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Gold Catalysis and Chiral Sulfoxides: Enantioselective Synthesis of Dihydroisoindol-4-ols

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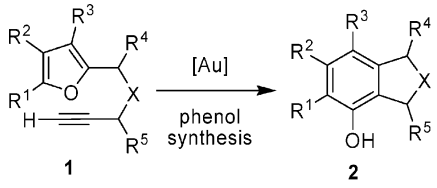
Keywords: Alkynes / Furans / Gold / Isoindoles / Sulfoxides / Sulfones

Furfurals and enantomerically pure sulfinamides have been condensed to *N*-sulfinylimines. Addition of organolithium or -magnesium compounds to these imines allowed a 1,2-induction. After propargylation, the sulfinamides gave low conversion with gold catalysts. Oxidation to chiral sulfonamides, propargylation and gold-catalysed cycloisomerization to the phenol delivered non-racemic dihydroisoindol-4-ols in good yields. In situ NMR studies prove the intermediacy of the arene oxide even with the $AuCl_3$ catalyst.

Introduction

Chiral sulfoxides[1] and sulfinamides[2–4] are excellent auxiliaries for asymmetric synthesis and provide access to a large variety of chiral amines,[5] amino acids[6,7] and heterocycles.[8,9] The combination of gold-catalysed[10–12] phenol synthesis[13] and chiral centres set by sulfoxides as asymmetric auxiliaries in **1** are expected to lead to dihydroisoindol-4-ols (**2**, X = NR) with a defined chiral centre at the 1-position (Scheme 1).

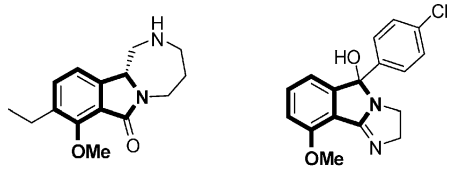


1 2

X = O, OCR_2, NR, CR_2NR, CR_2, ...
R^1 = H, alkyl, aryl, alkynyl
R^2 = H, alkyl, Br
R^3 = H, alkyl
R^4, R^5 = H, alkyl, aryl

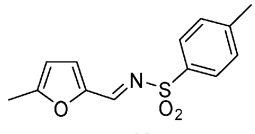
Scheme 1. Gold-catalysed phenol synthesis.

After the successful synthesis of chiral 8-hydroxytetrahydroisoquinolines by catalytic hydrogenation and subsequent gold catalysis,[14,15] efforts are now focused on the synthesis of chiral dihydroisoindole derivatives, which, for example, are of significance in medical applications.[16] Recently it was discovered that such compounds form a new class of powerful 5-HT_{2C} antagonist **3**, which have shown very promising results in the pharmaceutical treatment of obesity (Figure 1).[17] The mazindole derivative **4**, which



3 4

Figure 1. 5-HT_{2C} antagonist **3** and mazindol derivative **4**.



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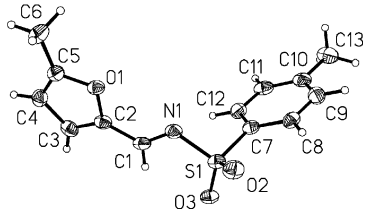

Figure 2. Crystal structure analysis of **10**.

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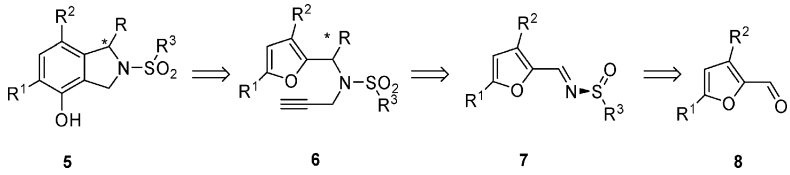
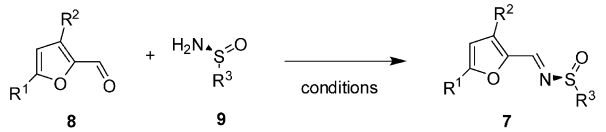


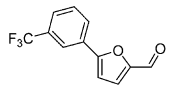
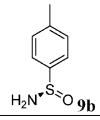
Scheme 2. Retrosynthesis of chiral, non-racemic dihydroisoindol-4-ols **5**.

also contains the tetrahydroisoindole substructure, is a potential inhibitor of the cocaine site at the dopamine transporter (Figure 2).[18]

Previous syntheses of the dihydroisoindole derivatives were carried out by the reaction of isobenzofuranones and urea, amides[19] or primary amines[20] and subsequent reduction[21] with $LiAlH_4$. This reduction is not a suitable method for sensitive or highly functionalized compounds. Herein we show a new synthetic route that tolerates all kinds of functional groups. Starting from furfurals **8** with different substituents at the 3- or 5-position, chiral, non-racemic imino sulfoxides **7** can be easily prepared by condensation using Ti^{IV} compounds as Lewis acid and water-trapping reagent. After tethering the stereocentre by 1,2-induction, oxidation of the sulfoxide to a sulfone and subsequent propargylation of the amine, substrates **6** can be tested in the gold-catalysed phenol synthesis aiming at chiral, non-racemic dihydroisoindol-4-ols **5** (Scheme 2).

Table 1. Generation of the imino sulfoxides **7**.



