DOI: 10.1002/chem.200600533

Gold Catalysis: No Steric Limitations in the Phenol Synthesis

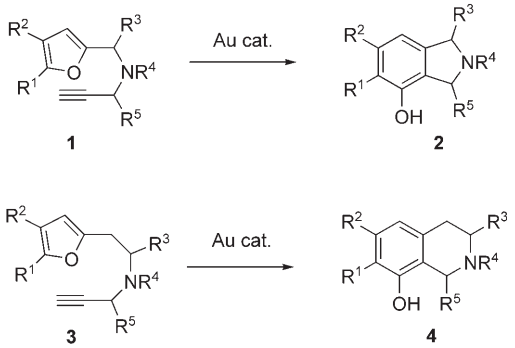
A. Stephen K. Hashmi,*[a] Ralph Salathé,[a] and Wolfgang Frey[a, b]

Abstract: Different dihydroisoindol-4-ols and 8-hydroxytetrahydroisoquinolines were prepared by the gold-catalyzed phenol synthesis. The reaction was investigated with several sterically demanding groups in the 5-position of the furan starting material. The influence of the reaction time and the catalyst on the yield was investigated.

Keywords: cyclization · dihydroisoindoles · gold · homogeneous catalysis · tetrahydroisoquinolines

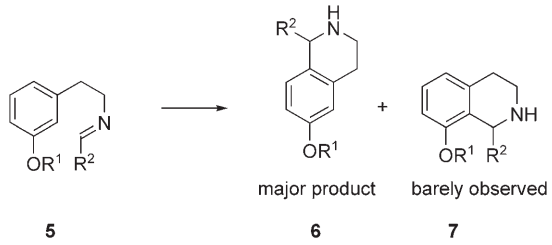
Introduction

In the arsenal of gold-catalyzed reactions,[1] the gold-catalyzed phenol synthesis developed by our group provides an easy entry to numerous benzoanellated heterocycles, among them dihydroisoindol-4-ols (**2**) and 8-hydroxytetrahydroisoquinolines (**4**; Scheme 1).[2]



Scheme 1. Gold-catalyzed phenol synthesis of dihydroisoindoles **2** and tetrahydroisoquinolines **4**.

In particular the placement of the hydroxy group next to the anellation point is difficult to achieve by classical routes—this is the major advantage of this reaction over classical routes for the synthesis of tetrahydroisoquinolines such as the Pictet–Spengler,[3] Bischler–Napieralski,[4] and Pomeranz–Fritsch[5] reactions. The latter methods are based on the principle of electrophilic aromatic substitution, the position of the OR-group *ortho* to the anellated ring is difficult to achieve, they deliver the wrong constitutional isomer (for example **6** and not **7**) as the major product (Scheme 2).[6]



Scheme 2. Undesired positional selectivity with the classical methods.

Thus, the gold-catalyzed phenol synthesis is maybe not always the best way to synthesize tetrahydroisoquinolines, but a unique tool to produce 8-hydroxytetrahydroisoquinolines.[7] These 8-hydroxytetrahydroisoquinolines are useful intermediates in the synthesis of many alkaloids and therefore interesting compounds for the pharmaceutical and the agricultural industry. Many such tetrahydroisoquinolines possess sterically demanding groups in the 7-position, specific examples **8**–**10** are shown in Scheme 3.[8]

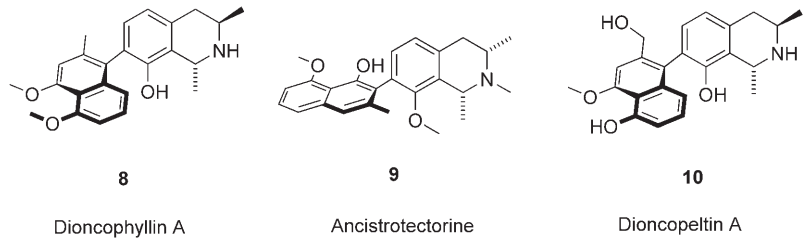
To explore the possible synthesis of such 8-hydroxytetrahydroisoquinolines by the gold-catalyzed phenol synthesis, the influence of such bulky substituents should be investigated.

