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# Asymmetric Rhodium-Catalyzed Hydrogenation Meets Gold-Catalyzed Cyclization: Enantioselective Synthesis of 8-Hydroxytetrahydroisoquinolines

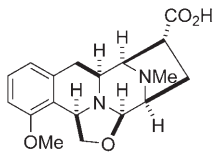
**A. Stephen K. Hashmi,*[a] Patrick Haufe,[a] Christoph Schmid,[a] Andreas Rivas Nass,[b] and Wolfgang Frey[a]**

**Abstract:** Different furyl-substituted (*Z*)-dehydroamino acid derivatives were hydrogenated with the rhodium/Mandyphos(OMe)-system to give enantiomeric excesses between 80 and 98%. The absolute configuration of the newly formed stereogenic center was determined by anomalous diffraction to be *R*. These chiral furyl alanines were transferred into 8-hydroxytetrahydroisoquinolines by employing gold-catalyzed arene synthesis as the key step. During the latter reaction sequence, also including either a propargylation or a reduction, a protection of the hydroxy group, and a subsequent propargylation, no racemization of the stereogenic center was observed. With very electron-rich furans, instead of the 8-hydroxytetrahydroquinolines as products, furans anellated to seven-membered rings with exocyclic C–C double bonds are formed under the same reaction conditions.

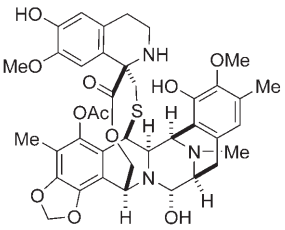
**Keywords:** asymmetric hydrogenation · cyclization · gold · homogeneous catalysis · rhodium

## Introduction

Chiral tetrahydroisoquinolines are useful intermediates in the synthesis of many alkaloids and therefore interesting compounds for the pharmaceutical industry. Currently, 55 examples of tetrahydrosioquinoline alkaloids are known to possess antitumor activity, for example, quinocarcine **1** or ecteinascidin 743 **2** (Yondelis) which is being studied in a phase III trial on ovarian cancer and evaluated in breast and prostate cancer.[1,2]




1




2

Some of these compounds contain an 8-hydroxytetrahydroisoquinoline-substructure, which is not easy to assemble by classical routes like the Bischler–Napieralski,[3] the Pomeranz–Fritsch,[4] or the Pictet–Spengler reaction.[5] All these methods are based upon the principle of electrophilic aromatic substitution and so the positional selectivity of the anellation step in the arene system is often problematic. In particular, the positioning of OR groups *ortho* to the anellated ring, as found in **1**, is difficult to achieve. The classical methods above, deliver the wrong constitutional isomer **4** as the major product (Scheme 1).

Laschat et al. have already carried out a diastereoselective synthesis towards **1**, but without the OR group at the 8-position of the tetrahydroisoquinoline system, as with this OR group the wrong constitutional isomer was found in the anellation step as shown in Scheme 1.[6] The new gold-catalyzed phenol synthesis is probably the best tool to obtain such 8-hydroxytetrahydroisoquinolines (Scheme 2).[7–9]

Starting from furfurals **12** with different substituents, (*Z*)-dehydroamino acid esters **11** can be prepared and subse-

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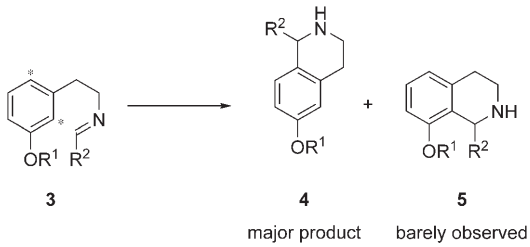
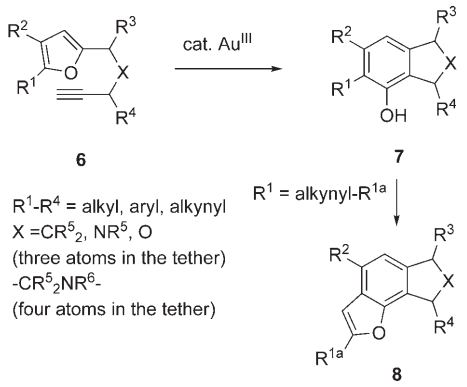



Scheme 1. Problem of positional selectivity in the anellation step (* shows the possible positions for an electrophilic attack).




