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Homogeneous gold-catalyzed synthesis of biphenyls and furfuryl-substituted arenes

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Abstract

The synthesis of phenyl- and furfuryl-substituted furans and their unique gold-catalyzed transformation to biaryl compounds and furfuryl arenes was investigated. With the aryl-substituted substrates the reactions proceeded very well, and in the case of a chloro-substituent in *o*-position of the phenyl group a minor side-product, that might be explained by a neighboring-group participation of that chloro-substituent, was isolated. In the case of the furfuryl-substitution the side reactions become more relevant, the two side-products provide evidence for a carbeniumion as intermediate that is transformed into a more stable furfuryl cation by a C–C bond cleavage.

Keywords: Homogeneous catalysis; Gold; Arene synthesis

1. Introduction

The preparative organometallic chemistry of gold has been investigated intensively by many groups [1,2]. On the other hand, the catalysis of *organic* reactions by gold-catalysts has received only little attention, this is especially true for *homogeneous catalysis of organic reactions* by gold-catalysts [3–5]. The two reactions, that were appreciated most by the organic community are the asymmetric aldol reaction developed by Ito and coworkers [6–8] and the activation of C–C multiple bond for the addition of nucleophiles investigated by Utimoto and coworkers [9–11] and later by Teles et al. [12].

In the course of our investigation of the potential of gold for the catalysis of other organic reactions [13], we recently discovered an entirely new organic reaction that is catalyzed by $AuCl_3$ in acetonitrile [14]. In this reaction, a furan **1** that bears a terminal alkyne in suitable distance is converted into a trisubstituted phenol **2** (Scheme 1).

This is an interesting synthesis of highly substituted arenes, especially, if one takes into account that a positional selectivity in substitution reactions can be achieved in furans much more easily than in benzoid arenes [15].

For a successful reaction a substituent in the 5-position of the furan ring was crucial: in all examples that, we investigated so far, this substituent was only a simple methyl group. Now we wanted to turn to sterically more demanding and electronically different substituents to test the scope and eventual limitations of the method.

2. Results

We decided to test an aryl substituent. The substrate **6a** was synthesized in three steps from commercially available 5-(4-chlorophenyl)furfural **3a** by condensation with propargylamine, reduction of the

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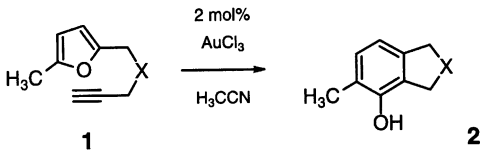
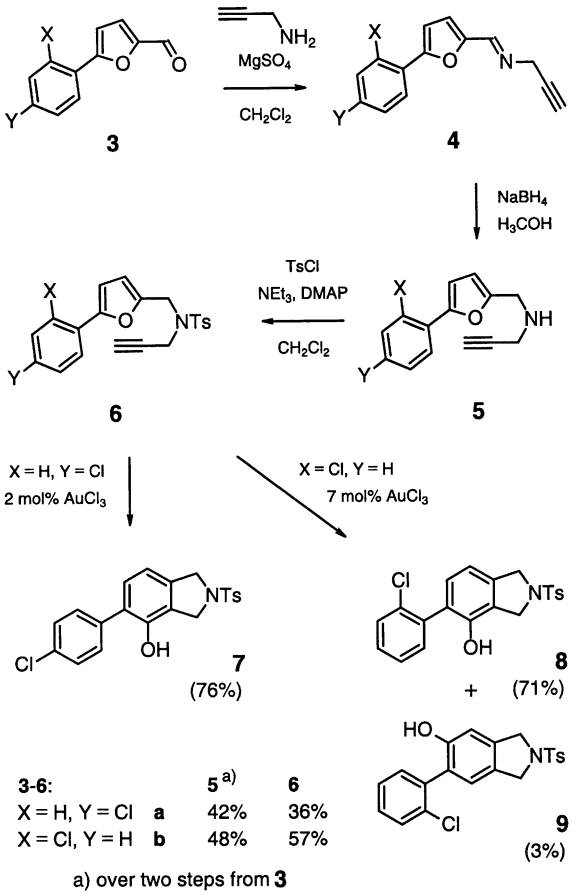


Scheme 1. Gold-catalyzed synthesis of phenols.

imine **4a** and tosylation of the amine **5a**. A crystal structure analysis of **6a** was obtained (Fig. 1) [16]. The chloro-substituted phenyl ring and the furyl ring are almost coplanar (only 13.5° twist between the planes). The nitrogen atom is pyramidalized. Most relevant for the reactivity is the relative arrangement of the furyl group and the alkynyl group which in the solid state structure of **6a** in fact (in an unfavorable way for the cyclization) point away from each other. A similar conformation resulted as a minimum from force field and semi-empirical calculations [17].

The cyclizations proceeded well, ^{1}H NMR spectra taken during the reaction show a clean reaction, the biaryl compound **7** was isolated in 76% yield (Scheme 2).

Then we turned towards a substrate that is sterically more hindered, the furan **6b**. It was available by a sequence analogous to **6a**. We also obtained a crystal structure analysis of **6b** (Fig. 2) [16]. Interestingly, **6a** and **6b** are isomorphous, both crystallize in the same space group with similar lattice constants and the molecules show almost identical conformations. In **6b**, the chloro-substituted phenyl ring and the furyl ring show a little stronger deviation from coplanarity (13.9°). This can be assigned to the Cl–H8 repulsion, which is slightly stronger than the H–H repulsion in



Scheme 2. Synthesis and conversion of phenyl-substituted derivatives (TsCl: *p*-toluenesulfonyl chloride, DMAP: 4-*N*,*N*-dimethylaminopyridine).