Entry	Furfural **8**	**9**	Conditions	% Yield
1	 **8a**	 **9a**	$TiCl_4$, NEt_3, DCM, 0 °C → r.t.	**7a** (85)
2	 **8b**	 **9a**	$TiCl_4$, NEt_3, DCM, 0 °C → r.t.	**7b** (84)
3	 **8c**	 **9a**	$TiCl_4$, NEt_3, DCM, 0 °C → r.t.	**7c** (65)
4	 **8d**	 **9b**	$Ti(OEt)_4$, DCM, reflux	**7d** (90)

Results and Discussion

Enantiomerically pure imino sulfoxides **7** were obtained by condensation reaction of the furfurals **8** and (*R*)-(+)-2-methyl-2-propanesulfinamide **9a**, using $TiCl_4$ or $Ti(OEt)_4$ for the condensation of 5-methylfurfural (**8a**) and (*R*)-(–)-4-toluenesulfinamide (**9b**).[22] The desired imino sulfoxides **7** were obtained in good-to-very-good yields. For the synthesis of **7d** all attempts to use $MgSO_4$, $TiCl_4$, or molecular sieves for condensation of the corresponding starting materials failed, only $Ti(OEt)_4$ was successful (Table 1).

Reaction of the (*R*)-configured imino sulfoxides **7** with Grignard reagents was achieved by a modified protocol of Ellman and co-workers.[23] The diastereoselectivity was determined by integration of well-separated signals in specific regions of the ^1H NMR spectra. Although the total yields of the reactions were good-to-excellent and not strongly dependent on the reaction conditions, the selectivities of the additions strongly depended on the solvent. Most reactions showed the highest diastereoselectivity in DCM. In THF a high or better diastereoselectivity was observed only in the reactions of phenyl- and cyclopropylmagnesium bromide with **7a**. Although in both cases the diastereoselectivity doubled in comparison to the reaction in DCM, the selectivity of the addition of cyclopropylmagnesium bromide to **7a** was relatively low. The biggest discrepancy in diastereoselectivity was found in the addition of phenyl- and ethylmagnesium bromide to **7a**. The addition of phenylmagnesium bromide in DCM showed quite a low selectivity of only 74:26 *dr*. In THF, the reaction was perfectly diastereoselective. In THF, the reaction of **7a** with ethylmagensium bromide furnished an almost 1:1 diastereomeric mixture of **11b**. However, in DCM the reaction was highly selective. On the other hand, the low selectivity for the addition of phenylmagnesium bromide to **7c** was independent of the solvent. Separation of the diastereomers by column chromatography was only possible for **11b**.

In addition, *N*-sulfonylimine **10**[24] could be obtained by a similar condensation of **8a** and tosylamide and single crystals could be grown (Figure 2).[25]

All efforts to add a Grignard compound to the tolyl-substituted imino sulfoxide **7d** failed, but aldol reaction with *N*,*N*-dimethylacetamide furnished **11g** in 88% yield. Although the diastereoselectivity of the reaction was quite good, it was lower than in the addition of the Grignard reagents to the *tert*-butyl sulfoxides **7**. This expected result derives from the lower steric demand of the *p*-tolyl group in comparison to the *tert*-butyl group.

Phenyllithium was also tested as the organometallic reaction partner. The addition of phenyllithium to ketimines is known,[26] but $AlMe_3$ is needed as a Lewis acid and the

solvent has to be toluene. The authors investigated the reaction of ketimines only under these reaction conditions. Thus we tested the addition of aldimine **7a** in the absence of an additional Lewis acid in THF and DCM. Our standard protocol, which had already been used for the addition of Grignard compounds to aldimines **7**, could deliver **11a** in good yields and diastereoselectivities. Still, the *de* values are not as good as the values obtained for the addition of phenylmagnesium bromide. Compared with phenylmagnesium bromide, which showed a higher diastereoselectivity in THF, with phenyllithium a better stereoselectivity and a higher yield were observed in DCM.

Single crystals for the crystal structure analysis of **11b** and **11c** were obtained.[25] By knowing the absolute configuration at the sulfur atom (which could also be confirmed by anomalous diffraction), the configuration of the newly formed stereogenic centre could be determined (Figure 3).

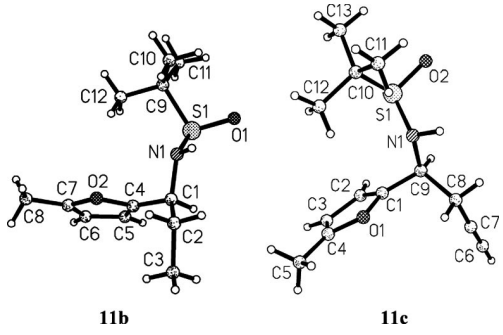


Figure 3. Solid-state structures of **11b** and **11c** showing the stereogenic centres at the carbon atoms (C1 for **11b** and C9 for **11c**) to be (*S*)-configured and at the sulfur atoms to be (*R*)-configured (anomalous diffraction).