Scheme 2. Gold-catalyzed phenol synthesis.

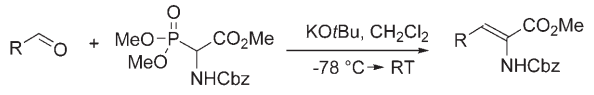
quently hydrogenated with a chiral rhodium catalyst. Further transformations to furyl alanines **10** and finally gold-catalyzed phenol synthesis leads to the chiral, nonracemic 8-hydroxytetrahydroisoquinolines **9** (Scheme 3).

Unlike the acetamidocinnamic acid (ACA) or its methyl ester (methyl acetamidocinnamate, MAC), which both possess a phenyl substituent and which are often used as test substrates for asymmetric hydrogenations of olefins, the corresponding furyl-substituted dehydroamino acids cause much more problems. The first attempt was published by Meléndez et al. in 1982, in which a substrate/rhodium ratio of 30 was used at 50 °C to achieve a 13 % *ee* (*ee* = enantiomeric excess).[10] Much better results were achieved by Döbler and Krause et al. in 1992. Depending on the substrates and catalyst systems they used, enantiomeric excesses between 67 and 90 % *ee* could be obtained.[11] The first highly selective asymmetric hydrogenation was performed by Masquelin et al. at 40 °C with 1 mol % $[Rh(cod)_2]BF_4$ and 1 mol % MeDuphos, producing the product with about 99 % *ee*.[12] So far, few examples are published in which new chiral ligands are tested with furyl-containing dehydroamino acid derivatives.[13]

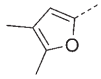
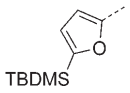
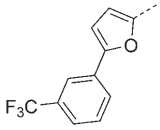
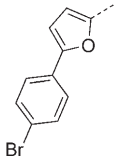
## Results and Discussion

Diastereomerically pure (*Z*)-dehydroamino acid esters **15** for asymmetric hydrogenation were prepared by a Horner–Wadsworth–Emmons protocol described by Schmidt et al. (Table 1).[14]

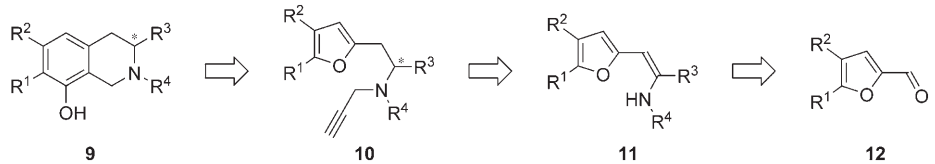
Table 1. Generation of the (*Z*)-dehydroamino acid esters **15** (Cbz = carboxybenzyloxy).




**13** **14** **15**

| Entry | **13** | R | Yield of **15** [%] |
|---|---|---|---|
| 1 | **a** |  | 81 |
| 2 | **b** |  | 71 |
| 3 | **c** |  | 49 |
| 4 | **d** |  | 70 |
| 5 | **e** |  | 80 |
| 6 | **f** |  | 34 |
| 7 | **g** |  | 82 |
| 8 | **h** |  | 63 |

The Horner–Wadsworth–Emmons protocol worked well for most furfurals, except for the 3-(trifluoromethyl)phenyl-substituted derivative **13 f** (entry 6) for which only 34 % of the (*Z*)-dehydroamino acid ester **15 f** could be isolated by crystallization (the residual product remained in the mother liquor). Initial hydrogenation reactions were attempted with compound **15 a**. Out of all



Scheme 3. Retrosynthesis of chiral 8-hydroxytetrahydroisoquinolines **9**.

