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Gold Catalysis: Chemoselective Indolin Synthesis in the Presence of Acrylate Units

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A sequence of an aza-Morita–Baylis–Hillman reaction, a simple sulfonamide propargylation, and a gold-catalyzed cycloisomerization delivers indoline derivatives with acrylate units in the side chain. The chemoselectivity in the last step is very high; out of the two C–C double bonds that are in equal distance to the alkyne, only the furan reacts, the acrylate neither participates in nor interferes with the gold catalysis.

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Introduction

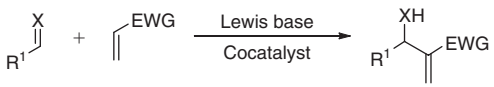
The impact of homogeneous gold catalysis on organic synthesis is continuously increasing,[1] one of the most popular reactions being the cyclization of en–ynes.[2a,b] In our group we developed the gold-catalyzed phenol synthesis (Scheme 1), which uses furan–yne substrates **1**, thus belongs to the family of en–yne cycloisomerization reactions and was the first reaction of that family of reactions reported in gold catalysis.[3a] Gold complexes convert these substrates into the phenols **2**, and this reaction is probably the most reliable transformation in the field of homogeneous gold catalysis, it has proven to be a powerful tool for the synthesis of various heterocycles such as dihydroisoindoles, tetrahydroisoquinolines, dihydroisobenzofurans and isochromanes, dihydroindoles, dihydrobenzofurans, chromanes, and tetrahydroquinolines.[3]

In these reactions, the functional group tolerance has been explored with only a very limited number of functional groups. Here we wanted to use the aza-Morita–Baylis–Hillman[4] reaction in order to modify furfurals **3** (Scheme 2), which can be prepared from renewable resources, and thus generate precursors **4** for the synthesis of the substrates **1** for gold catalysis. These substrates would have an α,β-unsaturated ester in the side chain, which would lead to a versatile unit for further functional group manipulation, but which also has to be investigated with regard to being tolerated in the gold-catalyzed step. The double-bond and the furan are positioned at a similar distance to the triple bond and thus could potentially compete. Since this Michael acceptor is an electron-poor unit, we were still hoping for a highly selective phenol synthesis.

Here we report our results on this short sequence that contains organocatalytic aza-Morita–Baylis–Hillman reactions and gold-catalyzed cycloisomerization chemistry.

Results and Discussion

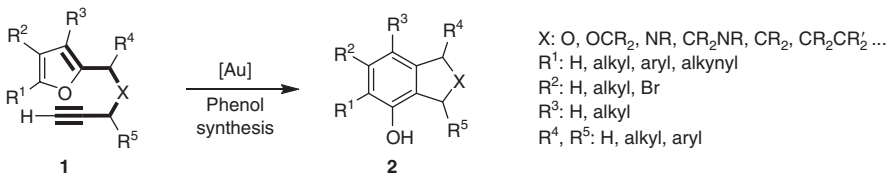
We started from the *N*-tosylimine of furfural. Following the work of Sasai et al.,[5] we tried triphenylphosphane as well as dimethylamino pyridine for the reaction with methyl vinyl ketone, and both conditions failed to deliver the product **4**. The same was true for the use of the use of N-heterocyclic carbenes.[6] After many more tests, we turned to a procedure by Adolfsson et al.[7] who generated the tosylimines in situ, use acrylic esters as Michael acceptors, and $La(OTf)_3$ in combination with 3-HDQ as catalysts. This finally gave access to the desired products **4a**–**d** in good yields (Scheme 3). In the 5-position of the furan ring alkyl



3 R^1: alkyl, aryl, hetaryl
X: O, NTs

4

Scheme 2. The Morita–Baylis–Hillman reaction (EWG = electron withdrawing group).



1 **2**

Scheme 1. The gold-catalyzed phenol synthesis.

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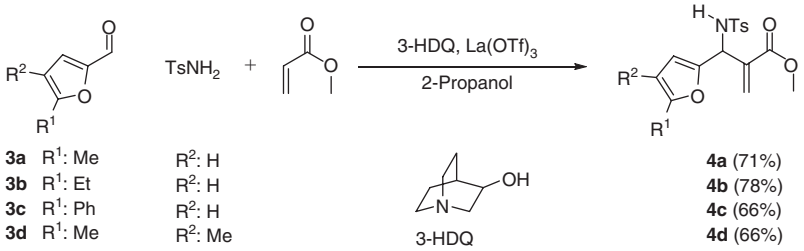
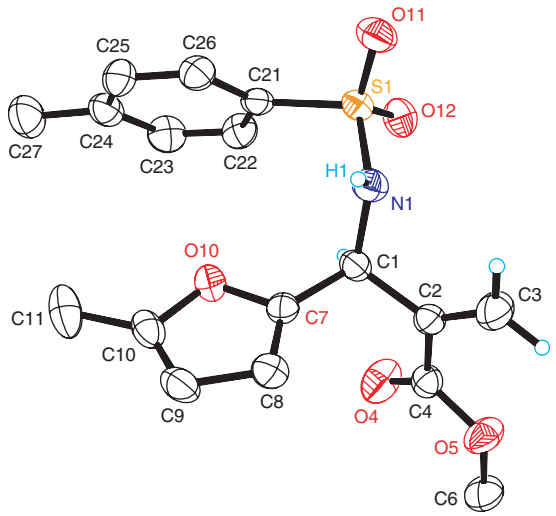
(**4a**, **4b**) and aryl (**4c**) groups are tolerated, 4,5-disubstituted furfural (**4d**) as well. However, heterosubstituents at the 5-position of the furan ring were not tolerated, 5-nitrofurural and 5-bromofurfural could not be converted.

All products were crystalline, they are shown in Fig. 1. All compounds (**4a**–**d**) form hydrogen-bonded dimers in the solid state. Three of these occupy a similar conformation in the solid state, only the tosyl group of **4c** is pointing in a different direction (see Accessory Publication).

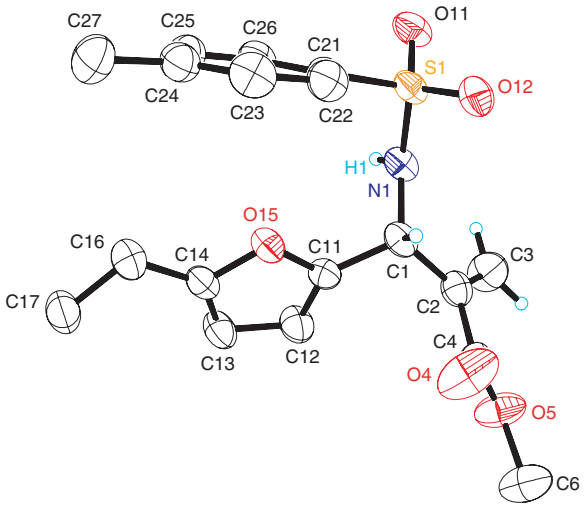
Efforts to achieve an asymmetric conversion with a tertiary amine catalyst like quinine or β-isocupreidin (Fig. 2) failed, again no significant conversion was observed.