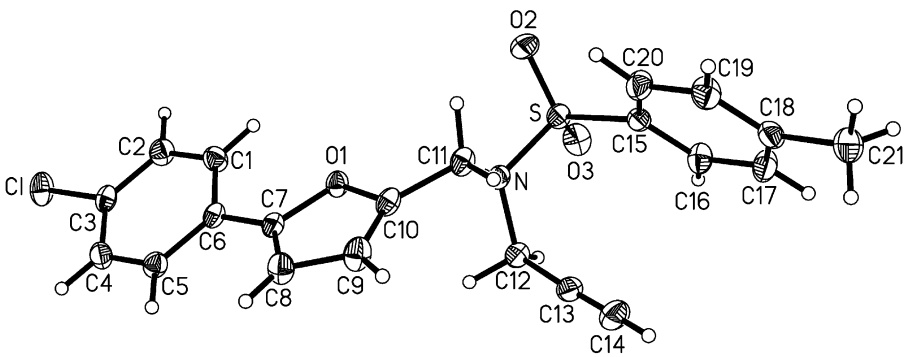


Fig. 1. ORTEP plot of compound **6a**.

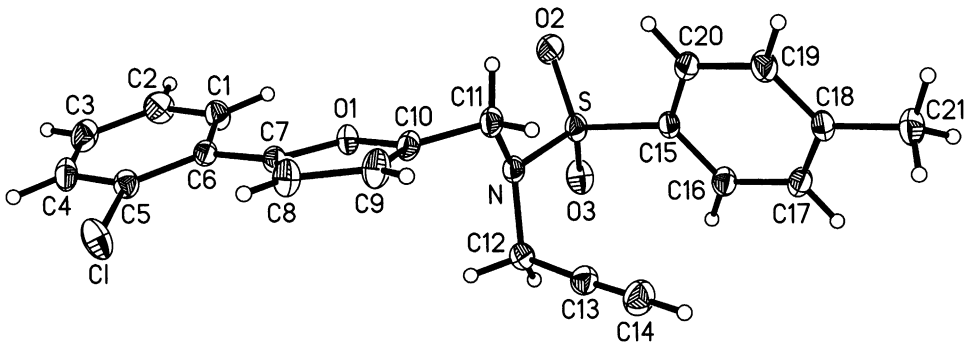
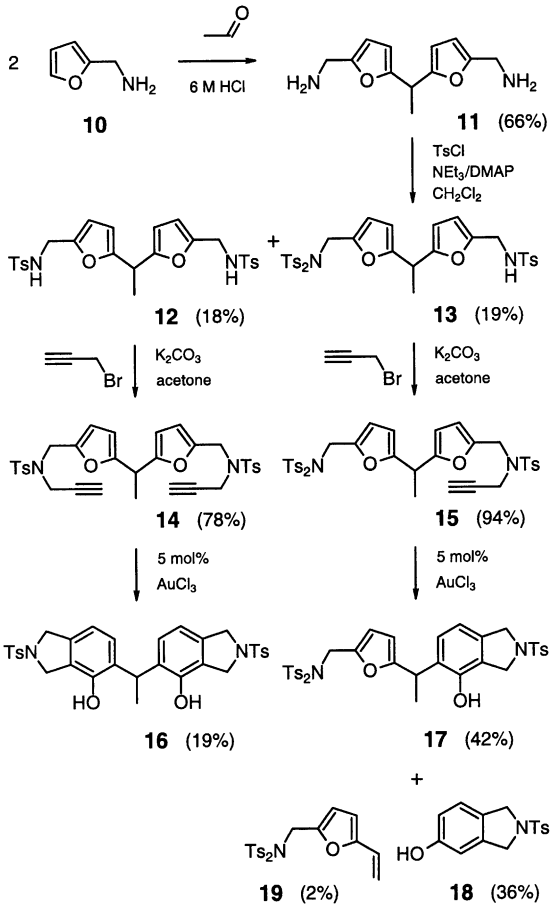


Fig. 2. ORTEP plot of compound **6b**.



Scheme 3. Synthesis and conversion of furfuryl-substituted derivatives (TsCl: *p*-toluenesulfonyl chloride, DMAP: 4-*N*,*N*-dimethylaminopyridine).

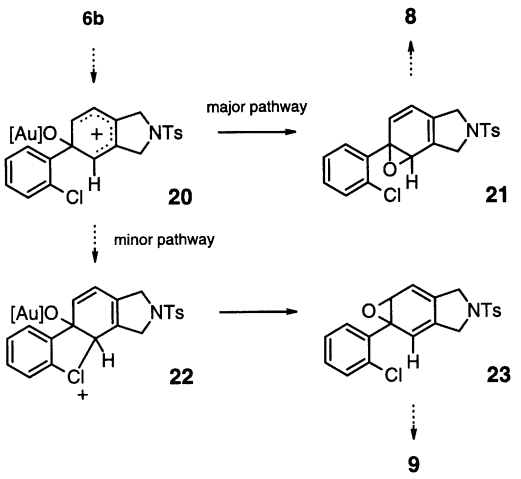
6a. In **6b**, nitrogen atom is also slightly pyramidalized, the furyl group and the alkynyl group point away from each other. Theses results were confirmed by calculations, too [17]. Again the gold-catalysis provided **8** in good yield. In addition, 3% of compound **9** was isolated.