tested catalyst precursors and ligands, only $[Rh(nbd)_2]BF_4$ and MandyPhos(OMe) **22** gave satisfying results (Table 2). In the other cases either no hydrogenation was observed

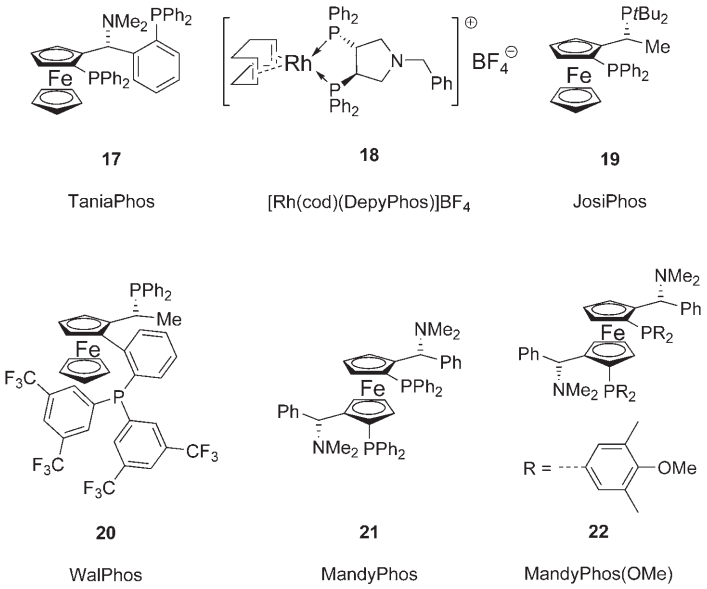
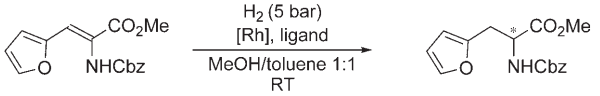



Table 2. Optimisation of hydrogenation conditions.




15a 16a

| Entry | Ligand (mol%) | $t$ [h] | Yield [%][b] | $ee$ [%][c] |
|---|---|---|---|---|
| 1 | **17**[a] (5) | 47.5 | – | – |
| 2 | **18** (10) | 18 | 43 | 3 |
| 3 | **18** (1) | 18 | 3[d] | – |
| 4 | **19**[a] (10) | 21.5 | 81 | 7 |
| 5 | **19**[a] (1) | 25 | 9[d] | 4 |
| 6 | **20**[a] (10) | 82 | 19[d] | 10 |
| 7 | **20**[a] (1) | 23 | 99 | 3 |
| 8 | **21**[a] (5) | 16 | 15 | 18 |
| 9 | **22**[a] (1) | 5.5 | 97 | 98 |

[a] Catalyst precursor: $[Rh(nbd)_2]BF_4$, ligand/[Rh] 1:1. [b] Isolated yield. [c] Determined by HPLC spectroscopy with a Chiralcel OD column. [d] Conversion determined by $^1H$ NMR spectroscopy.

(entry 1), the yield was very low (entries 3, 5, 6, and 8), or the *ee* was low (entries 2, 4, and 7).

By using the optimized reaction conditions, most dehydroamino acid esters were reduced and isolated in good yields and with good to excellent *ee* values (Table 3). In the case of silyl-substituted compound **15e**, just 0.1 mol% catalyst was used leading to longer reaction times and a better isolated yield, but slightly lower selectivity (entry 5). Only two derivatives caused problems, the 3-(trifluoromethyl)-phenyl-substituted derivative **15f** which was only reduced in 37% isolated yield (the remaining starting material could be recovered, entry 6), and the 4-bromophenyl-substituted compound **15g** which did not react at all under these conditions, presumably because of its very low solubility (entry 7).

For compound **15f**, both racemic and enantiomerically pure single crystals for X-ray structure analysis could be obtained (Figure 1).[15] Unfortunately, at this stage the determination of the absolute configuration by anomalous diffraction was impossible, as the enantiomerically pure **15f** lacked the necessary heavy atom.