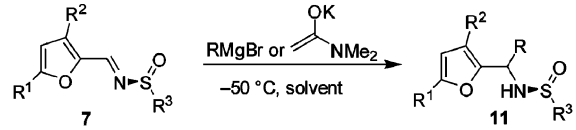
Crystal structures of all the stereochemically pure products **11** or of products derived from them were obtained. The absolute configurations of the stereogenic centres at the carbon atoms are indicated for the products **11** in Table 2. In the cases of **11d**, **11f** and **11g** the diastereomeric mixtures were used for further transformations (after the oxidation to the sulfonamides as enantiomeric mixtures).

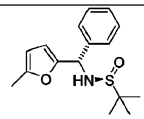
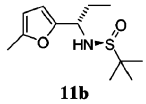
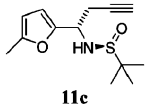
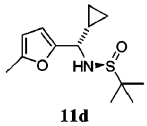
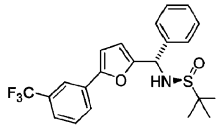
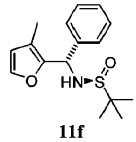
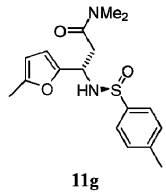
The elementary cells of both **11b** and **11c** contain only two molecules that are connected by a hydrogen bridge. In both structures the molecules form chains that are perfectly aligned. The (*S*) configuration of the newly generated stereogenic centres in the products suggests the transition state shown in Figure 4 for the addition of the organometallic compound to the chiral imino sulfoxide. Less polar solvents should favour the proposed transition state.[26]

For further transformations diastereomerically pure compounds **11a**–**c** and **11e** were used, whereas for **11d**, **11f** and **11g** the diastereomeric mixtures could not be separated and the mixtures were used for further reactions.

Initial efforts to propargylate the sulfinamide **11e** failed. The tested bases, Cs_2CO_3, K_2CO_3, Hünig's base and NEt_3, furnished only decomposition products. Even under Mitsunobu conditions, decomposition of the starting material was observed.[27,28] So the direct propargylation of **11e** was carried out with NaH and propargyl bromide in DMF.[29]

Table 2. Effect of solvent on Grignard addition to *N*-sulfinylimines **7**.



Entry	7	Organometal reagent	Solvent	Product 11	% Yield of 12	% *de*[a]
1	**a**		DCM	 **11a**	quant.	47
2	**a**		THF	**11a**	97	>95
3	**a**		DCM	 **11b**	75	>95
4	**a**		THF	**11b**	99	9
5	**a**		DCM	 **11c**	70	>95
6	**a**		THF	**11c**	75	81
7	**a**		DCM	 **11d**	84	13
8	**a**		THF	**11d**	85	27
9	**b**		DCM	 **11e**	91	>95
10	**b**		THF	**11e**	50	62
11	**c**		DCM	 **11f**	95	78
12	**c**		THF	**11f**	56	79
13	**d**		DCM	 **11g**	0	–
14	**d**		THF	**11g**	88	52
15	**a**	PhLi	DCM	**11a**	77	83
16	**a**	PhLi	THF	**11a**	27	56

[a] Major diastereomer.

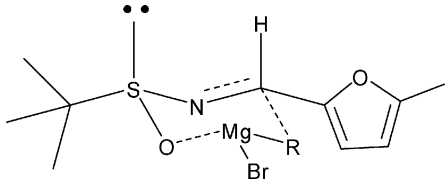
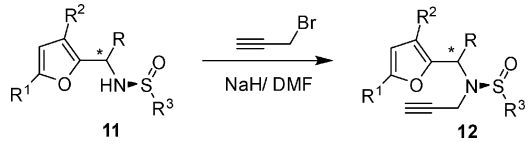


Figure 4. Proposed transition state for the addition of the Grignard reagent to **7**.

Under these conditions the desired product **12e** was obtained in 85% yield. The same protocol delivered **12a** from **11a** in 82% yield (Table 3).

Table 3. *N*-Propargylation of sulfinamide **11a** and **11e**.



Entry	**11**	R	R^1	R^2	R^3	% Yield of **12**
1	**11a**	phenyl	Me	H	*tert*-butyl	**12a** (82)
2	**11e**	phenyl	3-CF_3-phenyl	H	*tert*-butyl	**12e** (85)

Compounds **14a**–**d** and **14f** were obtained by oxidation of the sulfoxide to the corresponding sulfone with 1.1–2 equiv. of *m*CPBA in 36 (**14d**) to 63% (**14f**) yields. These low yields are caused by unselective reactions with numerous side-products. Different reaction conditions were tested, but most unfortunately gave no better results (Table 4).

After oxidation using the same conditions as used for **11a**–**d** and **11f**, **11e** was accessible in 57% yield. For the *p*-tolyl-substituted **11g**, the same synthetic route for **8** to **11** was chosen. As observed for compounds **8**, the oxidation did not work well, but the subsequent propargylation afforded the desired product in a quantitative yield without purification. For compound **14g**, single crystals suitable for X-ray structure analysis were obtained.[25] For this compound, the absolute configuration of the new stereogenic centre was also obtained by anomalous diffraction (Figure 5). Although the oxidation was not carried out with stereochemically pure material, only the (*S*)-configured enantiomer crystallized. Unfortunately not enough enantiomerically pure material could be obtained to measure the $[\alpha]_D^{20}$ value.