Then we tested two substrates with furfuryl substituents. Tosylation of the known **11** (accessible from commercially available **10** in one step) [18] caused some selectivity problems and delivered two products, the ditosylate **12** and the tritosylate **13**. Both could be propargylated (**12**–**14** and **13**–**15**, Scheme 3).

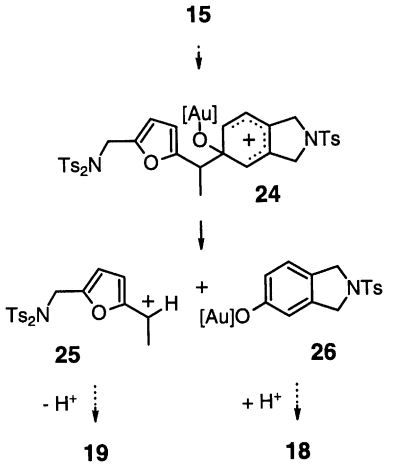
With the gold-catalyst, **14** gave only a low (19%) yield of the product of a twofold cyclization **16**, with **15** the yield of the product of the single cyclization **17** is only 42%, in addition 36% of **18** and 2% of **19** could be isolated.

3. Discussion

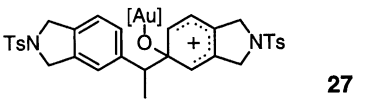
The clean conversion of **6a** and **6b** to the biaryls proves that the arene ring does not cause any difficulty in the reaction. This is not only true for electronic but also for steric factors, the product **6b** is an *o*,*o*-disubstituted biaryl-compound. Most remarkable is the observation of the constitutional isomer of the 'normal' product **8**, the compound **9**. The fact that **9** is observed with the *o*-chloro substituent exclusively suggests that this group might (of course only occasionally as **9** is a minor side-product) participate in the reaction as a neighboring group as shown in **22**. Intermediates like **20**–**23** have been suggested to be involved in the formation of the products [13] (Scheme 4).



Scheme 4. Suggestion for the formation of the side-product **9**; [Au] symbolizes a catalytical active gold complex of unknown composition.



Scheme 5. Suggestion for the formation of the side-products **18** and **19**; [Au] symbolizes a catalytical active gold complex of unknown composition.



Scheme 6. Possible intermediate of the second cyclization starting from **14**; [Au] symbolizes a catalytic active gold complex of unknown composition.

It will be interesting to investigate the participation of other intramolecular nucleophiles, that form new and stable bonds rather than reactive intermediates, in these reactions.

The low yield of **16** and **17** might be explained by similar intermediates. If one takes into account the good stabilization of a secondary furfuryl cation [19], one could imagine that from an intermediate pentadienyl cation **24** such a species could be formed by C–C bond cleavage. One product formed by such a process would be **18** (via **26**), the secondary furfuryl cation **25** then could loose a proton to form the olefin **19**. In the reaction of **14** side-products were formed, but their purification caused difficulties. However, in the reaction of the tritosylate **15** these side-products could be isolated and identified. The reason that more **18** than **19** was observed, is probably the high tendency of **19** to polymerize. Overall, the combined yield for both pathways (**17** and **18**) is 78%. Further evidence for this C–C bond cleavage was obtained from the mass spectromectic data of the compounds containing the furfuryl substituent, a similar cleavage of M^+ leading to the corresponding furfuryl cation was observed as a strong peak (Scheme 5).

The low yield of 19% for the twofold cyclization of **14** is equivalent to 44% for each cyclization and corresponds well to the 42% observed with **15**! As the secondary and electron-rich benzyl cation is also quite stable, the problem of the C–C bond cleavage is valid also for the substrate **27** after the first cyclization (Scheme 6).

In all these reactions, we applied 2–7 mol% of catalyst and a complete conversion of the starting material, usually after 1 day, was observed. As reported previously [14], 2 mol% would be sufficient and this amount corresponds to a turnover number (TON) of 50. In the case, where more catalyst was used, control experiments with small amounts of material were conducted on an NMR scale and then in the preparative experiment with more material more catalyst was used in order to save time.

4. Conclusions

The reactions of the aryl-substituted substrates show that substituents that are conjugated to the π-system of the furan do not cause difficulties. Substituents that can bear a cation-like the furfuryl substituent open a

competing pathway with a C–C bond cleavage. Thus reactions of both types of substrates deliver interesting information concerning the mechanism of the reaction, supporting the suggested carbeniumions as intermediates. In our hands, so far only gold had the ability to efficiently catalyze these and related transformations.

5. Experimental

^1H and ^{13}C spectra were recorded on a Bruker AM 250 spectrometer. Chemical shifts are reported down-field from $SiMe_4$ for ^1H and ^{13}C NMR spectroscopy. The assignments s ($C_{quart.}$), d (CH), t (CH_2), and q (CH_3) for the ^{13}C NMR signals are based on DEPT 135 and DEPT 90 spectra. IR spectra were measured on a Perkin Elmer 1600 spectrometer. Elemental analysis was carried out on a Foss-heraeus CHN-O-Rapid instrument. Melting points were measured on a Kofler hot-stage instrument. Column chromatography was conducted on Merck silica gel 60.