As the efforts with enantiomerically pure **15f** had shown (Figure 1), to determine the absolute configuration of the newly formed stereogenic center of **16a** by anomalous diffraction, a heavy atom was prerequisite and therefore the synthetically much more useful Cbz-protected (Cbz = carbobenzyloxy) **16a** was converted to the brosyl-protected amine **23a** (Bs = brosyl, 4-bromobenzenesulfonyl), which also facilitates crystallization. This was accomplished by reductive cleavage of the Cbz group and subsequent protection with brosyl chloride (Scheme 4). As expected, a suitable single crystal could be obtained and from the X-ray structure (anomalous diffraction). The configuration of the stereogenic center at C1 was assigned as *R* (Figure 2). This assignment was previously assumed by Miyazawa et al. for the Cbz-protected methyl esters of natural occurring and nonproteinogenic amino acids on the basis of enantiomeric separation by chiral HPLC spectroscopic analysis.[16]

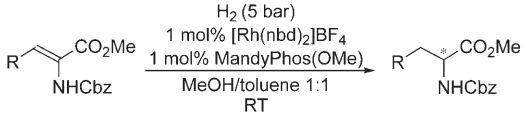
Only chiral furyl alanines **16a–e** were chosen to carry on further transformations to the corresponding 8-hydroxytetrahydroisoquinolines. Proceeding to the gold-catalyzed reaction, the brosyl-protected amine **23a** was alkylated with propargyl bromide in 85% yield. Gold catalysis of **24a** without a substituent at the 5-position of the furan with 5 mol% of the Uson–Laguna salt[17] $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$ in deuterated chloroform for 5 h furnished a mixture of the constitutional isomers **25aa** and **ab** (28 and 20%, respectively), which is in accordance with earlier results (Scheme 5).[7]

Deprotection, brosylation, and propargylation of methyl-substituted **16b** lead to **24b** in 52% overall yield. The following conversion of **24b** with 5 mol% $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$ in deuterated chloroform was complete in five minutes at room temperature to give the single isomer **25b** in 62% isolated yield (Scheme 6).

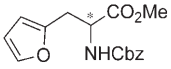
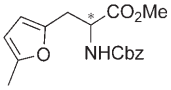
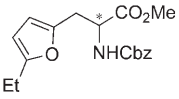
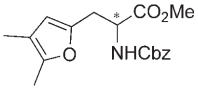
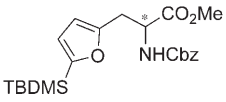
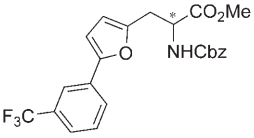
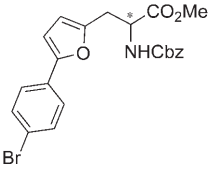
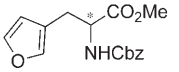
To test which additional functional groups can be tolerated in the gold-catalyzed phenol synthesis, methyl ester **23b** was reduced with diisobutylaluminum hydride (DIBAL-H) and alkylated again with propargyl bromide in 71% overall yield. Reaction of alcohol **27b** with 5 mol% $AuCl_3$ in deuterated acetonitrile did not afford the corresponding 8-hydroxytetrahydroisoquinoline; however, intramolecular nucleophilic attack of the hydroxy group onto the alkyne furnished dehydromorpholine **28b** in almost quantitative yield after spontaneous isomerization of the double bond to the thermodynamically more stable position. This proves that the 6-*exo*-*dig* attack of the OH-oxygen is significantly faster than the first step of the phenol synthesis. Addition of nucleophiles to alkynes is quite common, but a selective monoaddition to deliver enol ethers has never been observed before.[18] To drive the reaction to the 8-hydroxytetrahydroisoquinoline, the free hydroxy group was protected as the *tert*-butyldimethylsilyl (TBDMS) ether **29b**, which was then

Table 3. Effect of different substituents in the hydrogenation of **15**.