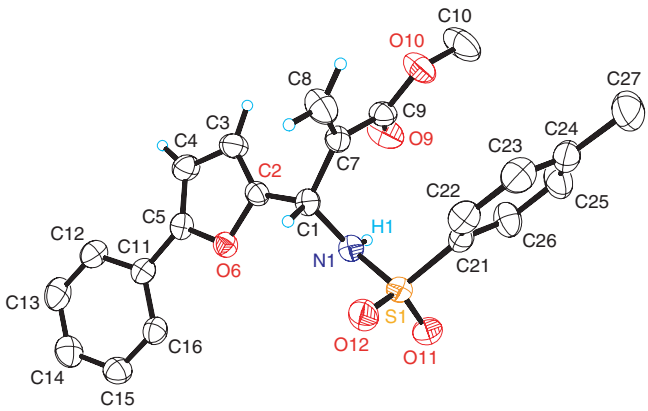
Scheme 3. Aza-Morita–Baylis–Hillman reaction of furfurals **3a**–**d**.



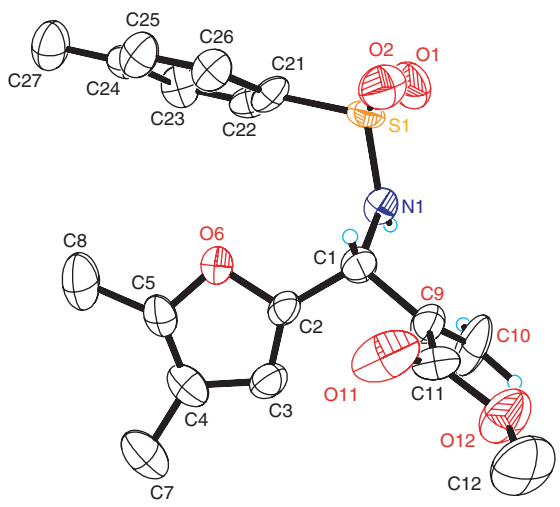
4a



4b



4c



4d

Fig. 1. Crystal structures of **4a**, **4b**, **4c**, and **4d**.

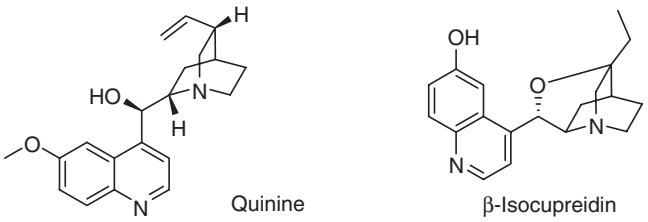


Fig. 2. Asymmetric organocatalysts tested.

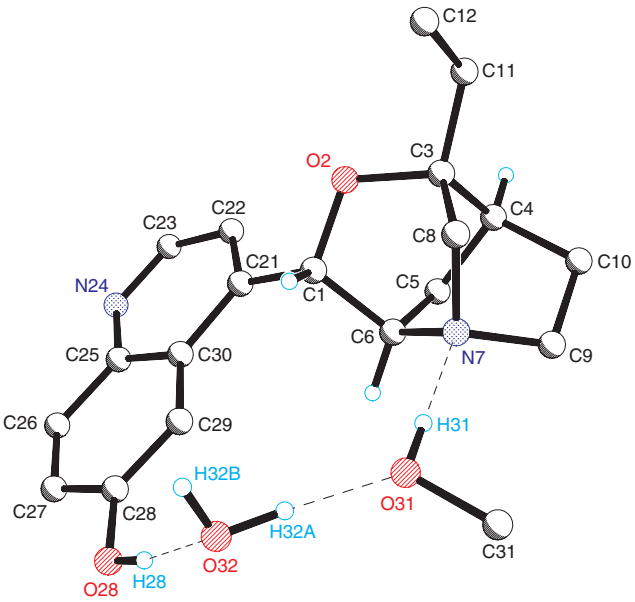


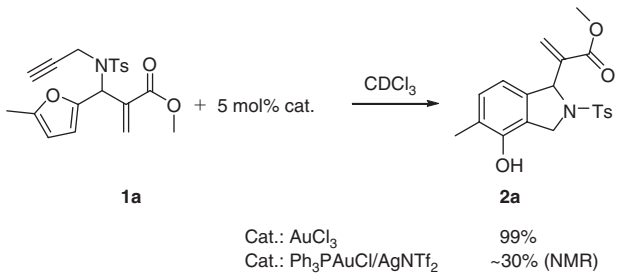
Fig. 3. Crystal structure analysis of isocupreidin with water and methanol.

In the course of the testing of these chiral catalysts, we were able to crystallize the β-isocupreidin with one molecule of water and one molecule of methanol to form an interesting hydrogen bond network (Fig. 3). This nicely shows an enzyme-like catalytic triad and might serve as a model for the orientation of the substrates at this catalyst.

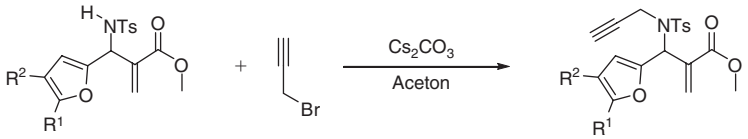
Now we turned to the propargylation step. We were delighted to observe that the tosylamide anions formed as nucleophiles by in-situ deprotonation with caesium carbonate did selectively react with propargyl bromide as the electrophile, and an intermolecular reaction with a second molecule **4** as a competing electrophile was observed. Again the products **1a**–**d** were formed in good yields (Scheme 4).

Once more, several crystal structure analyses were possible. In the solid state, all compounds occupy a conformation in which the two reaction partners, the furan and the alkyne, are close (Fig. 4, for a detailed comparison of the conformations see Accessory Publication).

Having the substrates for the gold catalysis in our hands, we first had to select the catalyst. A comparison of $[Ph_3PAu]NTf_2$



Scheme 5. Comparing gold(I) and gold(III) catalysts.



4a R^1: Me R^2: H
4b R^1: Et R^2: H
4c R^1: Ph R^2: H
4d R^1: Me R^2: Me

1a (94%)
1b (75%)
1c (74%)
1d (75%)

Scheme 4. Selective propargylation of **4a**–**d**.