Previous work by our group has shown that a *ortho*-chlorophenyl-substituted furan substrate, a furan with only

[a] Prof. Dr. A. S. K. Hashmi, Dipl.-Chem. R. Salathé, Dr. W. Frey
Institut für Organische Chemie, Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)
Fax (+49) 711-685-4321
E-mail: hashmi@hashmi.de

[b] Dr. W. Frey
Contact for crystallographic investigation

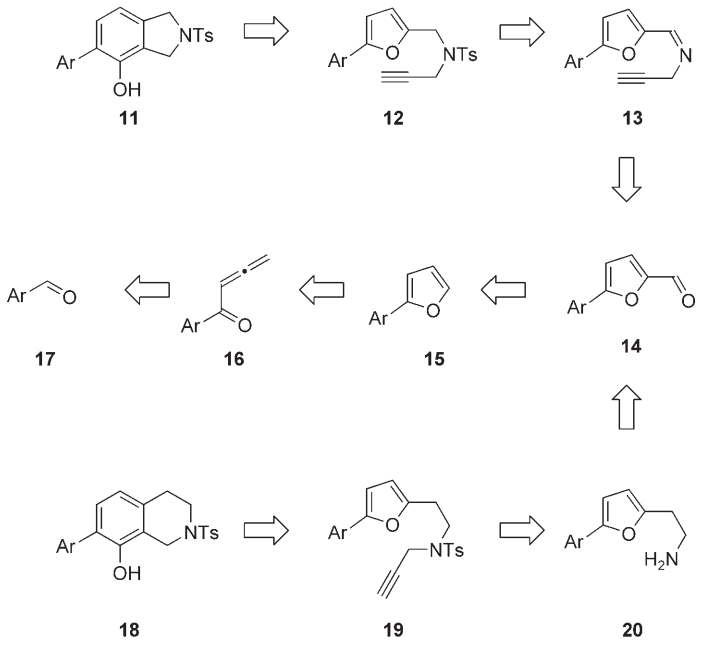
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.



Scheme 3. 8-Hydroxy- or 8-alkoxytetrahydroisoquinolines with sterically demanding substituents.

one *ortho*-substituted phenyl substituent in the 5-position, can be transformed to the corresponding phenol in a gold-catalyzed reaction with 71% yield.[9] Echavarren et al. investigated a *para*-methoxybenzyl(PMB)-protected *ortho*-oxymethylphenyl substituted furan substrate in platinum-catalyzed reactions, but obtained the corresponding phenol in only 48% yield. They assumed that the low yield was based on the steric bulk of the *ortho*-substituted phenyl group.[10] Thus the question arouse, whether with two *ortho* substituents or similar sterically demanding groups a phenol synthesis was still possible.

The retrosynthesis of such dihydroinsoindoles and 8-hydroxytetrahydroisoquinolines led to a route starting from aldehydes **17** (Scheme 4), allenyl ketones **16** should be prepared by a Grignard addition and subsequent oxidation. These allenyl ketones would be transformed to furans **15** by silver-catalyzed cycloisomerization. Further transformation to the furfural derivates **14** and subsequent condensation to the imine, reduction and tosylation in a one-pot sequence would deliver the furan-alkyne systems **12.** Compound **12** should be converted to the dihydroisoindoles **11** in the gold-catalyzed key-step.



Scheme 4. Retrosynthesis of dihydroisoindol-4-ols and 8-hydroxytetrahydroisoquinolines.

To access the 8-hydroxytetrahydroisoquinolines **18**, the furfural derivatives **14** would be transformed to **20** by nitroaldol condensation and subsequent reduction, tolsylation and propargylation to **19**; finally gold-catalyzed phenol synthesis would hopefully deliver **18**.