**15a-h** **16a-h**

| Entry | **16** | Product | *t* [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | **a** |  | 5.5 | 97 | 98 |
| 2 | **b** |  | 16.5 | 85 | 96 |
| 3 | **c** |  | 17.5 | 88 | 95 |
| 4 | **d** |  | 64 | 82 | 87 |
| 5 | **e** |  | 120 | 99[c] | 80 |
| 6 | **f** |  | 18 | 37[d] | 87 |
| 7 | **g** |  | 68 | –[d,e] | – |
| 8 | **h** |  | 14.5 | 85 | 93 |

[a] Isolated yield. [b] The *ee* was determined by HPLC analysis with a Chiralcel OD column. [c] 0.1 mol% of catalyst/ligand was used. [d] Recovered starting material. [e] Basically insoluble.

converted cleanly to **30b** with 1 mol% $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$ in two hours (70% isolated yield) (Scheme 7).

As both 8-hydroxytetrahydroisoquinolines **25b** and **30b** had the common precursor **23b** (96% *ee* after hydrogenation), we were interested as to whether the enantiomeric ratio changed during the reaction sequences, and especially in the gold-catalyzed step. Determination of both enantiomeric excesses showed that no significant racemization had occurred (94% *ee* for **25b**, 96% *ee* for **30b**). The 8-hydroxytetrahydroisoquinolines could be used for further transformations, but the brosyl group is difficult to remove, therefore the same reaction sequence was repeated with the Cbz group. Furyl alanines **16b–e** were reduced with DIBAL-H, protected with TBDMS, and alkylated with propargylbromide and sodium hydride as base. Reactions of **33b** and **c** with 1 mol% $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$ afforded the 8-hydroxytetrahydroisoquinolines **34b** and **c** in 84 and 80% yields, respectively (Scheme 8).

As the gold-catalyzed transformations were carried out in

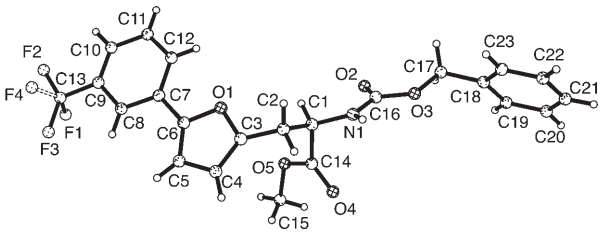
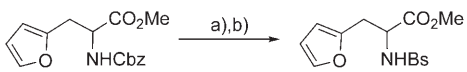



Figure 1. The lack of a heavy atom made the determination of the absolute configuration of enantiomerically pure (−)-**15f** impossible.




(-)-**16a** (-)-**23a**

Scheme 4. Changing the protecting group for crystallographic determination of the absolute configuration by anomalous diffraction. Reaction conditions: a) $H_2$ (1 bar), Pd/C, MeOH, 38 h, 38%; b) BsCl, $NEt_3$, DMAP (cat.), $CH_2CH_2$, 0°C→RT, overnight, 62%. DMAP = 4-(dimethylamino)pyridine.

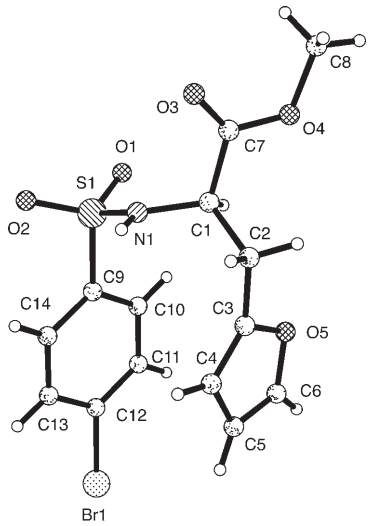
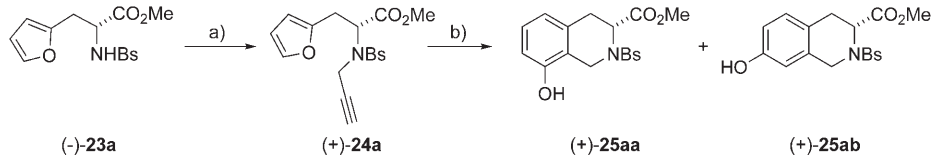
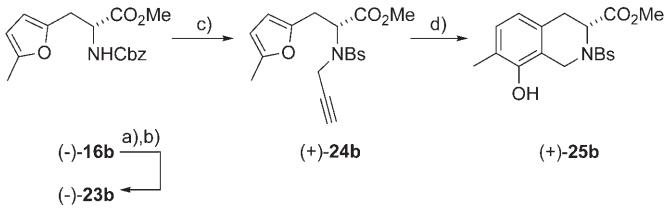