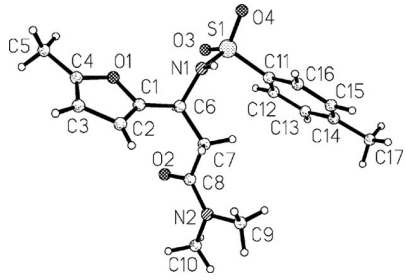
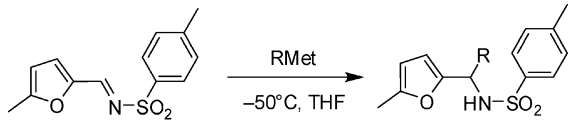


Figure 5. Solid-state structure of **14g** showing the stereogenic centre (C6) to be (*S*)-configured (anomalous diffraction).

Another route to some of the substrates **14** in racemic form involved the addition of the organometallic reagents to **10** (Table 5).

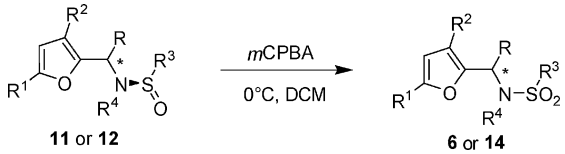
Table 5. *N*-Sulfonylimines **10** as precursors for **14**.



Entry		R-Met	% Yield of **14**
1	**10**	phenyllithium	**14h** (48)
2	**10**	cyclopropylmagnesium bromide	**14i** (94)

In an effort to crystallize **14e**, oxidation product **13** was obtained (Figure 6). The CF_3 groups are disordered. Again, the absolute configuration at the carbon atom showed an (*S*) configuration.[25] Thus, the absolute configuration of the

Table 4. Oxidation of the sulfoxide to the sulfone.



Entry	**11**	R	R^1	R^2	R^3	R^4	Product	% Yield
1	**11a**	phenyl	Me	H	*tert*-butyl	H	**14a**	41
2	**11b**	ethyl	Me	H	*tert*-butyl	H	**14b**	58
3	**11c**	propargyl	Me	H	*tert*-butyl	H	**14c**	51
4	**11d**	cyclopropyl	Me	H	*tert*-butyl	H	**14d**	36
5	**11e**	phenyl	*m*-CF_3-phenyl	H	*tert*-butyl	H	**14e**	70
6	**12e**	phenyl	*m*-CF_3-phenyl	H	*tert*-butyl	propargyl	**6e**	57
7	**11f**	phenyl	H	Me	*tert*-butyl	H	**14f**	63
8	**11g**	$CH_2C(O)NMe_2$	Me	H	*p*-tolyl	H	**14g**	52

starting material for the reaction sequence of this substrate could also be determined. The crystals were unstable, losing an included diethyl ether.

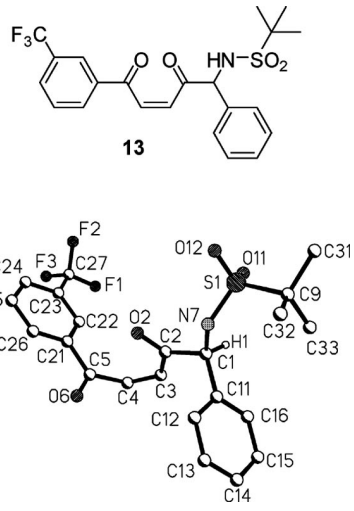
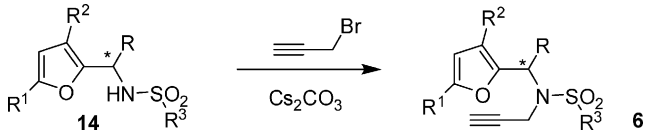


Figure 6. Crystal structure of **13** with an (*S*) configuration at C1 (absolute configuration by anomalous diffraction).

The last step in the reaction sequence for providing the starting material for the gold catalysis involved propargylation of the nitrogen moiety. Propargylation of compounds **14** under mild conditions with 3 equiv. Cs_2CO_3 and 3 equiv. propargyl bromide afforded the desired products **6** in good-to-excellent yields. Only traces of byproducts were detected. For some of the products (**14g** and **14i**) no purification was necessary (Table 6).

Table 6. *N*-Propargylation of the sulfonamide **14**.



Entry		R	R^1	R^2	R^3	% Yield of **6**
1	**14a**	phenyl	Me	H	*tert*-butyl	**6a** (60)
2	**14b**	ethyl	Me	H	*tert*-butyl	**6b** (84)
3	**14c**	propargyl	Me	H	*tert*-butyl	**6c** (82)
4	**14d**	cyclopropyl	Me	H	*tert*-butyl	**6d** (80)
7	**14f**	phenyl	H	Me	*tert*-butyl	**6f** (92)
8	**14g**	$CH_2C(O)NMe_2$	Me	H	*p*-tolyl	**6g** (quant.)
9	**14h**	phenyl	Me	H	*p*-tolyl	**6h** (92)
10	**14i**	cyclopropyl	Me	H	*p*-tolyl	**6i** (84)