Results and Discussion

Homopropargylic alcohols **22** were prepared from the corresponding aldehydes **21** and propargylmagnesium bromide in yields between 67–94% (Scheme 5).[11]

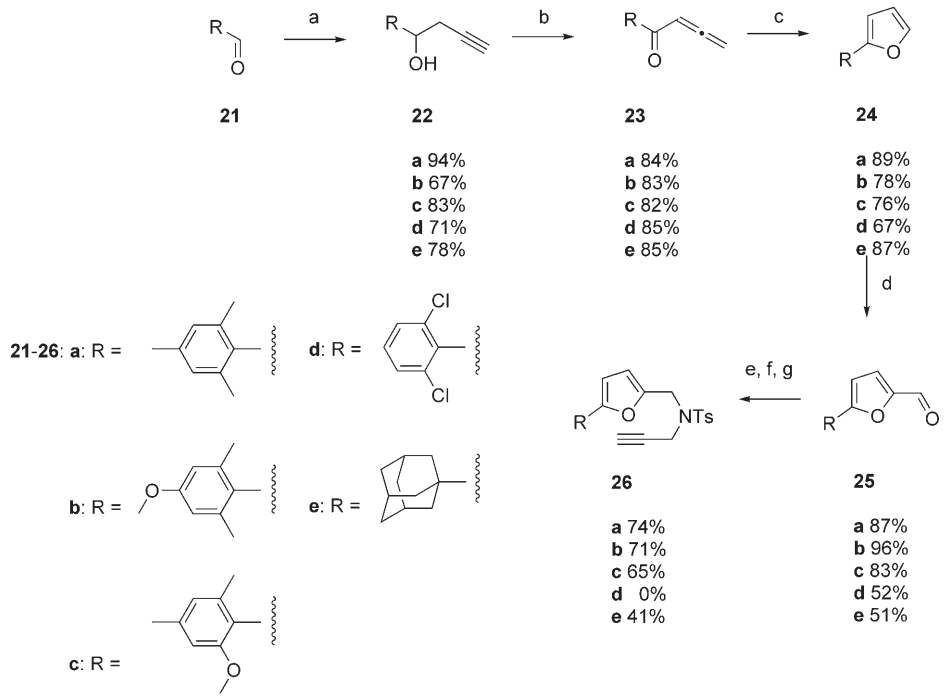
Oxidation of **22** with Dess–Martin periodinane afforded the allenyl ketones **23** in yields between 82–85%.[12] Using a high excess of Dess–Martin periodinane and after a long reaction time, enol-ester **27** could be obtained as a side product; it was generated by the addition of in situ formed acetic acid to the product allenyl ketone **23b** (Scheme 6).[13]

Then, using Marshall's protocol, 20 mol% silver nitrate in acetone was added to the allenyl ketones to promote furan formation in 67–89% yield.[14] The subsequent formylation of the furans **24** with *N,N*-dimethylformamide and phosphorus oxychloride by a Vilsmeier–Haack reaction delivered the corresponding furfural derivates **25** in good yields (71–96%), with the exception of the *o,o*-dichlorophenyl-substituted furan **24d** (52%) (however, the remaining starting material could be recovered).[15]