Figure 2. Solid-state structure of **23a** showing the stereogenic center (C1) to be *R* configurated (anomalous diffraction).

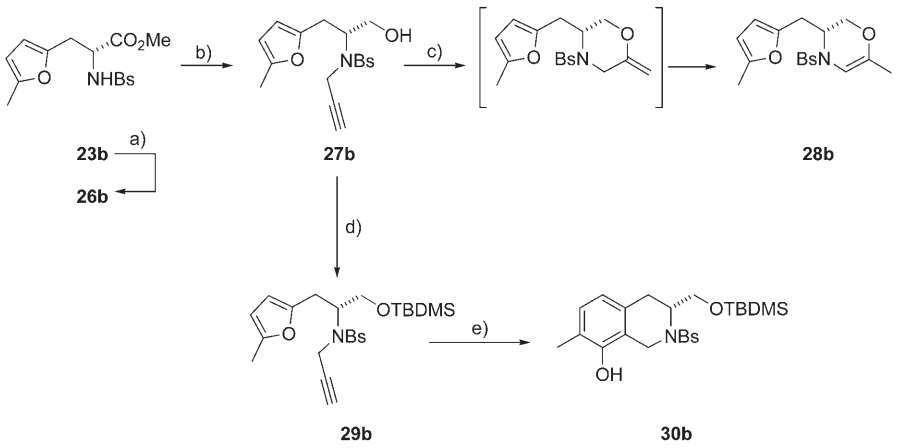
  




Scheme 5. The gold-catalyzed conversion of **24a** delivers two constitutional isomers **25aa** and **ab**. Reaction conditions: a) $BrCH_2C{\equiv}CH$, $Cs_2CO_3$, acetone, overnight, 85%; b) $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$, $CDCl_3$, RT, 5 h, **25aa** (28%), **25ab** (20%).




Scheme 6. Reaction sequence to 8-hydroxytetrahydroisoquinoline **25b**. Reaction conditions: a) Cyclohexene, Pd/C, MeOH, reflux; b) BsCl, $NEt_3$, DMAP (cat.), $CH_2Cl_2$, 0°C→RT, Σ77%; c) $BrCH_2C{\equiv}CH$, $Cs_2CO_3$, acetone, RT, 67%; d) $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$, $CDCl_3$, RT, 5 min, 62%.




Scheme 7. The unprotected alcohol leads to **28b**, while the protected one delivers **30b**. Reaction conditions: a) DIBAL-H, THF, −78°C→RT; b) $BrCH_2C{\equiv}CH$, $Cs_2CO_3$, acetone, RT, Σ77%; c) $AuCl_3$ (5 mol%), $CD_3CN$, RT, 99%; d) TBDMSCl, imidazole, DMF, RT, 66%; e) $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$, $CDCl_3$, RT, 70%.