5.1. General procedures

5.1.1. Secondary amines from aldehydes and primary amines

The aldehyde, the amine and $MgSO_4$ were stirred in CH_2Cl_2 overnight. The mixture was filtered, the solvent evaporated in vacuo and taken up in absolute methanol. Then $NaBH_4$ was added in small portions and the resulting mixture was stirred overnight. Water was added and the product was extracted with CH_2Cl_2, the solvent was evaporated in vacuo and the crude product was purified by column chromatography.

5.1.2. Tosylamides from secondary amines

The amine, NEt_3 and DMAP were taken up in CH_2Cl_2 and TsCl was added in small portions. The mixture was stirred overnight, water was added and the product was extracted with CH_2Cl_2. The solvent was evaporated in vacuo and the crude product was purified by column chromatography.

5.1.3. Gold-catalyzed reactions

The substrate was dissolved in acetonitrile. To this solution the given amount of a solution of $AuCl_3$ in acetonitrile with a known concentration was added. The progress of the reaction was monitored either by ^1H NMR or thin layer chromatography. After complete consumption of the starting material the solvent was removed in vacuo and the crude product was purified by column chromatography.

5.1.4. Propargylation of tosylamides of primary amines

The tosylamine was dissolved in acetone, K_2CO_3 and propargyl bromide were added. After stirring overnight the acetone was removed in vacuo, the residue was taken up in water and extraced with CH_2Cl_2. After removal of the solvent the crude product was purified by column chromatography.

5.2. Syntheses

5.2.1. Synthesis of [5-(4-chlorophenyl)furan-2-ylmethyl]prop-2-ynylamine (5a)

705 mg (3.41 mmol) aldehyde **3a**, 188 mg (3.41 mmol) propargylamine, 800 mg (6.56 mmol) $MgSO_4$ and 70.3 mg (1.86 mmol) $NaBH_4$ gave, after purification by column chromatography on silica gel (hexane/ethyl acetate, 3:1), 351 mg (42%) **5a** as a yellow oil. R_f (hexane/ethyl acetate, 2:1) = 0.32; IR (film): $\nu = 3298\,cm^{-1}$, 1482, 1093, 1012, 829; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.77$(s, 1H), 2.27 (t, $J = 2.3$ Hz, 1H), 3.49 (d, $J = 2.3$ Hz, 2H), 3.95 (s, 2H), 6.32 (d, $J = 3.3$ Hz, 1H), 6.57 (d, $J = 3.3$ Hz, 1H), 7.31–7.36 (dm, $J = 8.6$ Hz, 2H), 7.56–7.61 (dm, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 36.9$ (t), 44.5 (t), 71.9 (d), 81.0 (s), 105.9 (d), 109.9 (d), 124.7 (d, 2C), 128.7 (d, 2C), 129.1 (s), 132.7 (s), 152.4 (s), 152.5 (s); MS (70 eV; *m/z* (%)): 245 (44), 216 (63), 191 (100); HRMS (70 eV): calcd. for $C_{21}H_{21}NO_5S_2$, 431.0861; found, 431.0859.

5.2.2. Synthesis of [5-(2-chlorophenyl)furan-2-ylmethyl]prop-2-ynylamine (5b)

1.00 g (4.84 mmol) aldehyde **3b**, 267 mg (4.84 mmol) propargylamine, 1.00 g (83.1 mmol) $MgSO_4$ and 91.6 mg (2.42 mmol) $NaBH_4$ gave, after purification by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane, 5:1:1), 572 mg (48%) **5b** as a yellow oil. R_f (hexane/ethyl acetate, 2:1) = 0.21; IR (film):$\nu = 3298\,cm^{-1}$, 2920, 2834, 1471, 1434, 1037, 1023, 795; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.92$ (s, 1H), 2.27 (t, $J = 2.4$ Hz, 1H), 3.49 (d, $J = 2.4$ Hz, 2H), 3.96 (s, 2H), 6.37 (d, $J = 3.4$ Hz, 1H), 7.06 (d, $J = 3.4$ Hz, 1H), 7.14–7.20 (m, 1H), 7.27–7.33 (m,

1H), 7.42 (dd, $J = 7.9$ Hz, 1.3 Hz, 1H), 7.86 (dd, $J = 7.9$ Hz, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 37.0$ (t), 44.5 (t), 71.8 (d), 81.3 (s), 109.6 (d), 111.5 (d), 126.6 (d), 127.6 (d), 127.7 (d), 129.0 (s), 129.8 (s), 130.5 (d), 149.5 (s), 152.5 (s); MS (70 eV; *m/z* (%)): 245 (43), 216 (100), 191 (79), 128 (31).