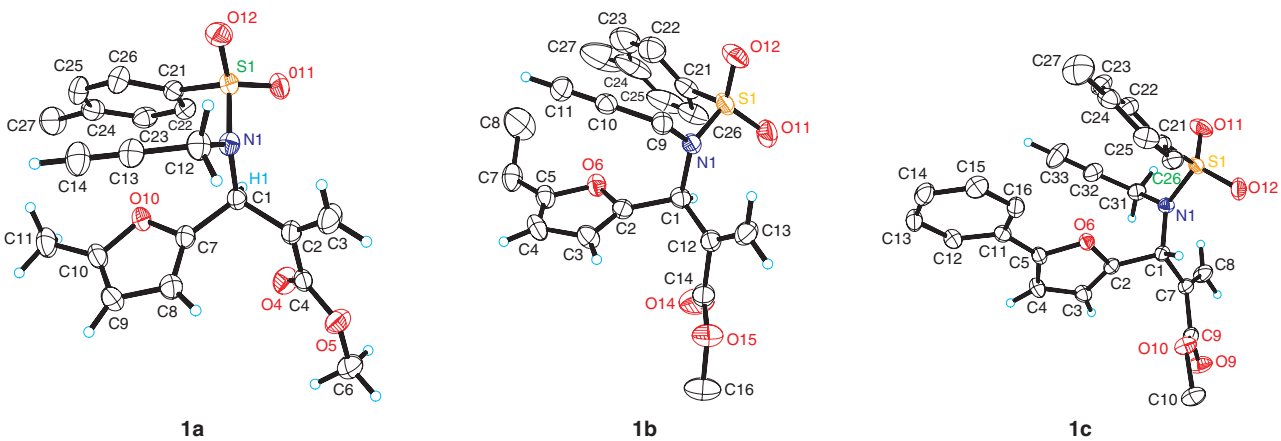
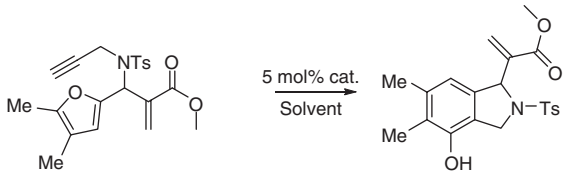


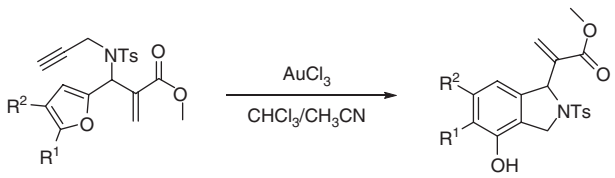
Fig. 4. Solid state structures of **1a**, **1b**, and **1c**.



1d **2d**

$[Ad_2{}^nBuP]_3AuNTf_2$, $CDCl_3$	~30% (NMR)
$AuCl_3$, $CDCl_3$	~30% (NMR)
$AuCl_3$, CD_3CN	96%

Scheme 6. Even **1d** selectively delivers only **2d**.



1a	R^1: Me	R^2: H	**2a** (99%)
1b	R^1: Et	R^2: H	**2b** (99%)
1c	R^1: Ph	R^2: H	**2c** (86%)
1d	R^1: Me	R^2: Me	**2d** (96%)

Scheme 7. Excellent chemoselectivity in the gold-catalyzed step.

and $AuCl_3$ clarified that for these substrates the simple $AuCl_3$ gives the best results (Scheme 5).

An extension of this catalyst testing to the dimethyl substrate **1d** gave similar results, but here the choice of acetonitrile as the solvent was crucial for a good conversion (Scheme 6). We were delighted by this result, as this type of dimethyl substrate can deliver mixtures of three products in gold catalysis.[3o]

The final results are summarized in Scheme 7. The high yield and selective conversion also apply to the conversion of **1b** and **1c**. In all cases very good yields were obtained, and this clearly shows that the acrylate unit in the side chain of the substrate does not interfere with the furan–yne cycloisomerization. So the chemoselectivity indeed could be directed with the help of the acceptor on the alkene. In addition, it was promising to observe that the acrylate in the product did not lead to any subsequent reactions under the conditions of the $AuCl_3$ catalysis.

The product **2a** was crystalline and single crystals for a X-ray crystal structure analysis could be obtained (Fig. 5). This is important proof for the proper structural assignment, as NMR analysis of the tetra-substituted benzene ring of the substrates **2** does not allow an unambiguous assignment of the sequence substituents.

A detailed proof of structure was also necessary for **2d**, here we could utilize NMR. Fig. 6 shows an inset of the HMBC spectrum of **2d**, the correlation peak of the benzylic carbon atom bearing the acrylate side chain (δ 66.19) with the aryl proton at δ 6.30 and the two olefinic protons at δ 6.07 and 6.23. In combination with the published spectroscopic data of the related substrate without the acrylate side chain,[3o] this allowed a safe assignment.

Finally, we wanted to explore whether a selective hydrogenation of **1** was possible. A hydrogenation with the Crabtree catalyst delivered **5** with a saturated side chain (Scheme 8). While the yield was very good, the diastereoselectivity was not, only a 12% diastereoisomeric excess (as detected by gas chromatography/mass spectrometry (GC/MS)) were obtained.

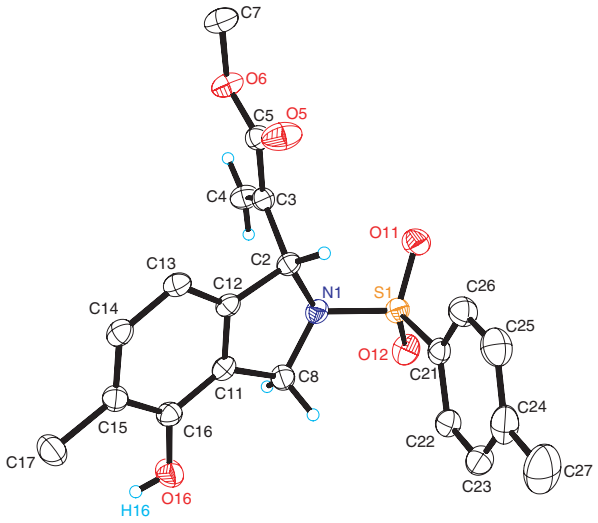


Fig. 5. Solid state structure of **2a**.

This mixture of both diastereomers was carried through. Propargylation to **6** and finally gold-catalyzed ring-closure to **7** proved successful, again in very good yield.

The products **6** and **7** were crystalline and single crystals for an X-ray crystal structure analysis could be obtained (Fig. 7). Compound **6** occupies a conformation similar to the substrates **1**. In the structure of **7** there are four independent molecules, the space group is $P2_1$. There is no additional element of symmetry, the crystals were enantiomerically pure. Because **7** is racemic, a conglomerate of enantiomeric crystals was formed.

Conclusions

A short and high-yielding sequence delivering functionalized indolines as interesting building blocks for further synthetic manipulation has been developed. It combines organocatalysis, a simple propargylation, and gold catalysis. The Michael acceptor in the side chain does not cause selectivity problems in the gold-catalyzed step, a principle that might have a broad scope for other gold-catalyzed reactions in the future.

Experimental

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Propan-2-ol was dried by distillation over metallic sodium. Flash chromatography was performed on Macherey & Nagel silica gel (0.043–0.063 mm). NMR spectra were recorded with Bruker ARX 250, Bruker Avance ARX 300, or Bruker Avance DRX 500 spectrometers. Chemical shifts are reported as δ values relative to the solvent peak. Melting points are uncorrected. Mass spectrometry (MS) analyses were performed on a JEOL JMS-700 (electron ionization (EI), 70 eV), JEOL JMS-700 (fast atom bombardment (FAB)), or a Finnigan MAT TSQ 700 (electrospray ionization (ESI)). Crystal structure analyses were conducted on a Bruker APEX instrument.

