99 (br s, 2 H), 0.85 (s, 9 H), 0.04 (s, 3 H), –0.01 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5 131.7, 128.5, 128.4, 128.2, 127.7, 127.6, 122.9, 88.6, 86.4, 69.9, 61.5, 29.9, 25.9, –4.6, –5.1. ESI-HRMS: *m/z* calcd for $C_{22}H_{30}NOSi$ $[M + H]^+$: 352.2097; found: 352.2086.

(4*R*,5*S*)-*N*-*tert*-Butoxycarbonyl-2,5-diphenyl-4-hydroxy-2-pyrroline (38)

To a solution of **30** (50.0 mg, 0.11 mmol) in dry THF (2 mL) was added dropwise TBAF (110 μL, 1.1 equiv) at 0 °C. The reaction mixture was warmed to r.t. and stirred for 1 h. It was quenched with sat. aq NH_4Cl (10 mL), diluted with CH_2Cl_2 (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The resulting colorless oil was dissolved in dry THF (2 mL) and $NaAuCl_4 \cdot 2H_2O$ (4.4 mg, 0.1 equiv) was added at r.t. The reaction temperature was increased to 50 °C, and the mixture was stirred for 6 h. After cooling to r.t., Et_3N (10 μL, 5.0 equiv) was added, and the solvent was removed in vacuo. Purification by column chromatography [EtOAc–heptane–1% Et_3N (v/v), 0:1 to 1:3] afforded **38** (30 mg, 87% yield) as a yellowish oil. R_f = 0.17 [EtOAc–heptane–1% Et_3N (v/v), 1:3]. $[\alpha]_D^{20}$ +22.4 (*c* 0.71, CH_2Cl_2). IR (ATR): 3408, 2980, 2924, 1698, 1636, 1367, 1166, 1018, 752, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2 H), 7.42–7.36 (m, 7 H), 7.32–7.26 (m, 1 H), 5.34 (dd, *J* = 0.4, 3.3 Hz, 1 H), 5.10 (d, *J* = 1.2 Hz, 1 H), 4.35 (dd, *J* = 1.2, 3.3 Hz, 1 H), 1.15 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 149.6, 142.5, 135.3, 129.8, 129.5, 128.9, 128.5, 126.3, 112.2, 82.1, 79.5, 74.2, 60.2, 28.1. ESI-HRMS: *m/z* calcd for $C_{21}H_{24}NO_3$ $[M + H]^+$: 338.1756; found: 338.1769.

(17) The gene encoding for (*S*)-HNL, originating from the rubber tree *Hevea brasiliensis*, was cloned and efficiently expressed in the yeast strain *Pichia pastoris* as an intracellular protein; the enzyme preparation was obtained by homogenization (French press) of the cells, removal of insolubles by filtration, and subsequent concentration of the clear filtrate using ultrafiltration/diafiltration.[18] The wild-type gene encoding for (*R*)-HNL, originating from bitter almonds (*Prunus amygdalus*), was cloned and efficiently expressed in the yeast strain *Pichia pastoris*. The enzyme was secreted from the cells and was obtained from cell-free supernatant by concentration using ultrafiltration/diafiltration.[19] The crude lysates (cell-free extracts) containing (*R*)-HNL and (*S*)-HNL were kindly provided by DSM Innovative Synthesis (Geleen, the Netherlands).

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