5.2.3. Synthesis of N-[5-(4-chlorophenyl)furan-2-ylmethyl]-4-methyl-N-prop-2-ynylbenzenesulfonamide (**6a**)

300 mg (1.22 mmol) amine **5a**, 233 mg (1.22 mmol) TsCl, 123 mg (1.22 mmol) NEt_3 and 7.5 mg (61.4 μmol) DMAP gave, after purification by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane, 20:1:1), 176 mg (36%) **6a** as colorless crystals. m.p. 142–144 °C; R_f (hexane/ethyl acetate, 2:1) = 0.42; IR (film):$\nu = 2970$, 1739, 1665, 1349, 1228, 1217, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.11$ (t, $J = 2.5$ Hz, 1H), 2.39 (s, 3H), 4.09 (d, $J = 2.5$ Hz, 2H), 4.50 (s, 2H), 6.38 (d, $J = 3.3$ Hz, 1H), 6.54 (d, $J = 3.3$ Hz, 1H), 7.29–7.35 (m, 4H), 7.46–7.50 (m, 2H), 7.73–7.76 (dm, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 21.4$ (q), 36.2 (t), 42.8 (t), 73.9 (d), 76.3 (s) 105.9 (d), 112.1 (d), 124.8 (d, 2C), 127.5 (d, 2C), 128.7 (d, 2C), 129.4 (d, 2C), 133.0 (s), 135.8 (s), 143.5 (s), 148.3 (s), 153.1 (s), 1 aryl s hidden; MS (70 eV; *m/z* (%)): 399 (4), 243 (10), 84 (100); $C_{21}H_{18}NO_3S$ (399.9): calcd. C 63.07, H 4.54, N 3.50; found C 62.85, H 4.67, N 3.38.

5.2.4. Synthesis of N-[5-(2-chlorophenyl)furan-2-ylmethyl]-4-methyl-N-prop-2-ynylbenzenesulfonamide (**6b**)

527 mg (2.33 mmol) amine **5b**, 533 mg (2.80 mmol) TsCl, 290 mg (2.87 mmol) NEt_3 and 14.2 mg (116 μmol) DMAP gave, after purification by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane, 20:1:1), 531 mg (57%) **6b** as colorless crystals. m.p. 131–132 °C; R_f (hexane/ethyl acetate, 2:1) = 0.40; IR (film):$\nu = 3294$ cm^{-1}, 1471, 1350, 1161, 1094, 1025, 893, 802; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.13$ (t, $J = 2.4$ Hz, 1H), 2.37 (s, 3H), 4.11 (d, $J = 2.4$ Hz, 2H), 4.53 (s, 2H), 6.42 (d, $J = 3.4$ Hz, 1H), 7.03 (d, $J = 3.4$ Hz, 1H), 7.02–7.32 (m, 4H), 7.40–7.43 (m, 2H), 7.67–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 21.4$ (q), 36.3 (t), 42.7 (t), 73.9 (d), 76.4 (s), 111.5 (d), 112.0 (d), 126.7 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.6 (s), 129.4 (d, 2C),129.8 (s), 130.5 (d, 2C), 135.8 (s), 143.5 (s), 148.0 (s), 150.3 (s); MS (70 eV; *m/z* (%)): 399 (1), 243 (2), 212 (3), 84 (100); $C_{21}H_{18}NO_3S$ (399.9): calcd. C 63.07, H 4.54, N 3.50; found C 62.90, H 4.65, N 3.45.

5.2.5. Synthesis of 5-(4-chlorophenyl)-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol-4-ol (**7**)

80.2 mg (201 μmol) furan **6a** and 24.5 mg of a 5.0% solution of $AuCl_3$ in CH_3CN (1.23 mg, 4.0 μmol $AuCl_3$, 2 mol%) gave, after purification by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane, 10:1:1), 61.1 mg (76%) **7** as colorless crystals. m.p. 181–185 °C; R_f (hexane/ethyl acetate, 2:1) = 0.32; IR (film): $\nu = 3418$ cm^{-1}, 2923, 1702, 1593, 1480, 1448, 1344, 1324, 1218, 1161, 1093, 1068, 1016, 804; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.33$ (s, 3H), 4.57 (s, 4H), 5.27 (s, 1H), 6.72 (d, $J = 7.7$ Hz, 1H), 7.01 (d, $J = 7.7$ Hz, 1H), 7.18–7.23 (m, 4H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 21.4$ (q), 51.6 (t), 53.9 (t), 114.7 (d), 123.3 (s), 126.0 (s), 127.5 (d, 2C), 129.5 (d, 2C), 129.7 (d, 2C), 130.0 (d), 130.2 (d, 2C), 133.5 (s), 134.1 (s), 134.4 (s), 137.9 (s), 143.6 (s), 147.3 (s); MS (70 eV; *m/z* (%)): 399 (29), 243 (100), 91 (43); HRMS (70 eV): calcd. for $C_{21}H_{18}ClNO_3S$, 399.0696; found, 399.0696.

5.2.6. Synthesis of 5-(2-chlorophenyl)-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol-4-ol (**8**) and 6-(2-chlorophenyl)-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol-5-ol (**9**)

320 mg (800 μmol) furan **6b** and 91.0 mg of a 20% solution of $AuCl_3$ in CH_3CN (18.2 mg, 60.0 μmol $AuCl_3$, 7 mol%) gave, after purification by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane, 10:0.5:5), 227 mg (71%) **8** as colorless crystals and 9.2 mg (3%) **9** as an colorless oil. **8**: m.p. 176–179 °C; R_f (hexane/ethyl acetate/dichloromethane, 5:1:5) = 0.28; IR (film): $\nu = 3424$ cm^{-1}, 1458, 1345, 1325, 1298, 1220, 1160, 1099, 1044, 1003, 814; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.35$ (s, 3H), 4.59 (s, 4H), 4.48 (s, 1H), 6.74 (d, $J = 7.7$ Hz, 1H), 6.98 (d, $J = 7.7$ Hz, 1H), 7.19–7.33 (m, 5H), 4.43–7.48 (m, 1H), 7.70–7.74 (dm, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 21.4$ (q), 51.6 (t), 54.0 (t), 114.3 (d), 123.1 (s),