General Procedure A: Aza-Morita–Baylis–Hillman One-Pot Synthesis

Exemplified for the formation of methyl 2-((5-methylfuran-2-yl) (4-methylphenylsulfon amido)methyl)acrylate (**4a**): In a flame dried flask, tosylamide (1.71 g, 10.0 mmol), 3-HDQ (190.5 mg, 1.50 mmol), and $La(OTf)_3$ (117 mg, 200 μmol) were

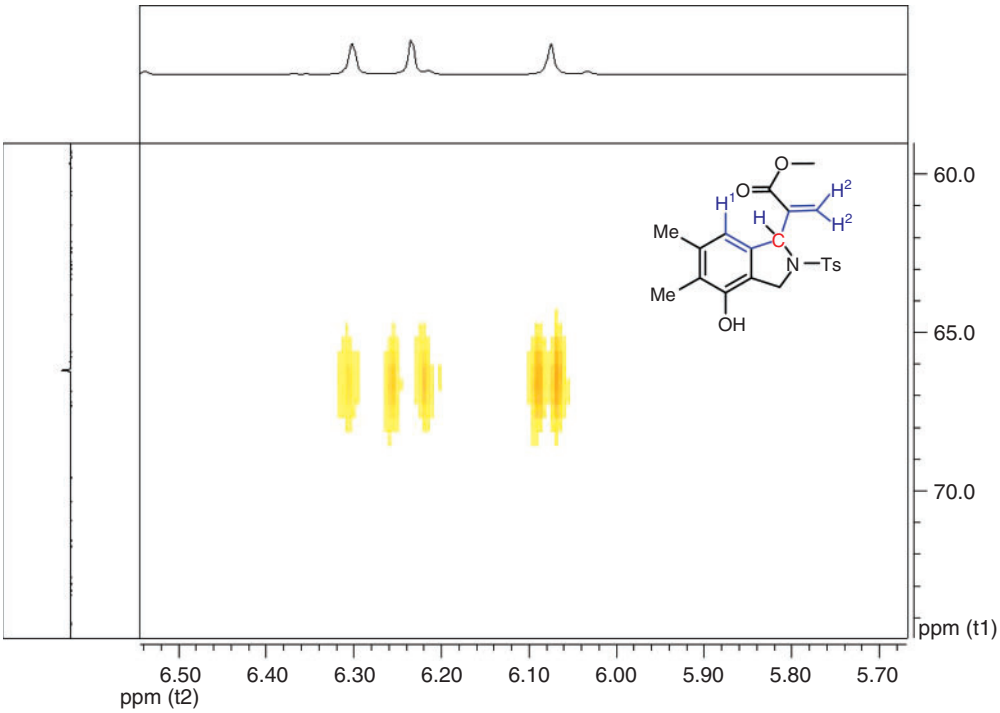
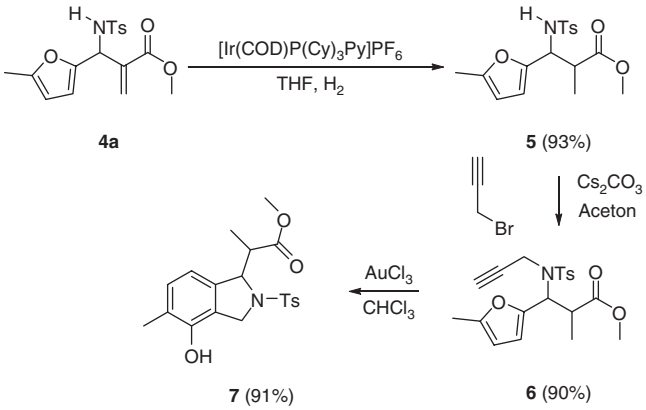


Fig. 6. Section of the HMBC spectrum of **2d**.



Scheme 8. In reactions with reduced side chains selectivity issues are irrelevant.

measured together with molecular sieves (4 Å, 900 mg). Propan-2-ol (2.5 mL), 5-methylfufural (1.21 g, 10.0 mmol), and methyl acrylate (860 mg, 10.0 mmol) were added, and the reaction mixture was stirred for 16 h at ambient temperature. The mixture was filtered through a thin layer of Celite, which was rinsed three times with tetrahydrofuran (THF). The solvent was evaporated. The crude reaction mixture was separated on silica gel (eluent: petroleum ether (PE)/ethyl acetate (EE)/dichloromethane (DCM): 6/1/1) followed by recrystallization in *n*-pentane to afford **4a**: Yield: 2.47 g (7.07 mmol, 71%). R_f 0.27 (PE/EE/DCM: 6/1/1), mp 117°C. ν_{max} (KBr)/cm^{-1} 3284, 1718, 1437, 1326, 1289, 1274, 1196, 1187, 1162, 1092, 1064, 1023, 966, 931, 816, 683, 657, 568, 555. δ_H (CD_3CN, 500 MHz) 2.08 (s, 3H), 2.39 (s, 3H), 3.63 (s, 3H), 5.36 (d, *J* 8.8, 1H), 5.80 (d, *J* 3.0, 1H), 5.85 (s, 1H), 5.88 (d, *J* 3.0, 1H), 6.20 (s, 1H), 6.30 (d, *J* 8.8, 1H), 7.32 (d, *J* 8.2, 2H), 7.65 (d, *J* 8.2, 2H). δ_C (CD_3CN, 125 MHz) 13.28 (q), 21.40 (q), 52.62 (q), 52.78 (d), 107.17 (d), 109.52 (d), 118.21 (d), 127.85 (d, 2C), 130.32 (d, 2C), 138.96 (s), 144.43 (s), 150.51 (s), 153.09 (s), 166.45 (s). *m/z* (EI$^+$) 349 [M]$^+$, 318 [M − CH_3O]$^+$, 194 [M − $C_7H_7O_2S$]$^+$. (Found: C 58.44, H 5.46, N 3.97, S 8.97; 349.0992 [M]$^+$. Calcd for $C_{17}H_{19}NO_5S$: C 58.44, H 5.48, N 4.01, S 9.18%; 349.0984.) λ_{max} (0.19 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 258 (3.98), 264 (3.45), 276 (3.23).

Crystal data and structure refinement for (**4a**): colourless crystal (plate), dimensions 0.30 × 0.22 × 0.06 mm^3, crystal system triclinic, space group $P\bar{1}$, *Z* 2, *a* 8.9510(3) Å, *b* 9.8556(3) Å, *c* 10.7560(3) Å, α 95.9100(10)°, β 108.3730(10)°, γ 102.9480(10)°, *V* 862.01(5) Å^3, ρ 1.346 g cm^{-3}, *t* 200(2) K, θ_{max} 27.47°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 8723 reflections measured, 3899 unique (*R*(int) 0.0507), 2496 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.21 mm^{-1}, T_{min} 0.94, T_{max} 0.99, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 224 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H1 at N1, which was refined isotropically, goodness of fit 1.02 for observed reflections, final residual values $R_1(F)$ 0.057, $wR(F^2)$ 0.115 for observed reflections, residual electron density −0.33 to 0.37 e Å^{-3}.