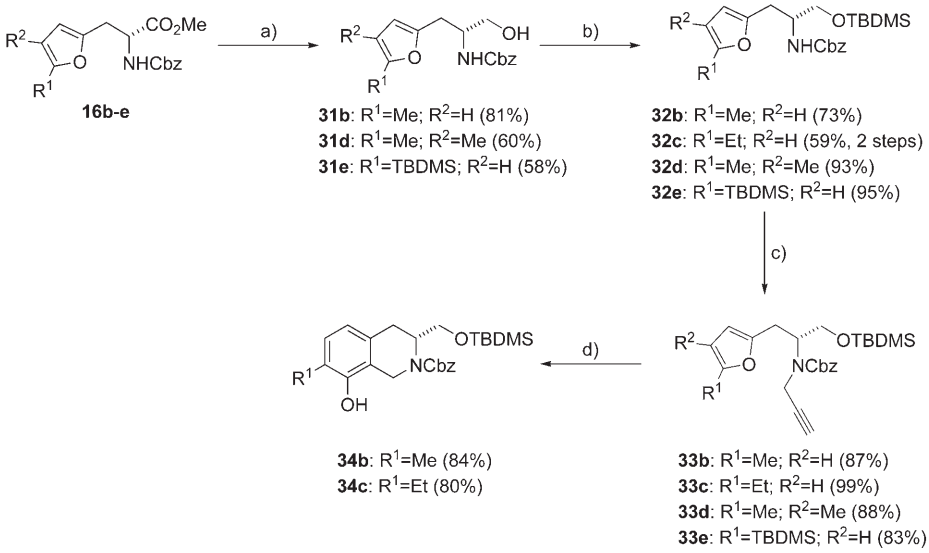
NMR tubes, the progress of the reactions could normally be monitored by $^1$H NMR spectroscopy. However, for the Cbz-protecting group this was difficult due to the high rotational barrier of the carbamate. This was particularly the case for **33d** and **e** for which the reaction progress could not be followed by $^1$H NMR spectroscopy. Thus we decided to use brosyl-protected compounds again, which were much easier to observe spectroscopically by NMR. This time the Cbz group was cleaved under transfer hydrogenation conditions with cyclohexene as the hydrogen source. Subsequent protection and alkylation furnished the starting materials for the gold-catalyzed transformations. Conversion of **29d** with 1 mol% of the Schmidbaur–Bayler salt[19] $[\mu\text{-Cl}(AuPMes_3)_2]BF_4$ (Mes = mesityl, 2,4,6-trimethylphenyl) afforded the tetrasubstituted phenol **30d** in 37% isolated yield. Under the same reaction conditions **29e** did not deliver the phenol, the alkyne attacked at the 3-position of the furan to form the previously unknown furan **36e** anellated to a seven-membered heterocycle with an exocyclic C–C double bond in 84% isolated yield (Scheme 9). A similar reaction pathway was also observed by Echavarren et al.; however, a furan anellated to a six-membered ring was formed.[20]

We also tried to alkylate the carbamates **31b**, **d**, and **e** in the presence of the free hydroxy group. Three equivalents of sodium hydride and propargyl bromide in DMF afforded the cyclic carbamates **37b**, **d**, and **e** (Scheme 10). These compounds were also substrates for the gold-catalyzed phenol synthesis. The reactions of the cyclic carbamates proceeded significantly slower than those of the corresponding open chained derivatives. While conversion of **37b** with 1 mol% $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$ furnished phenol **38b** in 50% isolated yield, compounds **37d** and **e** again afforded furans anellated to seven-membered heterocycles with an exocyclic C–C double bond in 31 (**39d**) and 37% (**39e**) yields, respectively (Scheme 11).