In an initial test reaction, the diastereomeric mixture of **12a** was treated with 5 mol-% $AuCl_3$ in deuteriated acetonitrile to afford the corresponding diastereomeric mixture of dihydroisoindol-4-ol **15** in 13% yield after 24 h. The relatively low yield is due to the fact that many side-products were observed during the reaction. One problem is the free electron pair at sulfur, which can coordinate the gold catalyst. Gold(I) catalysis with $[Ph_3PAu]NTf_2$ delivered a mixture of three inseparable products. After recrystallization single crystals of **15** were obtained, suitable for X-ray diffraction. Anomalous diffraction showed that the crystal contains a diastereomeric mixture of **15** with an (*R*) configuration at the sulfur atom and both an (*R*) and (*S*) configuration at the carbon atom (Figure 7).[25]

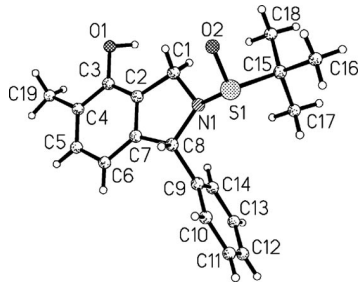
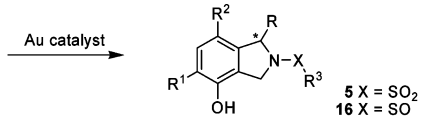


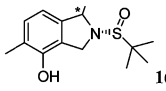
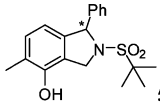
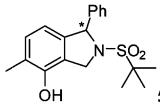
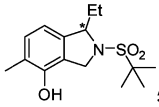
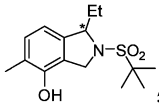
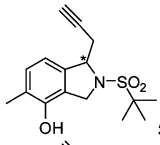
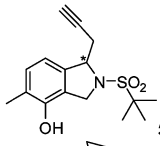
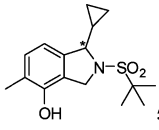
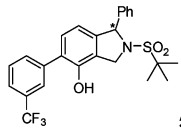
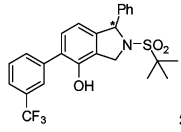
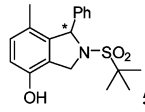
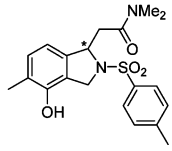
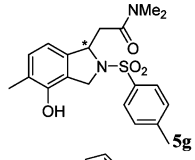
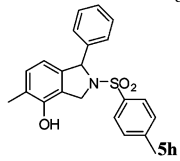
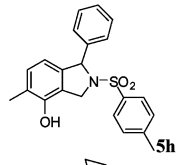
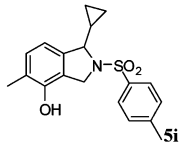
Figure 7. Solid-state structure of **15** showing the stereogenic centre (C8).

The gold-catalysed reactions of **6a**–**g** were carried out on the NMR scale by using either $AuCl_3$ in deuteriated acetonitrile or the Gagosz catalyst,[30] $[Ph_3PAu]NTf_2$, in deuteriated DCM and were monitored by in situ ^1H NMR spectroscopy. Gold(III) catalysis with 5 mol-% $AuCl_3$ as catalyst furnished for the compounds **6a**–**g** the expected dihydroisoindol-4-ols in good-to-excellent isolated yields. Compound **6a** was converted into **5a** within 3 min and the desired product was isolated in quantitative yield. Also **5c** was obtained in 99% yield after 3 min of reaction. The reaction times of **6d** and **6g** at 10 and 6 min, respectively, were also quite short and the isolated yields of 96 and 90% very good. After 19 h **6e** was converted into **5e** in 53% isolated yield. The conversion of **6b** was finished after 3 min and 85% of the corresponding dihydroisoindol-4-ol could be isolated. The longest reaction time was observed for **6f** which needed 6 days for full conversion. Compound **5f** was isolated in 51% yield (Table 7). Single crystals of **5a**, **5b**, **5f** and *rac*-**5g** were obtained.[25] The absolute configurations of these compounds could be obtained by anomalous diffraction. Products **5a** and **5b** showed only the (*S*) configuration at the carbon atoms (C8 for **5a** and C1 for **5b**). As compound **5b** derives from **11b** and both show the same configuration, this shows that no significant racemization occurred during the synthetic route (Figure 8). With this result in hand, the configuration of the starting material for the synthesis of **5a** (**11a**) could also be determined. The crystal structures of **5g** and **5f** showed the stereogenic centres at C1 to be (*R*)- and (*S*)-configured, respectively. As compounds **11g** and **11f** were used as diastereomeric mixtures in further transformations leading to the catalysis products **5g** and **5f**, these products gave the expected racemic mixtures.

Gold(I) catalysis with 5 mol-% $[Ph_3PAu]NTf_2$ catalyst furnished for **6a**–**c**, **6e** and **6f** the expected dihydroisoindol-4-ols in medium-to-excellent yields in different periods of time (Table 7). All the catalytic reactions with $[Ph_3PAu]NTf_2$ as catalyst were finished in 3–5 min except for **6a** which needed 20 h for complete conversion. Compounds **5a** and **5c** were isolated in 65 and 76% yields, values that are significantly lower than those obtained in the gold(III) ca-

Table 7. Gold-catalysed conversion of **12a**, **6a**–**i**.