Methyl-2-[(5-ethylfuran-2-yl){[(4-methylphenyl)sulfonyl]amino}methyl]prop-2-enoat (**4b**): Yield: 1.42 g (3.91 mmol, 78%). R_f 0.23 (PE/EE/DCM: 6/1/1). ν_{max} (KBr)/cm^{-1} 3259, 1718, 1553, 1437, 1327, 1304, 1289, 1273, 1186, 1163, 1094, 1062, 1021, 959, 935, 817, 683, 659, 555. δ_H ($CDCl_3$, 300 MHz) 1.08 (t, *J* 7.5, 3H), 2.39 (s, 3H), 2.44 (q, *J* 7.5, 2H), 3.66 (s, 3H), 5.35 (d, *J* 8.3, 1H), 5.65 (d, *J* 8.3, 1H), 5.75 (d, *J* 3.1, 1H), 5.84 (s, 1H), 5.89 (d, *J* 3.1, 1H), 6.22 (s, 1H), 7.23 (d, *J* 8.2, 2H), 7.69 (d, *J* 8.2, 2H). δ_C ($CDCl_3$, 75 MHz) 11.08 (q), 21.10 (q), 21.41 (t), 51.97 (q), 53.21 (d), 104.70 (d), 108.05 (d),

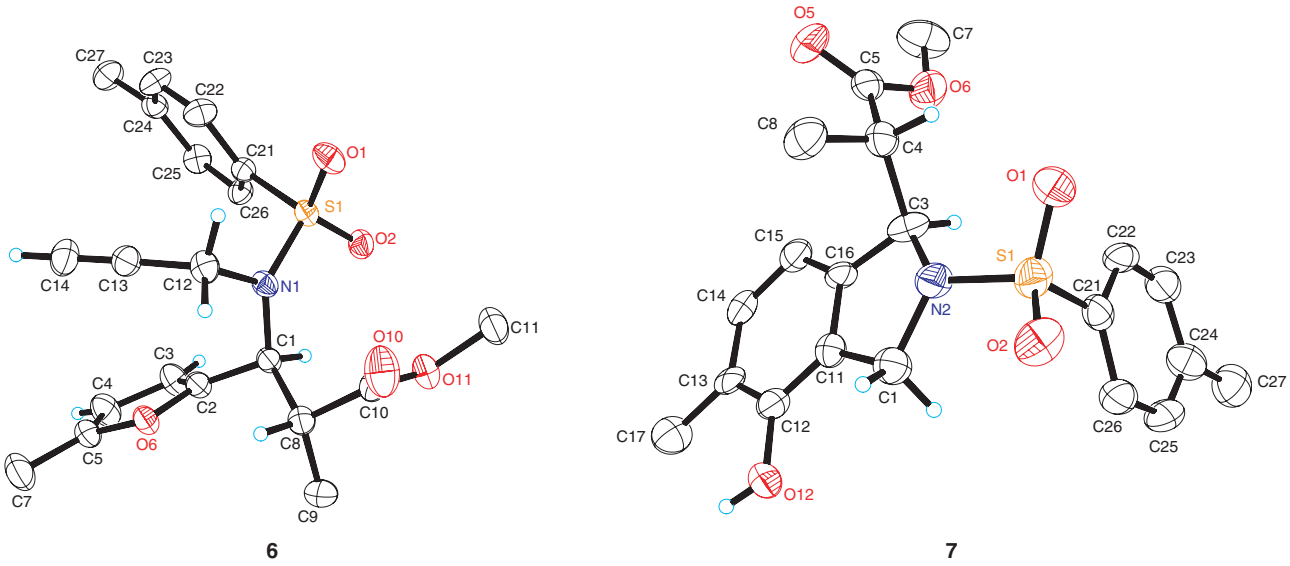


Fig. 7. Solid state structures of **6** and **7**.

127.15 (d, 2C), 127.86 (t), 129.30 (d, 2C), 137.24 (s), 137.58 (s), 143.17 (s), 148.99 (s), 157.65 (s), 165.63 (s). *m/z* (EI^+) 363 $[M]^+$, 332 $[M - CH_3O]^+$, 208 $[M - C_7H_7O_2S]^+$. (Found: 364.12132 $[M+H]^+$. Calcd for $C_{18}H_{22}NO_5S$: 364.12187.) λ_{max} (0.164 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 262 (3.12), 274 (2.95), 326 (3.42).

Crystal data and structure refinement for (**4b**): colourless crystal (polyhedron), dimensions 0.38 × 0.23 × 0.07 mm^3, crystal system triclinic, space group $P\bar{1}$, Z 2, a 9.3813(11) Å, b 9.8710(12) Å, c 11.2205(14) Å, α 96.796(2)°, β 111.814(2)°, γ 103.903(2)°, V 911.20(19) $Å^3$, ρ 1.325 g cm^{-3}, t 200(2) K, θ_{max} 28.32°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 9617 reflections measured, 4487 unique (R(int) 0.0206), 3982 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.20 mm^{-1}, T_{min} 0.93, T_{max} 0.99, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 233 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H1 at N1, which was refined isotropically, goodness of fit 1.12 for observed reflections, final residual values $R_1(F)$ 0.052, $wR(F^2)$ 0.125 for observed reflections, residual electron density −0.27 to 0.47 e $Å^{-3}$.

Methyl-2-[{[(4-methylphenyl)sulfonyl]amino}(5-phenylfuran-2-yl)methyl]prop-2-enoat (**4c**): Yield: 1.36 g (3.31 mmol, 66%). R_f 0.14 (PE/EE/DCM: 7/1/1), mp 136°C. ν_{max} (KBr)/cm^{-1} 3441, 3289, 1715, 1446, 1331, 1306, 1286, 1204, 1163, 1092, 1080, 1023, 815, 765, 705, 692, 681, 666, 563, 549. δ_H ($CDCl_3$, 300 MHz) 2.32 (s, 3H), 3.70 (s, 3H), 5.46 (d, J 9.1, 1H), 5.75 (d, J 9.1, 1H), 5.93 (s, 1H), 6.12 (d, J 3.3, 1H), 6.30 (s, 1H), 6.43 (d, J 3.3, 1H), 7.19 (d, J 8.1, 2H), 7.32 (m, 5H), 7.70 (d, J 8.1, 2H). δ_C ($CDCl_3$, 75 MHz) 21.40 (q), 52.12 (q), 53.49 (d), 105.65 (d), 106.65 (d), 123.60 (d, 2C), 127.09 (d, 2C), 127.46 (d), 128.32 (t), 128.51 (d, 2C), 129.45 (d, 2C), 130.21 (d), 137.03 (s), 137.51 (s), 143.36 (s), 150.55 (s), 153.69 (s), 165.16 (s). *m/z* (EI^+) 411 $[M]^+$, 380 $[M - CH_3O]^+$, 256 $[M - C_7H_7O_2S]^+$. (Found: 411.1090 $[M]^+$. Calcd for $C_{22}H_{21}NO_5SNa$: 411.1140.) λ_{max} (0.164 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 288 (4.29), 302 (4.13).