124.6 (s), 127.4 (d, 2C), 127.5 (d), 129.7 (d, 2C), 129.9 (d), 130.2 (d), 130.5 (d), 132.0 (d), 133.6 (s), 133.9 (s), 134.2 (s), 138.3 (s), 143.5 (s), 147.5 (s); MS (70 eV; *m/z* (%)): 399 (35), 244 (100), 208 (33), 91 (35). **9**: R_f (hexane/ethyl acetate/dichloromethane, 5:1:5) = 0.18; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.42 (s, 3H), 4.58 (s, 2H), 4.62 (s, 2H), 4.79 (s, 1H), 6.80 (s, 1H), 6.95 (s, 1H), 7.25–7.38 (m, 5H), 7.48–7.53 (m, 1H), 7.78 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 21.4 (q), 53.0 (t), 53.5 (t), 109.8 (d), 124.3 (d), 125.6 (s), 127.3 (d), 127.5 (d, 2C), 128.0 (s), 129.7 (d), 129.8 (d, 2C), 130.0 (d), 131.9 (d), 133.5 (s), 133.8 (s), 134.8 (s), 137.9 (s), 143.5 (s), 152.3 (s); MS (EI); *m/z* (%): 399 (11) [M^+], 243 (74), 139 (100), 91 (91).

*5.2.7. Synthesis of C-{5-[1-(5-aminomethyl-furan-2-yl)-ethyl]-furan-2-yl}-methylamine (**11**)*

9.71 g (100 mmol) furfurylamine **10**, 2.42 g (55.0 mmol) acetaldehyde and 34 ml 6 N HCl gave according to the literature procedure [18] 7.28 g (66%) **11** as a red oil that was identified by proton NMR. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.47 (s, 4H), 1.50 (d, J = 7.2 Hz, 3H), 3.70 (s, 4H), 4.07 (q, J = 7.2 Hz, 1H), 5.87 (d, J = 3.1 Hz, 2H), 5.96 (d, J = 3.1 Hz, 2H).

*5.2.8. Synthesis of 4-methyl-N-{5-[1-(5-[N-(toluene-4-sulfonyl)aminomethyl]furan-2-yl)ethyl]furan-2-ylmethyl}benzenesulfonamide (**12**) and 4-methyl-N-{5-[1-(5-[N,N-di(toluene-4-sulfonyl)aminomethyl]furan-2-yl)ethyl]furan-2-ylmethyl}benzenesulfonamide (**13**)*

1.93 g (8.76 mmol) diamine **11**, 3.33 g (17.5 mmol) TsCl, 1.77 g (17.5 mmol) NEt_3 and 214 mg (1.75 mmol) DMAP gave, after purification by column chromatography on silica gel (hexane/ethyl acetate, 2:1), 869 mg (19%) **12** as a yellow oil and 1.06 g (18%) **13** as a yellow oil. **12**: R_f (hexane/ethyl acetate, 1:1) = 0.33; IR (film): ν = 3281 cm^{-1}, 2979, 2922, 1705, 1598, 1434, 1326, 1160, 1093, 1056, 1019, 814; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.33 (d, J = 7.2 Hz, 3H), 2.33 (s, 6H), 3.81 (q, J = 7.2 Hz, 1H), 4.03 (d, J = 6.0 Hz, 4H), 4.88 (t, J = 6.0 Hz, 2H), 5.74 (d, J = 3.2 Hz, 2H), 5.91 (d, J = 3.2 Hz, 2H), 7.15–7.19 (m, 4H), 7.62 (d, J = 8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 17.5 (q), 21.4 (q, 2C), 32.8 (d), 40.1 (t, 2C), 105.6 (d, 2C), 108.7 (d, 2C), 127.0 (d, 4C), 129.5 (d, 4C), 136.9 (s, 2C), 143.3 (s, 2C), 148.2 (s, 2C), 156.1 (s, 2C); $C_{26}H_{28}N_2O_6S_2$ (528.6): calcd. C 59.07, H 5.34, N 5.30; found C 59.31, H 5.61, N 5.37. **13**: R_f (hexane/ethyl acetate, 1:1) = 0.42; IR (film): ν = 3301 cm^{-1}, 2984, 2925, 1598, 1556, 1494, 1447, 1427, 1406, 1372, 1349, 1307, 1292, 1188, 1165, 1086, 1046, 1018, 949, 912, 815; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.32 (d, J = 7.2 Hz, 3H), 2.28 (s, 3H), 2.32 (s, 6H), 3.77 (q, J = 7.2 Hz, 1H), 4.00 (d, J = 6.0 Hz, 2H), 4.77 (s, 2H), 4.99 (t, J = 6.0 Hz, 1H), 5.74 (d, J = 3.2 Hz, 1H), 5.77 (d, J = 3.2 Hz, 1H), 5.88 (d, J = 3.2 Hz, 1H), 6.14 (d, J = 3.2 Hz, 1H), 7.07–7.18 (m, 6H), 7.55–7.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 17.3 (q), 21.3 (q), 21.5 (q, 2C), 32.6 (d), 40.0 (t), 44.9 (t), 105.4 (d), 105.5 (d), 108.6 (d), 111.0 (d), 126.9 (d, 2C), 128.0 (d), 129.3 (d, 4C), 129.4 (d, 6C), 137.0 (s, 2C), 143.0 (s), 144.5 (s, 2C), 147.1 (s), 148.3 (s), 155.8 (s), 156.3 (s); MS (FAB$^+$, nitrobenzyl alcohol, NaI; *m/z* (%)): 705 (40) [M + Na^+], 370 (1 0 0); $C_{33}H_{34}N_2O_8S_3$ (682.8): calcd. C 57.85, H 5.22; found C 58.05, H 5.23.