	Compd.	Au catalyst	*t*	Solvent	Product	% Yield
1	**12a**	$AuCl_3$	24 h	CD_3CN	 **16a**	13
2	**12a**	$[Ph_3PAu]NTf_2$	20 h	DCM	unselective reaction	–
3	**6a**	$AuCl_3$	3 min	CD_3CN	 **5a**	quant.
4	**6a**	$[Ph_3PAu]NTf_2$	20 h	DCM	 **5a**	quant.
5	**6b**	$AuCl_3$	3 min	CD_3CN	 **5b**	85
6	**6b**	$[Ph_3PAu]NTf_2$	3 min	DCM	 **5b**	65
7	**6c**	$AuCl_3$	3 min	CD_3CN	 **5c**	99
8	**6c**	$[Ph_3PAu]NTf_2$	3 min	DCM	 **5c**	76
9	**6d**	$AuCl_3$	10 min	CD_3CN	 **5d**	96
11	**6e**	$AuCl_3$	19 h	CD_3CN	 **5e**	69
12	**6e**	$[Ph_3PAu]NTf_2$	5 min	DCM	 **5e**	53
13	**6f**	$AuCl_3$	6 days	CD_3CN	 **5f**	51
15	**6g**	$AuCl_3$	6 min	CD_3CN		90
16	**6g**	$[Ph_3PAu]NTf_2$	3 min	DCM	 **5g**	62
17	**6h**	$AuCl_3$	3 min	CD_3CN	 **5h**	95
	6h	2.5 mol-% $[\mu Cl(PMes_3Au)]_2BF_4$	3 min	DCM	 **5h**	93
18	**6i**	$AuCl_3$	3 min	CD_3CN	 **5i**	80

talysis, whereas **5b** was isolated in quantitative yield, which was higher than in the reaction with gold(III) chloride. The same isolated yield (57%) was observed for **5e** in gold(I) and gold(III) catalysis, but the reaction was faster with only 5 min required for complete conversion in the gold(I) catalysis (Table 3).

In order to find the lower limit of catalyst loading, compound **6h** was subjected to decreasing amounts of $AuCl_3$ and the reaction was monitored by ^1H NMR spectroscopy. In analogy to the previous conversions, the reactions were conducted at room temperature in deuteriated acetonitrile.

With 5 mol-% $AuCl_3$ complete conversion was observed after only 3 min, with 2 mol-% catalyst the reaction time increased to 5 min and with 1 mol-% to 10 min (Table 8, entries 1–3). Within the error limits this means that half the amount of catalyst needs about twice the time. With only 0.1 mol-% $AuCl_3$ loading, the reaction time increased dramatically to about 6 days, a clear deviation from linearity (Table 8, entry 4). Still, even with the long reaction time, the catalyst remained active until full conversion was achieved. The formation of a side-product was observed during the experiment with 0.1 mol-% $AuCl_3$. For several hours this

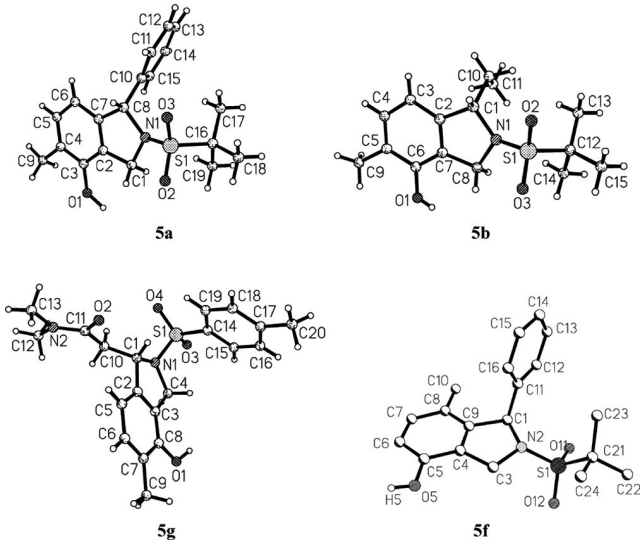
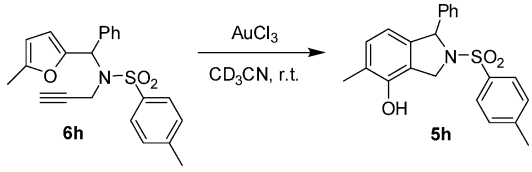


Figure 8. Solid-state structures of **5a**, **5b**, **5g** and **5f** showing the stereogenic centre (C8 for **5a**, C1 for **5b**, **5g** and **5f**) to be (*S*)-configured for **5a** and **5b** and racemic for **5f** and **5g**, respectively (anomalous diffraction).

intermediate, probably the arene oxide **16**, increased in the reaction mixture (reaching a steady-state concentration after about 90 min; see Figure 10).[31] The in situ ^{1}H NMR spectroscopic data supports this assignment (Figure 9).

The intermediate concentration increased for the first 90 min, stayed constant for about 700 min and then slowly decreased to an undetectable amount at the end of the reaction (Figures 10 and 11). The concentration of the phenol **5h** increased continuously (Figure 12).

Table 8. Gold-catalysed reaction of **6h**.



Entry	$AuCl_3$ [mol-%]	*t*	% Yield of phenol **5h**[a]	% Conversion[a]
1	5	3 min	96	quant.
2	2	5 min	95	quant.
3	1	10 min	97	quant.
4	0.1	6 d	97	quant.