Crystal data and structure refinement for (**4c**): colourless crystal (polyhedron), dimensions 0.30 × 0.16 × 0.06 mm^3, crystal system triclinic, space group $P\bar{1}$, Z 2, a 10.1989(4) Å, b 10.6847(3) Å, c 10.7835(4) Å, α 66.4550(10)°, β 75.1010(10)°, γ 76.2380(10)°, V 1028.86(6) $Å^3$, ρ 1.328 g cm^{-3}, t 200(2) K, θ_{max} 27.50°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 10 482 reflections measured, 4685 unique (R(int) 0.0566), 3052 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.19 mm^{-1}, T_{min} 0.95, T_{max} 0.99, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 268 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H1 at N1, which was refined isotropically, goodness of fit 1.02 for observed reflections, final residual values $R_1(F)$ 0.057, $wR(F^2)$ 0.117 for observed reflections, residual electron density −0.34 to 0.24 e $Å^{-3}$.

Methyl-2-[(4,5-dimethylfuran-2-yl){[(4-methylphenyl)sulfonyl]amino}methyl]prop-2-enoate (**4d**): Yield: 1.20 g (3.30 mmol, 66%). R_f 0.11 (PE/EE/DCM: 8/1/1), mp 64°C. ν_{max} (KBr)/cm^{-1} 3433, 3292, 1722, 1619, 1574, 1441, 1327, 1297, 1283, 1157, 1091, 1058, 955, 822, 811, 704, 677, 661, 560. δ_H ($CDCl_3$, 300 MHz) 1.77 (s, 3H), 1.99 (s, 3H), 2.39 (s, 3H), 3.67 (s, 3H), 5.29 (d, J 9.0, 1H), 5.56 (d, J 9.0, 1H), 5.76 (s, 1H), 5.82 (s, 1H), 6.21 (s, 1H), 7.22 (d, J 8.1, 2H), 7.67 (d, J 8.1, 2H). δ_C ($CDCl_3$, 75 MHz) 9.64 (q), 11.10 (q), 21.43 (q), 51.99 (q), 53.25 (d), 110.73 (d), 114.72 (s), 127.20 (d, 2C), 127.81 (t), 129.24 (d, 2C), 137.16 (s), 143.14 (s), 147.21 (s), 147.77 (s), 154.51 (s), 165.66 (s). *m/z* (EI^+) 363 $[M]^+$, 332 $[M - CH_3O]^+$, 208 $[M - C_7H_7O_2S]^+$. (Found: 363.1123 $[M]^+$. Calcd for $C_{18}H_{21}NO_5S$: 363.1140.) λ_{max} (0.099 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 336 (2.87).

Crystal data and structure refinement for (**4d**): colourless crystal (polyhedron), dimensions 0.35 × 0.15 × 0.03 mm^3, crystal system orthorhombic, space group $Pna2_1$, Z 8,

a 39.005(6) Å, *b* 5.3223(9) Å, *c* 17.744(3) Å, α 90°, β 90°, γ 90°, *V* 3683.5(10) Å^3, ρ 1.311 g cm^{-3}, *t* 200(2) K, θ_{max} 19.81°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 15 941 reflections measured, 3313 unique (*R*(int) 0.1021), 3020 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.20 mm^{-1}, T_{min} 0.93, T_{max} 0.99, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 471 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H1 at N1, which were refined restrained, Flack absolute structure parameter 0.0(2), goodness of fit 1.21 for observed reflections, final residual values $R_1(F)$ 0.078, $wR(F^2)$ 0.137 for observed reflections, residual electron density: 0.24 to 0.22 e Å^{-3}.

General Procedure B: Propargylation

Exemplified by the formation of methyl 2-((4-methyl-*N*-(prop-2-ynyl)phenylsulfon amido) (5-methylfuran-2-yl)methyl) acrylate (**1a**): Compound **4a** (349 mg, 1.00 mmol) was dissolved in acetone (2 mL), and Cs_2CO_3 (390 mg, 1.20 mmol) and 3-bromoprop-1-yne (295 mg, 2.00 mmol) were added and the mixture was stirred at ambient temperature for 2 h. After filtration the solvent was removed under reduced pressure and the residue was separated on silica gel (eluent: PE/EE/DCM: 6/1/1) to afford **1a**: Yield: 364 mg (940 µmol, 94%). R_f 0.33 (PE/EE/DCM: 6/1/1), mp 78°C. ν_{max} (KBr)/cm^{-1} 3256, 1720, 1434, 1346, 1336, 1320, 1286, 1277, 1161, 1154, 1119, 1090, 1056, 941, 882, 774, 675, 650, 561, 545. δ_H ($CDCl_3$, 300 MHz) 1.97 (t, *J* 2.4, 1H), 2.09 (s, 3H), 2.42 (s, 3H), 3.96 (s, 3H), 3.99 (d, *J* 16, *J* 2.4, 2H), 5.81 (d, *J* 3.0, 1H), 5.98 (d, *J* 3.0, 1H), 5.99 (d, *J* 1.5, 1H), 6.09 (s, 1H), 6.43 (d, *J* 1.5, 1H), 7.27 (d, *J* 7.8, 2H), 7.79 (d, *J* 7.8, 2H). δ_C ($CDCl_3$, 75 MHz) 13.41 (q), 21.51 (q), 34.76 (t), 52.08 (q), 55.77 (d), 71.93 (d), 78.15 (s), 106.41 (d), 111.15 (d), 127.84 (t), 127.91 (d, 2C), 129.17 (d, 2C), 136.81 (s), 137.37 (s), 143.38 (s), 147.55 (s), 152.43 (s), 165.99 (s). (Found: 388.12132 $[M+H]^+$. Calcd for $C_{20}H_{22}NO_5S$: 388.12187.) λ_{max} (0.052 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 266 (3.21), 274 (3.36).

Crystal data and structure refinement for (**1a**): colourless crystal (polyhedron), dimensions 0.40 × 0.20 × 0.13 mm^3, crystal system triclinic, space group $P\bar{1}$, *Z* 2, *a* 6.9365(2) Å, *b* 8.0983(2) Å, *c* 17.7720(5) Å, α 86.4660(10)°, β 81.4060(10)°, γ 76.6670(10)°, *V* 960.12(5) Å^3, ρ 1.340 g cm^{-3}, *t* 200(2) K, θ_{max} 27.48°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 9805 reflections measured, 4349 unique (*R*(int) 0.0311), 3525 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.20 mm^{-1}, T_{min} 0.92, T_{max} 0.97, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 247 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.03 for observed reflections, final residual values $R_1(F)$ 0.038, $wR(F^2)$ 0.096 for observed reflections, residual electron density −0.39 to 0.32 e Å^{-3}.