*5.2.9. Synthesis of 4-methyl-N-{5-[1-(5-[N-(prop-2-ynyl)-N-(toluene-4-sulfonyl)aminomethyl]furan-2-yl)ethyl]furan-2-ylmethyl}-N-(prop-2-ynyl)benzenesulfonamide (**14**)*

703 mg (1.33 mmol) ditosylate **12**, 316 mg (2.66 mmol) propargylbromide and 368 mg (2.66 mmol) K_2CO_3 gave, after column chromatography on silica gel (hexane/ethyl acetate, 3:1), 625 mg (78%) **14** as a yellow oil. R_f (hexane/ethyl acetate, 1:1) = 0.40; IR (film): ν = 3288 cm^{-1}, 2980, 2924, 1598, 1556, 1434, 1348, 1306, 1161, 1120, 1093, 1066, 1018, 9970, 892, 801; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.38 (d, J = 7.2 Hz, 3H), 1.99 (t, J = 2.5 Hz, 2H), 2.34 (s, 6H), 3.90 (q, J = 7.2 Hz, 1H), 3.92 (d, J = 2.5 Hz, 4H), 4.31 (s, 4H), 5.81 (d, J = 3.2 Hz, 2H), 6.11 (d, J = 3.2 Hz, 2H), 7.18–7.22 (m, 4H), 7.64 (d, J = 8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 17.72 (q), 21.39 (q, 2C), 32.92 (d), 35.99 (t, 2C), 42.74 (t, 2C), 73.80 (s, 2C), 76.31 (d, 2C), 105.76 (d, 2C), 110.65 (d, 2C), 127.59 (d, 4C), 129.33 (d, 4C), 135.77 (s, 2C), 143.47 (s, 2C), 147.03 (s, 2C), 156.61 (s, 2C); MS (FAB$^+$; *m/z* (%)): 604 (20), 627 (9), 396 (100); $C_{32}H_{32}N_2O_6S_2$ (604.8): calcd. C 63.56, H 5.33, N 4.63.; found C 63.57, H 5.44, N 4.70.

*5.2.10. Synthesis of 4-methyl-N-{5-[1-(5-[N,N-di(toluene-4-sulfonyl)aminomethyl]-furan-2-yl)ethyl]furan-2-ylmethyl}-N-(prop-2-ynyl)benzenesulfonamide (**15**)*

889 mg (1.30 mmol) tritosylate **13**, 171 mg (1.44 mmol) propargylbromide and 199 mg (1.44 mmol) K_2CO_3 gave, after purification by column chromatography on silica gel (hexane/ethyl acetate, 2:1), 876 mg (94%) as a yellow oil. R_f (hexane/ethyl acetate, 1:1) = 0.33; IR (film): $\nu = 2979\,cm^{-1}$, 1597, 1373, 1351, 1164, 1092, 1017, 815; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.35$ (d, $J = 7.2$ Hz, 3H), 1.98 (t, $J = 2.4$ Hz, 1H), 2.33 (s, 3H), 2.35 (s, 6H), 3.85 (q, $J = 7.2$ Hz, 1H), 3.94 (d, $J = 2.4$ Hz, 2H), 4.33 (s, 2H), 4.80 (s, 2H), 5.77 (d, $J = 3.2$ Hz, 1H), 5.83 (d, $J = 3.2$ Hz, 1H), 6.13 (d, $J = 3.2$ Hz, 1H), 6.15 (d, $J = 3.2$ Hz, 1H), 7.16–7.22 (m, 6H), 7.63–7.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 17.9$ (q), 21.4 (q), 21.5 (q, 2C), 32.9 (d), 36.0 (t), 42.8 (t), 44.8 (t), 73.7 (s), 76.7 (d), 105.9 (d, 2C), 110.7 (d), 111.1 (d), 127.6 (d, 2C), 128.0 (d, 4C), 129.3 (d, 6C), 135.8 (s), 137.0 (s, 2C), 143.4 (s), 144.5 (s, 2C), 147.0 (s), 147.1 (s), 156.3 (s), 156.5 (s); MS (FAB^+, nitrobenzylalcohol, NaI; *m/z* (%)): 743 (1 0 0) [$M + Na^+$], 512 (40), 418 (80), 396 (96), 370 (82); $C_{36}H_{36}N_2O_8S_3$ (720.9): calcd. C 59.98, H 5.03, N 3.89; found C 59.75, H 5.19, N 3.86.

*5.2.11. Synthesis of 5-{1-[4-hydroxy-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol-5-yl]ethyl}-4-hydroxy-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol (**16**)*