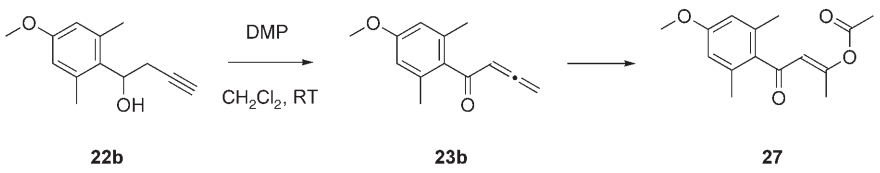
The next step was the condensation of **25** with propargylamine to the imine, followed by a reduction to the amine with sodium borohydride. The amines were tosylated to deliver the catalysis substrates **26** in yields of between 65 and 74%. A crystal structure analysis of **26b** (Figure 1)[16] nicely showed, how the phenyl and the furyl ring planes are almost perpendicular to each other, and the two methyl substituents on C10 and C14 shield C8 of the furan ring, which has to form a new C–C bond to C4 of the alkyne in the gold-catalyzed reaction. The dihedral angle O1-C8-C9-C14, which is an indicator for the angle between the planes of the furyl and the phenyl ring, is 117.5(4)°.

Only in case of the *o,o*-dichlorophenyl-substituted furfural **25d**, did the usual condensation with propargyl amine not work, maybe due to the sterically demanding groups. Thus **25d** was reduced to the furfurol derivative with $NaBH_4$, then **26d** could be synthesized by a Mitsunobu reaction with tosylated propargyl amine in 82% yield over the two steps (Scheme 7).[17]

Now the gold-catalyzed key reactions could be investigated (Table 1). With **26a** as substrate, the yield and the rate of the reaction were dependent on the catalyst and solvent used. With gold(III) chloride as catalyst and acetonitrile as solvent, the reaction needed 5 days to afford 79% of **28a**. However when using complex **30**[18] in chloroform, the reac-



Scheme 5. Synthesis of the ω-alkynyl furans as substrates for the gold-catalyzed synthesis of dihydroisoindoles. a) HC≡CCH$_2$MgBr, Et$_2$O, −40 °C to 10 °C; b) DMP, CH$_2$Cl$_2$, RT; c) AgNO$_3$, acetone, RT; d) POCl$_3$, DMF, 40 °C; e) HC≡CCH$_2$NH$_2$, MgSO$_4$, CH$_2$Cl$_2$, RT; f) NaBH$_4$, MeOH, RT; g) TsCl, Et$_3$N, CH$_2$Cl$_2$, RT. DMP = Dess–Martin periodinane.



Scheme 6. Side product of the Dess–Martin oxidation.

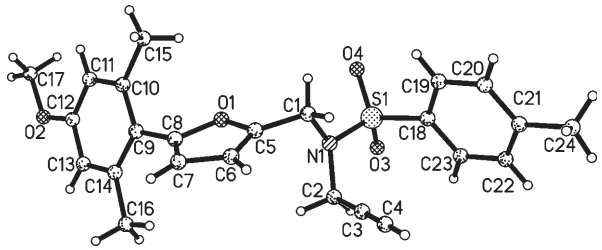
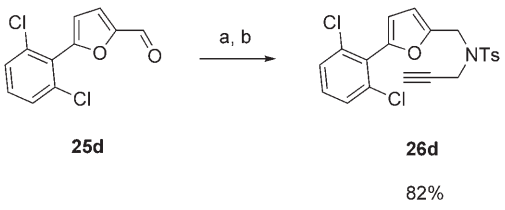


Figure 1. Solid-state structure of **26b**.



Scheme 7. Mitsunobu reaction of **25d** to give the *o,o*-dichlorophenyl-substituted furan-alkyne system **26d** in good yield. a) NaBH$_4$, MeOH, RT; b) HC≡CCH$_2$NHTs, DEAD, PPh$_3$, THF, RT. DEAD = diethylazodicarboxylate.

tion was finished in 20 h, delivering **28a** in 87% yield (entry 1, Table 1). A crystal structure analysis of **28a** nicely shows the *o,o,o'*-trisubstituted biaryl subunit with its almost perpendicular aryl rings (dihedral angle C6-C5-C9-C10 79.7(6)°; Figure 2).[16]