Methyl-2-[(5-ethylfuran-2-yl){[(4-methylphenyl)sulfonyl](prop-2-in-1-yl)amino}methyl]prop-2-enoate (**1b**): Yield: 300 mg (748 µmol, 75%), R_f 0.36 (PE/EE/DCM: 6/1/1), mp 54°C. δ_H ($CDCl_3$, 500 MHz) 1.05 (t, *J* 7.5, 3H), 1.94 (t, *J* 2.4, 1H), 2.41 (s, 3H), 2.42 (q, *J* 7.5, 2H), 3.69 (s, 3H), 3.97 (dd, *J* 15, *J* 2.4, 2H), 3.98 (d, *J* 2.4, 1H), 5.81 (d, *J* 3.1, 1H), 5.97 (d, *J* 3.1, 1H), 5.99 (d, *J* 1.7, 1H), 6.09 (s, 1H), 7.27 (d, *J* 8.3, 2H), 7.79 (d, *J* 8.3, 2H). δ_C ($CDCl_3$, 125 MHz) 11.97 (q), 21.20 (t), 21.49 (q), 34.66 (t), 52.06 (q), 55.75 (d), 71.85 (d), 78.65 (s), 104.84 (d), 110.85 (d), 127.70 (d, 2C), 127.87 (t), 129.17 (d, 2C), 136.81 (s), 137.42 (s), 143.38 (s), 147.42 (s), 158.07 (s), 165.98 (s). (Found: 402.1357 $[M+H]^+$. Calcd for $C_{21}H_{23}NO_5SNa$: 402.1195.)

Crystal data and structure refinement for (**1b**): colourless crystal (polyhedron), dimensions 0.42 × 0.20 × 0.09 mm^3, crystal system monoclinic, space group *C*2/*c*, *Z* 8, *a* 28.302(3) Å, *b* 10.5741(13) Å, *c* 16.590(2) Å, α 90°, β 123.602(3)°, γ 90°, *V* 4135.2(9) Å^3, ρ 1.290 g cm^{-3}, *t* 200(2) K, θ_{max} 28.38°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 21 212 reflections measured, 5156 unique (*R*(int) 0.0557), 4130 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.19 mm^{-1}, T_{min} 0.93, T_{max} 0.98, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 256 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.20 for observed reflections, final residual values $R_1(F)$ 0.078, $wR(F^2)$ 0.149 for observed reflections, residual electron density −0.35 to 0.44 e Å^{-3}.

Methyl-2-[{[(4-methylphenyl)sulfonyl](prop-2-in-1-yl)amino}(5-phenylfuran-2-yl)methyl]prop-2-enoate (**1c**): Yield: 1.10 g (2.45 mmol, 74%). R_f 0.38 (PE/EE/DCM: 6/1/1), mp 103°C. δ_H ($CDCl_3$, 300 MHz) 1.88 (t, *J* 2.4, 1H), 2.41 (s, 3H), 3.70 (s, 3H), 4.08 (dd, *J* 14.7, *J* 2.4, 2H), 6.09 (d, *J* 1.7, 1H), 6.17 (s, 1H), 6.19 (d, *J* 3.4, 1H), 6.49 (d, *J* 3.4, 1H), 6.52 (d, *J* 1.7, 1H), 7.23–7.34 (m, 7H), 7.85 (d, *J* 8.3, 2H). δ_C ($CDCl_3$, 75 MHz) 21.52 (q), 34.98 (t), 52.16 (q), 55.69 (d), 72.31 (d), 78.19 (s), 105.73 (d), 112.40 (d), 123.71 (d), 127.52 (d, 2C), 127.84 (t), 127.96 (d, 2C), 128.43 (d, 2C), 129.36 (d, 2C), 130.27 (s), 136.75 (s), 137.14 (s), 143.53 (s), 148.87 (s), 154.01 (s), 165.92 (s). (Found: 449.1310 $[M]^+$. Calcd for $C_{25}H_{23}NO_5S$: 449.1297.)

Crystal data and structure refinement for **1c**: colourless crystal (polyhedron), dimensions 0.20 × 0.19 × 0.08 mm^3, crystal system monoclinic, space group *C*2/*c*, *Z* 8, *a* 32.860(3) Å, *b* 9.7552(10) Å, *c* 20.803(2) Å, α 90°, β 129.2770(10)°, γ 90°, *V* 5162.1(9) Å^3, ρ 1.375 g cm^{-3}, *t* 200(2) K, θ_{max} 28.32°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 26 308 reflections measured, 6393 unique (*R*(int) 0.0478), 5252 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.37 mm^{-1}, T_{min} 0.93, T_{max} 0.97, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 318 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.18 for observed reflections, final residual values $R_1(F)$ 0.072, $wR(F^2)$ 0.132 for observed reflections, residual electron density −0.41 to 0.67 e Å^{-3}.

Methyl-2-[{[(4-methylphenyl)sulfonyl](prop-2-in-1-yl)amino}(4,5-dimethylfuran-2-yl)methyl]prop-2-enoate (**1d**): Yield: 559 mg (1.39 mmol, 75%). R_f 0.30 (PE/EE/DCM: 8/1/1).

δ_H ($CDCl_3$, 500 MHz) 1.81 (s, 3H), 1.98 (s, 3H), 2.03 (s, 1H), 2.41 (s, 3H), 3.68 (s, 3H), 3.94 (dd, *J* 18.4, *J* 2.4, 2H), 5.86 (s, 1H), 6.01 (d, *J* 1.6, 1H), 6.04 (s, 1H), 6.42 (d, *J* 1.6, 1H), 7.25 (d, *J* 8.2, 2H), 7.78 (d, *J* 8.2, 2H). δ_C ($CDCl_3$, 125 MHz) 9.71 (q), 11.20 (q), 21.48 (q), 34.78 (t), 52.06 (q), 55.87 (d), 71.96 (d), 78.91 (s), 113.59 (d), 114.73 (s), 127.87 (d, 2C), 127.92 (t), 129.12 (d, 2C), 136.78 (s), 137.45 (s), 143.31 (s), 146.13 (s), 147.71 (s), 166.01 (s).