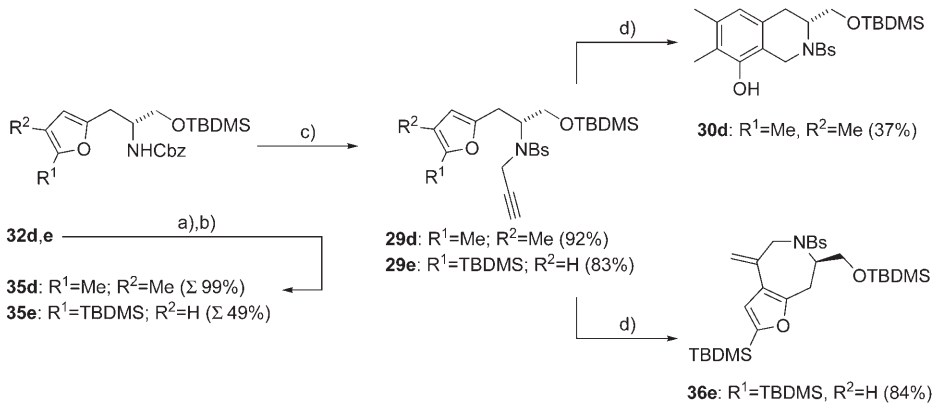
## Conclusion

The combination of asymmetric rhodium-catalyzed hydrogenation and gold-catalyzed cyclization offers a short and easy access to chiral, nonracemic 8-hydroxytetrahydroisoquinoline systems. No significant racemization was observed while carrying out the reaction sequence. The absolute configuration of the newly-formed stereogenic center was unambiguously assigned by anomalous diffraction. Both ester and silyl-protected alcohol groups are tolerated at the γ-position to the alkyne moiety during cyclization. Even cyclic carbamates are converted, but the reaction proceeds significantly slower. However, depending on the employed substrates, gold-catalysis affords interesting and so far unknown furans anellated to seven-membered rings with an exocyclic C–C double bond, which themselves are interesting building blocks and could also be used for further transformations.

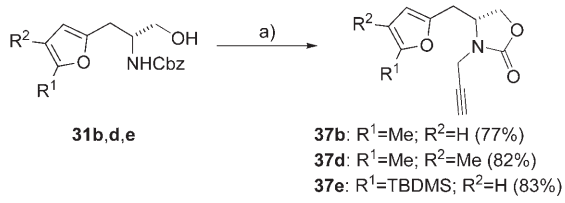
  




Scheme 8. Synthesis of the Cbz-protected substrates **33b–e** and **34b–c**. Reaction conditions: a) DIBAL-H, THF, −78 °C→RT; b) TBDMSCl, imidazole, DMF, RT; c) $BrCH_2C{\equiv}CH$, NaH, DMF, RT; d) $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$, $CDCl_3$, RT.



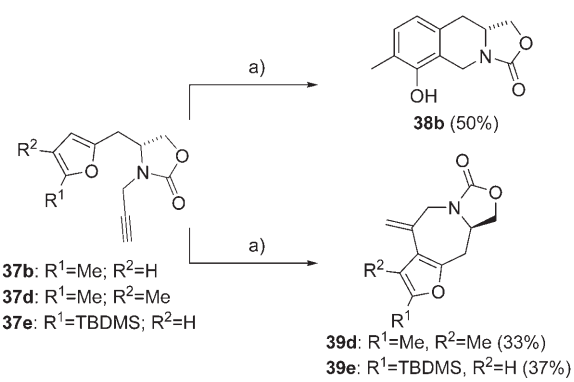

Scheme 9. Synthesis of **29d** and **e** and their conversion to **30d** and **36e**. Reaction conditions: a) Cyclohexene, Pd/C, MeOH, reflux; b) BsCl, $NEt_3$, $CH_2Cl_2$, 0 °C→RT; c) $BrCH_2C{\equiv}CH$, $Cs_2CO_3$, acetone, RT; d) $[\mu\text{-Cl}(AuPMes_3)_2]BF_4$, $CDCl_3$, RT.




Scheme 10. Formation of cyclic carbamates **37b**, **d**, and **e** during the propargylation. Reaction conditions: a) $BrCH_2C{\equiv}CH$, NaH, DMF, RT.

## Experimental Section

Detailed reaction and catalysis conditions, as well as full characterization of all unknown compounds are given in the Supporting Information.




Scheme 11. Formation of 8-hydroxytetrahydroisoquinoline **38b** and furo-[2,3-*d*]azepines **39d** and **e** by gold-catalyzed conversion. Reaction conditions: a) $[\mu\text{-Cl}(AuPPh_3)_2]BF_4$ (1 mol%), $CDCl_3$, RT.

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