[a] Determined by ^{1}H NMR spectroscopy.

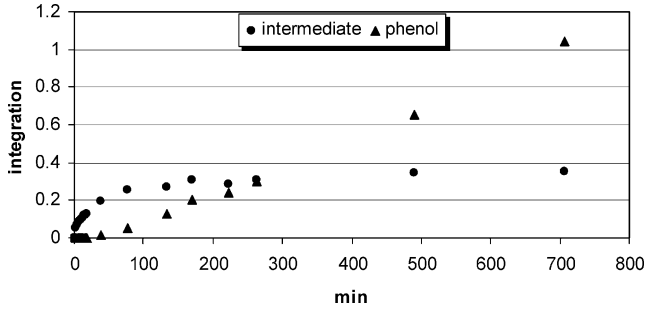


Figure 10. Concentration of the intermediate **16** and the product **5h** during the first 800 min.

If one takes a close look at the first 40 min (Figure 12), it becomes clear that a significant concentration of **16** has to build up before **5h** starts to form; the induction period

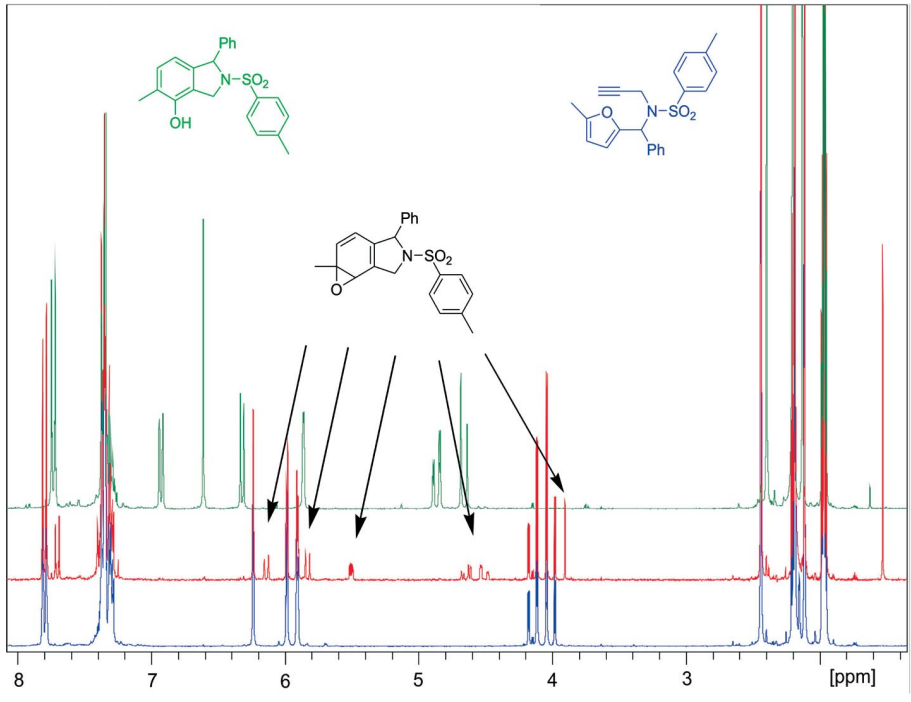


Figure 9. ^{1}H NMR spectra recorded during the conversion of **6h** showing signals of the intermediate **16** and the phenol **5h**.

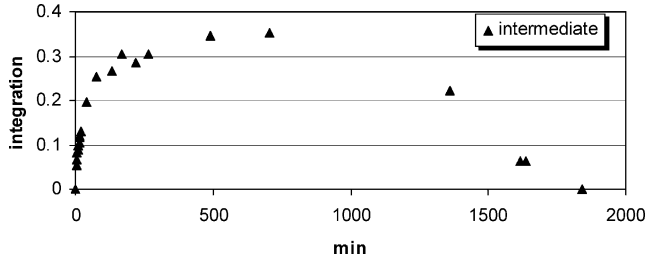


Figure 11. Concentration of the intermediate **16** during the first 31 h.

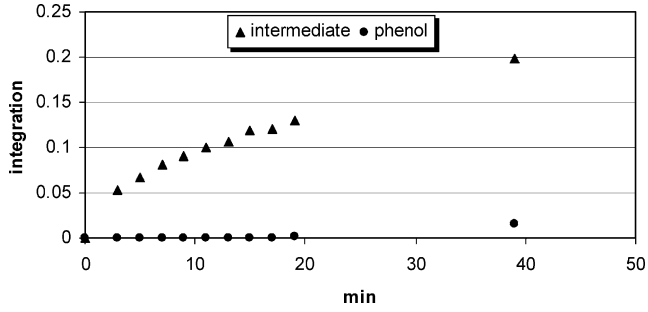


Figure 12. Concentration of the intermediate **16** and the product **5h** during the first 40 min.

for the formation of **5h** is about 20 min. These observations fit with the initial findings of arene oxides as transient species in the phenol synthesis.[32] The difference is the use of gold–pyridine complexes in the former case and the use of $AuCl_3$ as the catalyst here.