The reaction of **26b** to the phenol **28b** with gold(III) chloride as catalyst was performed in acetonitrile and provided the product in 88% yield after a reaction time of 10 h (entry 3, Table 1). A crystal structure analysis again confirmed the presence of the biaryl axis with a dihedral angle C4-C5-C9-C10 of 104.8(10)° and the constitution of the product (hydroxy group on C4, aryl substituent on C5; no migration of the aryl group by a Wagner–Meerwein rearrangement of an intermediate; Figure 3).[16]

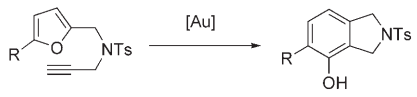
Most amazingly, for the *o*-methoxy-substituted substrate **26c** the reaction time under similar conditions was only 50 minutes, the phenol **28c** was obtained in an excellent 88% yield (entry 4, Table 1). Presumably, the methoxy group in the *ortho* position coordinates to the gold in the rate-limiting step and this favorable interaction lowers the energy of activation for the whole process.

Gold catalysis of **26d** with 5 mol% of complex **30** as catalyst in deuterated chloroform after three days gave the phenol **28d** in 63% yield (entry 5, Table 1), the *o,o*-dichloro substituents significantly slowed down the reaction. The choice of catalyst is decisive for the selectivity, the rate and the yield. In the case of **26d**, using catalyst **32**,[19] a mixture of constitutional isomers is obtained: **28d** (39%) and **31** (43%) (entry 6, Table 1), in contrast to the reaction with catalyst **30**, where only the desired product **28d** was observed in 63% yield.

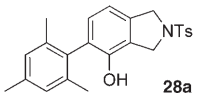
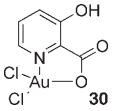
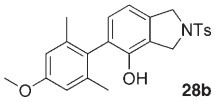
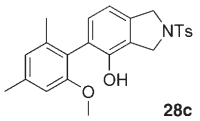
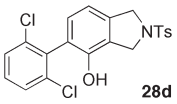
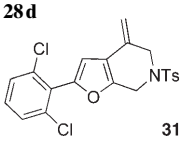
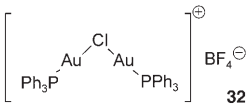
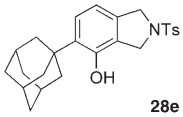
All furyl compounds described so far (**26a–d**) contain a sterically demanding phenyl substituent with planar sp^2-hybridized carbon atoms next to the furan, thus in principle still being able to create free space by rotation around the biaryl bond. To additionally test the tolerance of the phenol synthesis towards sterically demanding substituents, the nonplanar adamantyl substituent was used.

The commercially available adamantanecarboxylic acid **33** was esterified according to the literature to give the ada-

Table 1. Gold catalyzed synthesis of dihydroisoindol-4-ols.



26 28

Entry	Product	Solvent	Catalyst (5 mol %)	Reaction time	Yield [%]
1	 **28a**	$CDCl_3$	 **30**	20 h	87
2	**28a**	CD_3CN	$AuCl_3$	5 days	79
3	 **28b**	CD_3CN	$AuCl_3$	10 h	88
4	 **28c**	CD_3CN	$AuCl_3$	50 min	88
5	 **28d**	$CDCl_3$	**30**	3 days	63
6	**28d**  **31**	$CDCl_3$	 **32**	2 days	39 43
7	 **28e**	$CDCl_3$	**30**	10 min	67

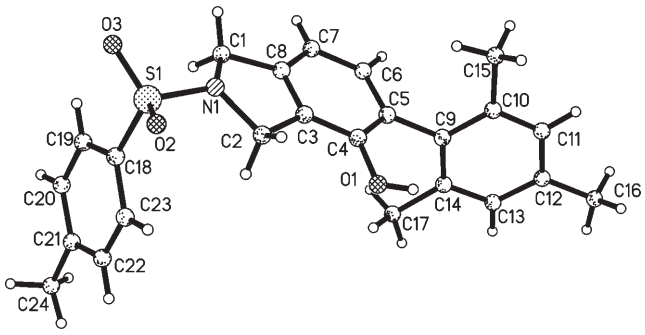


Figure 2. Solid-state structure of **28a**.