290 mg (479 μmol) dialkyne **14** and 68.4 mg of a 11% solution of $AuCl_3$ in CH_3CN (7.5 mg, 25 μmol $AuCl_3$, 5 mol%) gave, after purification by column chromatography on silica gel (hexane/ethyl acetate, 3:1), 54.3 mg (19%) of **16** as a yellow oil. R_f (hexane/ethyl acetate, 1:1) = 0.27; IR (film): $\nu = 3385\,cm^{-1}$, 1596, 1458, 1445, 1343, 1318, 1161, 1098, 1062, 1017, 915, 815; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.57$ (d, $J = 7.1$ Hz, 3H), 2.39 (s, 6H), 4.47–4.65 (m, 9H), 6.70 (d, $J = 7.9$ Hz, 2H), 6.84 (s, 2 H), 7.16 (d, $J = 7.9$ Hz, 2 H), 7.28 (d, $J = 7.9$ Hz, 4H), 7.72 (d, $J = 7.9$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 19.7$ (q), 21.3 (q, 2C), 29.0 (d), 51.6 (t, 2C), 53.7 (t, 2C), 115.1 (d, 2C), 123.2 (s, 2C), 126.7 (d, 2C), 127.4 (d, 4C), 129.7 (d, 4C), 130.6 (s, 2C), 133.2 (s, 2C), 135.8 (s, 2C), 143.7 (s, 2C), 147.6 (s, 2C); MS (FAB^+, nitrobenzylalcohol, NaI; *m/z* (%)): 627 (1 0 0) [$M + Na^+$], 173 (1 0 0); $C_{32}H_{32}N_2O_6S_2$ (604.8): calcd. C 63.56, H 5.33, N 4.63.; found C 63.51, H 5.33, N 4.51.

*5.2.12. Synthesis of N-(5-{1-[4-hydroxy-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol-5-yl]ethyl}furan-2-ylmethyl)-4-methyl-N-(toluene-4-sulfonyl)benezenesulfonamide (**17**), 2-(toluene-4-sulfonyl)-2,3-dihydro-1H-isoindol-5-ol (**18**) and 4-methyl-N-(toluene-4-sulfonyl)-N-(5-vinylfuran-2-ylmethyl)benzenesulfonamide (**19**)*

87.6 mg (122 μmol) alkyne **15** and 43.3 mg of a 4.3% solution of $AuCl_3$ in CH_3CN (1.86 mg, 6.14 μmol $AuCl_3$, 5 mol%) gave, after purification by column chromatography on silica gel (hexane/ethyl acetate, 3:1) 37.2 mg (42%) **17** as a yellow oil, 12.7 mg (36%) **18** as colorless crystals and, after further elution with hexane/ethyl acetate = 2:1, 2.1 mg (2%) of **19** as a colorless oil. **17**: R_f (hexane/ethyl acetate, 1:1) = 0.29; IR (film): $\nu = 3474\,cm^{-1}$, 1597, 1597, 1452, 1372, 1347, 1184, 1097, 1017, 911, 815; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.49$ (d, $J = 7.3$ Hz, 3 H), 2.37 (s, 3H), 2.39 (s, 6H), 4.12 (q, $J = 7.3$ Hz, 1H), 4.57 (s, 4H), 4.81 (s, 2H), 5.81 (s, 1H), 5.93 (d, $J = 3.1$ Hz, 1H), 6.22 (d, $J = 3.1$ Hz, 1H), 6.70 (d, $J = 7.8$ Hz, 1H), 6.99 (d, $J = 7.8$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 2H), 7.16–7.32 (m, 4H), 6.69–7.77 (m, 4H), 7.85 (d, $J = 8.4$ Hz, 2H); MS (FAB^+; *m/z* (%)): 720 (8)[M^+], 719 (6), 432 (100), 276 (93); HRMS (70 eV): calcd. for $C_{36}H_{36}N_2O_8S_3$, 717.1399; found, 717.1390. **18**: m.p. 175–177 °C; R_f (hexane/ethyl acetate, 1:1) = 0.48; IR (film): $\nu = 3406\,cm^{-1}$, 2920, 2845, 1598, 1500, 1459, 1337, 1285, 1159, 1095, 814; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 2.40$ (s, 3H), 4.53 (s, 4H), 5.10 (s, 1H), 6.64 (d, $J = 2.3$ Hz, 1H), 6.70 (dd, $J = 2.3$ Hz, 8.2 Hz, 1H), 7.00 (d, $J = 8, 2$ Hz, 1H), 7.31 (d, $J = 8.3$ Hz, 2 H), 7.74–7.78 (dm, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 21.3$ (q), 53.0 (t), 53.5 (t), 109.3 (d), 115.0 (d), 123.4 (d), 127.4 (d, 2C), 127.8 (s), 129.7 (d, 2C), 133.6 (s), 137.5 (s), 143.5 (s), 155.4 (s); MS (70 eV; *m/z* (%)): 289 (4)[M^+], 288 (6), 155 (1 0 0), 134 (79), 91 (48); $C_{15}H_{15}NO_3S$ (289.4): calcd. C 62.26, H 5.23, N 4.84; found C 62.25, H 5.45, N 4.63. **19**: R_f (hexane/ethyl acetate, 1:1) = 0.62; IR (film): $\nu = 1597\,cm^{-1}$, 1372, 1353, 1166, 1085, 1016, 946, 815; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 2.42$ (s, 6H), 4.91 (s, 2H), 5.12 (d, $J = 11.9$ Hz, 1H), 5.52 (d, $J = 17.4$ Hz, 1H), 6.09

(d, $J = 3.1$ Hz, 1H), 6.29 (d, $J = 3.1$ Hz, 1H), 6.35 (dd, $J = 11.9$ Hz, 17.4 Hz, 1H), 7.26 (d, $J = 8.3$ Hz, 4H), 7.80 (d, $J = 8.3$ Hz, 4H); MS (70 eV; *m*/*z* (%)): 431 (3), 276 (91), 91 (100); HRMS (70 eV): calcd. for $C_{21}H_{21}NO_5S_2$, 431.0861; found, 431.0859.

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