Conclusions

A combination of enantiomerically pure sulfoxides as chiral auxiliaries for the addition of Grignard reagents to form diastereomeric pure sulfoxamines and subsequent gold-catalysed cyclization offers a short and easy access to chiral, non-racemic 2,3-dihydro-1*H*-isoindol-4-ol systems. No significant racemization was observed during the reaction sequence. The absolute configurations of the newly formed stereogenic centres were unambiguously assigned by anomalous diffraction. Alkyl, phenyl, amide and alkynyl groups are tolerated at the position γ to the alkyne moiety during the cyclization process. A range of different furan precursors were successfully applied in the synthesis of the new dihydroisoindol-4-ol derivatives. Newly designed gold catalysts will provide dihydroisoindol-4-ol derivatives faster and in better yield.

Experimental Section

General Methods: Chemicals were purchased from commercial suppliers (Aldrich, Fluka, Lancaster, Strem and Merck) and were used without further purification. THF and Et_2O were distilled from Na/benzophenone prior to use. Et_3N was distilled from $LiAlH_4$. DCM was dried with Al_2O_3. Dry DMF was placed under a protecting atmosphere with a crown cap and used without further purification. Unless indicated otherwise, all reactions were carried out using Schlenk techniques under nitrogen. NMR spectra were recorded with Bruker ARX500, ARX300 and ARX250 spectrometers. ^{13}C NMR assignment was achieved by analysis of DEPT 90 and DEPT 135 spectra. Mass spectra were recorded with a Finnigan MAT 90, Varian 711 or Bruker daltonics microtof spectrometer. IR spectra were recorded with a Bruker Vector 22 spectrometer. Elemental analyses were performed with a Carlo–Erba Strumentazione Elemental Analyser Modell 1106. Optical rotations were measured with a Perkin–Elmer 241 instrument.

General Procedure 1 (GP 1) − Synthesis of Imino Sulfoxides from Substituted Furfural Derivatives and (*R*)-(+)-2-Methyl-2-propanesulfinamide: In a Schlenk flask furfural, (*R*)-(+)-2-methyl-2-propanesulfinamide and Et_3N (5 equiv.) were dissolved in DCM under nitrogen and cooled to 0 °C. Afterwards $TiCl_4$ (0.5 equiv.) was added dropwise and the reaction mixture was stirred for 20 min at 0 °C and 2 h at r.t. The reaction was quenched by adding saturated aqueous $NaHCO_3$. The mixture was extracted with DCM and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA) or recrystallization.

General Procedure 2 (GP 2) − Addition of Grignard Compounds or Phenyllithium to Imino Sulfoxides or Imino Sulfones:[23] In a Schlenk flask the imino sulfoxide was dissolved in DCM or THF under nitrogen and cooled to –50 °C. Afterwards the Grignard compound (2 equiv.) was added dropwise and the reaction mixture was stirred for 6 h at –50 °C, allowed to warm up to r.t. and then stirred overnight. The reaction was quenched by adding saturated aqueous NH_4Cl. The mixture was extracted with DCM or Et_2O and the combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA) or recrystallization.

General Procedure 3 (GP 3) − Propargylation of Amino Sulfoxides:[29] In a Schlenk flask the amino sulfoxide was dissolved in DMF under nitrogen. After 15 min of stirring, NaH was added followed by propargyl bromide (80% solution in toluene). The reaction mixture was stirred overnight at r.t. The reaction was quenched by adding saturated aqueous NH_4Cl. The mixture was extracted with Et_2O and the combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA).

General Procedure 4 (GP 4) − Oxidation of Propargylated or Non-propargylated Amino Sulfoxides to Propargylated or Non-propargylated Amino Sulfones: In a Schlenk flask the amino sulfoxide was dissolved in DCM under nitrogen and cooled to 0 °C. Afterwards *m*CPBA dissolved in DCM was added dropwise and the reaction mixture was stirred for 20 min at 0 °C, allowed to warm up to r.t. and stirred overnight. The reaction was quenched by adding saturated aqueous $NaHCO_3$. The mixture was extracted with DCM and the combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA).

General Procedure 5 (GP 5) − Propargylation of Amino Sulfones:[29] The amino sulfone was dissolved in acetone and Cs_2CO_3 (3 equiv.) and propargyl bromide (3 equiv., 80% solution in toluene) were added. The mixture was stirred at r.t. overnight. Afterwards the solvent was removed under reduced pressure. The resulting solid was partitioned between water and DCM and the aqueous phase extracted with DCM. The combined organic phases were dried

with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA).

General Procedure 6 (GP 6) − Gold Catalysis on the NMR Scale Using Gold(III) Chloride as Catalyst: In a NMR tube the starting material (1 equiv.) was dissolved in deuteriated acetonitrile and the catalyst precursor was added. The reaction was followed by ^1H NMR spectroscopy. After completion, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (PE/EA) or recrystallization.

General Procedure 7 (GP 7) − Gold Catalysis on the NMR Scale Using [Ph_3PAu]NTf_2 (or [Mes_3PAu]NTf_2 and [*n*Bu$(Ad)_2Au$]NTf_2, respectively) as Catalyst: In a NMR tube 1 equiv. of the starting material was dissolved in deuteriated DCM and the catalyst precursor was added. The reaction was followed by ^1H NMR spectroscopy. After completion, the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel (PE/EA) or recrystallization.

Supporting Information (see also the footnote on the first page of this article): Full characterisation of all unknown compounds.

Acknowledgments

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