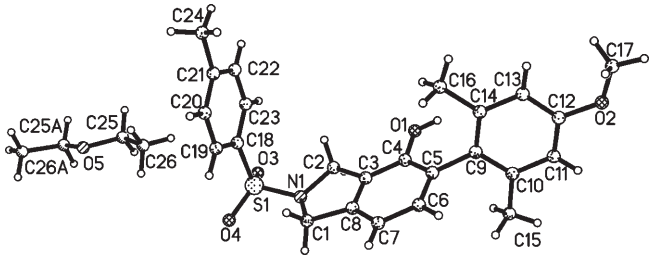


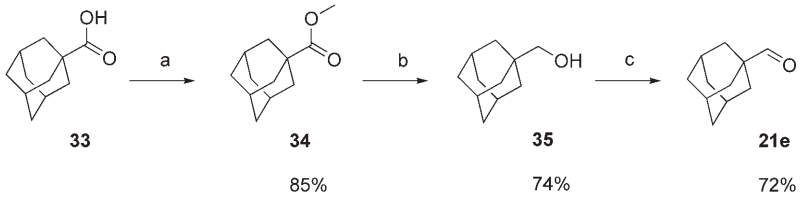
Figure 3. Solid-state structure of **28b**.

mantane carboxyl methyl ester **34**.[20] The desired aldehyde **21e** was obtained by reduction of the ester **34** with DIBALH, which afforded the adamantyl alcohol **35,** and subsequent Swern oxidation (Scheme 8).[21]

The homopropargyl alcohol **22e** was formed as described above in 78% yield and oxidized to allenyl ketone **23e** in 85%. The cyclization to the furan **24e** with 20 mol% silver nitrate succeeded in 87% yield. The furan formylation gave a 51% yield of **25e**, similar to the bulky *o,o*-dichlororphenyl-substituted furan **25d** (52%). The one-pot synthesis of the furan-alkyne substrate gave **26e** in 41% yield over the three steps (Scheme 5).

The reaction of **26e** with complex **30** in chloroform reached a quantitative conversion (monitored by ^{1}H NMR spectroscopy) after only 10 minutes at room temperature (67% yield of **28e** after work-up; entry 7, Table 1). Again, the structure of **28e** was confirmed by a crystal structure analysis (Figure 4).[16]

For the synthesis of the 8-hydroxytetrahydroisoquinolines **39** the furfural derivates **25** were subjected to a nitroaldol condensation with nitromethane, which led to the corresponding nitroolefins **36** in yields between 48 and 59%, which is in accordance with similar reactions reported in the literature.[22]



Scheme 8. Synthesis of adamantyl-substituted **21e**. a) MeOH, *p*-TsOH, CCl_4, 80°C; b) DIBALH, CH_2Cl_2, −78°C; c) DMSO, TFAA, CH_2Cl_2, −60°C. DIBALH = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, TFAA = trifluoroacetic anhydride.

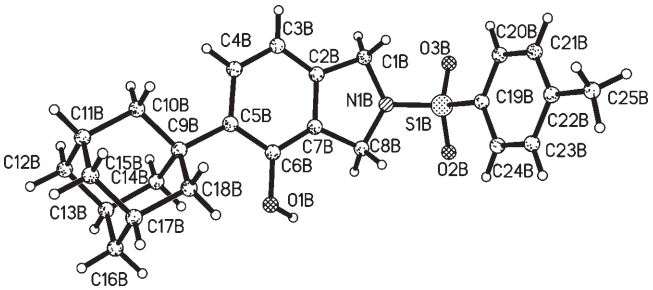
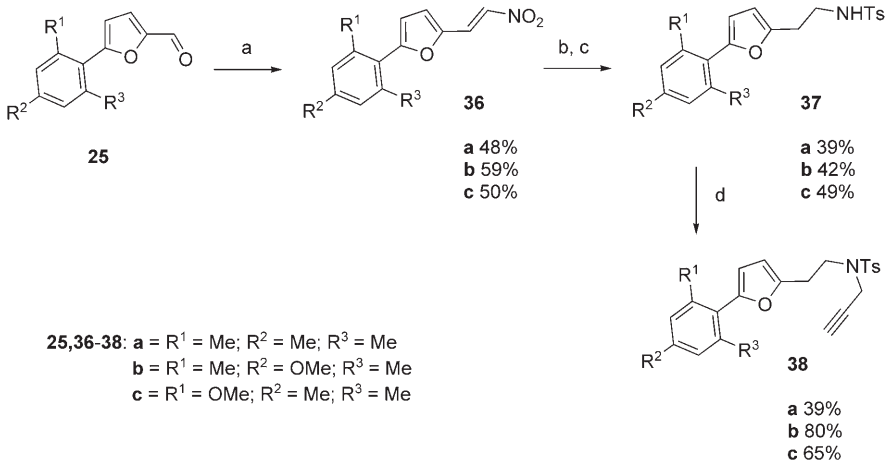


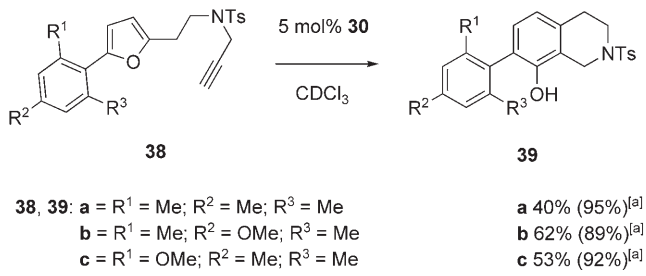
Figure 4. Solid-state structure of **28e**.

Reduction with $LiAlH_4$ and subsequent tosylation gave the sulfonamide **37** in yields between 39–49%.[23] Compound **37** was alkylated with propargyl bromide to deliver **38** in yields between 39 and 80% (Scheme 9).



Scheme 9. Reaction sequence to ω-alkynyl furans **38**. a) CH_3NO_2, KOH, MeOH, 0°C; b) $LiAlH_4$, Et_2O, 35°C; c) TsCl, CH_2Cl_2, RT; d) $HC{\equiv}CCH_2Br$, Cs_2CO_3 acetone, RT.

Reactions of **38a**, **38b**, and **38c** with 5 mol% of complex **30** in chloroform as solvent afforded the 8-hydroxytetrahydroisoquinoline **39a** in three days and 40% yield, **39b** in five days and 62% yield, and **39c** in 2 h and 53% yield (Scheme 10). Again the *o*-methoxy substituent influenced the rate of reaction dramatically. The conversion was monitored by ^1H NMR spectroscopy and the reaction mixtures were worked up when no further conversion was observed.



Scheme 10. Gold-catalyzed tetrahydroisoquinoline synthesis. [a] Conversion monitored by ^1H NMR spectroscopy.

Conclusion

The gold-catalyzed phenol reaction is well-suited to be one of the key steps in the synthesis of tetrahydroisoquinoline alkaloids even with sterically demanding group in the 7-position of that heterocyclic framework. The related dihydroisoindoles were also synthesized by gold catalysis in good yield. Even very bulky substituents, such as 2,6-dichlorophenyl or the adamantyl group, could be converted to the phenols by the gold catalysts in good yields. The influence of these sterically demanding substituents seems to be stronger in the previous steps, the substrate synthesis, in the gold-catalyzed step the effect is less pronounced. Probably, the following can be applied in general: if one can make the substrate, one can also successfully cyclize it with the gold catalyst. A methoxy donor in the 2-position of the phenyl substituents had, unlike the same group in the 4-position, a strongly accelerating effect on the reaction. Further details of the mechanism and rate-limiting step are under investigation.

Experimental Section

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

Acknowledgements

We thank Johnson Mattey for the donation of gold complexes, the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (HA 1932/9–1), and the AURICAT EU-RTN (HPRN-CT-2002–00174).

[1] For reviews, see: a) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3–9; b) A. S. K. Hashmi, *Gold. Bull.* **2004**, *37*, 51–65; c) N. Krause, A. Hoffmann-Röder, *Org. Biomol. Chem.* **2005**, *3*, 387–391; d) A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150–7154; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990–6993.

[2] a) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, *3*, 3769–3771; c) A. S. K. Hashmi, L. Grundl, *Tetrahedron* **2005**, *61*, 6231–6236; d) A. S. K. Hashmi, M. C. Blanco, E. Kurpejovic, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713.

[3] A. Pictet, T. Spengler, *Chem. Ber.* **1911**, *44*, 2030–2036.

[4] A. Bischler, B. Napieralski, *Chem. Ber.* **1893**, *26*, 1903–1908.

[5] a) C. Pomeranz, *Monatsh. Chem.* **1893**, *14*, 116–119; b) P. Fritsch, *Chem. Ber.* **1893**, *26*, 419–422.

[6] Even a recent example of a gold-catalyzed Pictet–Spengler reaction only showed the selectivity known for other Lewis acids and Brønsted acids: S. W. Youn, *J. Org. Chem.* **2006**, *71*, 2521–2523.

[7] a) A. S. K. Hashmi, L. Ding, J. W. Bats, P. Fischer, W. Frey, *Chem. Eur. J.* **2003**, *9*, 4339–4345; b) A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem.* **2004**, *116*, 6707–6709;

Angew. Chem. Int. Ed. **2004**, *43*, 6545–6547; c) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfle, W. Frey, J. W. Bats, *Angew. Chem.* **2005**, *117*, 2858–2861; *Angew. Chem. Int. Ed.* **2005**, *44*, 2798–2801.
[8] G. Bringmann, D. Feineis, *J. Exp. Bot.* **2001**, *52*, 2015–2022.
[9] A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Catal. Today* **2002**, *72*, 19–27.
[10] B. Martin-Matute, C. Nevado, J. Cardenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.
[11] L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, **1971**, 34–37, 94–97, 103.
[12] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.
[13] A. S. K. Hashmi, J. W. Bats, J.-H. Choi, L. Schwarz, *Tetrahedron Lett.* **1998**, *39*, 7491–7494.
[14] a) J. A. Marshall, E. D. Robinson, *J. Org. Chem.* **1990**, *55*, 3450–3451; b) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169–7171.
[15] A. Vilsmeier, A. Haack, *Chem. Ber.* **1927**, *60*, 119–122.
[16] CCDC-603475 (**26b**), CCDC-603474 (**28a**), CCDC-603476 (**28b**), and CCDC-603477 (**28e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[17] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.
[18] A. Dar, K. Moss, S. M. Cottrill, R. V. Parish, C. A. McAuliffe, R. G. Pritchard, B. Beagley, J. Sandbank, *J. Chem. Soc. Dalton Trans.* **1992**, *1*, 1907–1913.
[19] R. Uson, A. Laguna, M. V. Castrillo, *Synth. React. Inorg. Met.-Org. Chem.* **1979**, *9*, 317–324.
[20] *Organikum*, Wiley-VCH, 20th ed., Weinheim, **1999**, p. 442; procedure C.
[21] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165–185.
[22] L. Sader-Bakaouni, O. Charton, N. Kunesch, F. Tillequin, *Tetrahedron* **1998**, *54*, 1773–1782.
[23] M. E. Jung, S. J. Miller, *Heterocycles* **1990**, *30*, 839–853.

Received: April 13, 2006
Published online: July 5, 2006