General Procedure C: Gold Catalysis

Exemplified for the Formation of Methyl 2-(4-hydroxy-5-methyl-2-tosyl isoindolin-1-yl)acrylate (**2a**): Compound **1a** (100 mg, 258 μmol) was taken up in $CDCl_3$ (0.5 mL) and $AuCl_3$ (3.91 mg, 12.9 μmol) was added. The reaction was monitored by NMR spectroscopy. When complete, the solvent was removed under reduced pressure and the crude reaction mixture was separated on silica gel (eluent: PE/EE: 3/1) to afford **2a**: Yield: 99.0 mg (256 μmol, 99%). R_f 0.18 (PE/EE: 3/1), mp 138°C. ν_{max} (KBr)/cm^{-1} 3448, 1711, 1597, 1487, 1439, 1348, 1310, 1294, 1265, 1218, 1194, 1166, 1093, 1051, 821, 814, 671, 658, 593, 549. δ_H ($CDCl_3$, 300 MHz) 2.14 (s, 3H), 2.37 (s, 3H), 3.67 (s, 3H), 4.67 (d, *J* 13.4, 1H), 4.80 (dd, *J* 13.4, *J* 2.8, 1H), 5.75 (m, 1H), 6.00 (s, 1H), 6.35 (s, 1H), 6.54 (d, *J* 7.7, 1H), 6.93 (d, *J* 7.7, 1H), 7.26 (d, *J* 8.1, 2H), 7.73 (d, *J* 8.1, 2H). δ_C ($CDCl_3$, 75 MHz) 15.19 (q), 21.42 (q), 51.82 (d), 52.02 (q), 66.29 (d), 114.42 (d), 122.10 (s), 122.71 (s), 127.44 (d, 2C), 127.81 (t), 129.71 (d, 2C), 130.79 (d), 134.64 (s), 138.90 (s), 140.68 (s), 143.55 (s), 148.80 (s), 165.87 (s). (Found: 388.1273 $[M+H]^+$. Calcd for $C_{20}H_{22}NO_5S$: 388.1219.) λ_{max} (0.074 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 270 (3.27).

Crystal data and structure refinement for **2a**: colourless crystal (polyhedron), dimensions $0.24 \times 0.18 \times 0.16\,mm^3$, crystal system monoclinic, space group $P2_1/c$, *Z* 4, *a* 15.1057(13) Å, *b* 8.1047(7) Å, *c* 15.6102(13) Å, α 90°, β 105.728(2)°, γ 90°, *V* 1839.6(3) $Å^3$, ρ 1.399 g cm^{-3}, *t* 200(2) K, θ_{max} 28.31°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 18 710 reflections measured, 4575 unique (R(int) 0.0282), 4123 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.21 mm^{-1}, T_{min} 0.95, T_{max} 0.97, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 251 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H16 of the hydroxyl group, which was refined isotropically, goodness of fit 1.16 for observed reflections, final residual values $R_1(F)$ 0.051, $wR(F^2)$ 0.122 for observed reflections, residual electron density −0.35 to 0.49 e $Å^{-3}$.

Methyl 2-(5-ethyl-4-hydroxy-2-tosyl isoindolin-1-yl)acrylate (**2b**): Yield: 70.0 mg (174 μmol, 99%). R_f 0.26 (PE/EE: 3/1). ν_{max} (KBr)/cm^{-1} 3447, 2966, 1718, 1628, 1597, 1493, 1430, 1306, 1292, 1198, 1163, 1095, 1093, 1060, 1018, 814, 671, 593, 549. δ_H ($CDCl_3$, 300 MHz) 1.14 (t, *J* 7.5, 3H), 2.36 (s, 3H), 2.52 (q, *J* 7.5, 2H), 3.68 (s, 3H), 4.69 (d, *J* 13.4, 1H), 4.83 (dd, *J* 13.4, *J* 2.5, 1H), 5.55 (s, 1H), 5.77 (d, *J* 2.5, 1H), 6.01 (s, 1H), 6.35 (s, 1H), 6.58 (d, *J* 7.7, 1H), 6.95 (d, *J* 7.7, 1H), 7.25 (d, *J* 8.1, 2H), 7.73 (d, *J* 8.1, 2H). δ_C ($CDCl_3$, 75 MHz) 13.77 (q), 21.23 (q), 22.10 (t), 51.64 (q), 51.86 (t), 65.99 (d), 114.38 (d), 122.03 (s), 127.29 (d, 2C), 127.61 (t), 128.92 (d, 2C), 129.52 (d, 2C), 134.34 (s), 138.54 (s), 140.65 (s), 143.37 (s), 148.21 (s), 165.76 (s). (Found: 402.1342 $[M+H]^+$. Calcd for $C_{21}H_{24}NO_5S$: 402.1375.) λ_{max} (0.055 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 270 (3.34), 280 (3.26).

Methyl 2-(4-hydroxy-5-phenyl-2-tosyl isoindolin-1-yl) acrylate (**2c**): Yield: 557 mg (1.24 mmol, 86%). R_f 0.21 (PE/EE: 3/1), mp 58°C. ν_{max} (KBr)/cm^{-1} 3442, 1718, 1629, 1599, 1462, 1437, 1345, 1307, 1292, 1230, 1196, 1163, 1097, 1072, 1054, 815, 760, 672, 597, 551. δ_H ($CDCl_3$, 300 MHz) 2.39 (s, 3H), 3.74 (s, 3H), 4.72 (d, *J* 13.8, 1H), 4.84 (dd, *J* 13.8, *J* 2.4, 1H), 5.38 (s, 1H), 5.86 (d, *J* 2.4, 1H), 6.08 (s, 1H), 6.41 (s, 1H), 6.72 (d, *J* 7.8, 1H), 7.07 (d, *J* 7.8, 1H), 7.27 (d, *J* 8.3, 2H), 7.41 (m, 5H), 7.77 (d, *J* 8.3, 2H). δ_C ($CDCl_3$, 75 MHz) 21.48 (q), 51.88 (q), 52.13 (t), 66.23 (d), 114.84 (d), 122.64 (s), 127.34 (t), 127.57 (d, 2C), 127.93 (s), 128.17 (d), 128.87 (d, 2C), 129.52 (d, 2C), 129.73 (d, 2C), 130.25 (d), 134.80 (s), 135.97 (s), 140.76 (s), 141.00 (s), 143.53 (s), 147.22 (s), 165.93 (s). (Found: 450.1359 $[M+H]^+$. Calcd for $C_{25}H_{24}NO_5S$: 450.1375.) λ_{max} (0.051 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 250 (4.14), 284 (3.62), 352 (2.94), 338 (3.39).

Methyl 2-(4-hydroxy-5,6-dimethyl-2-tosylisoindolin-1-yl) acrylate (**2d**): Compound **1d** (473 mg, 1.18 mmol) was dissolved in CH_3CN (4 mL) and $AuCl_3$ (17.8 mg, 58.9 μmol) was added. The reaction was monitored by thin layer chromatography. After 16 h the solvent was removed under reduced pressure and the residue was separated on silica gel (eluent: PE/EE: 3/1) to afford **2d**: Yield: 453 mg (1.13 mmol, 96%). R_f 0.21 (PE/EE: 3/1), mp 176°C. ν_{max} (KBr)/cm^{-1} 3438, 1717, 1630, 1597, 1465, 1440, 1336, 1306, 1235, 1194, 1163, 1092, 1058, 816, 670, 608, 595 cm^{-1}. δ_H ((D_6)DMSO, 300 MHz) 1.96 (s, 3H), 2.06 (s, 3H), 2.34 (s, 3H), 3.62 (s, 3H), 4.53 (d, *J* 13.8, 1H), 4.63 (d, *J* 13.8, 1H), 5.58 (s, 1H), 6.07 (s, 1H), 6.23 (s, 1H), 6.30 (s, 1H), 7.40 (d, *J* 8.1, 2H), 7.69 (d, *J* 8.1, 2H), 8.88 (s, 1H). δ_C ((D_6)DMSO, 75 MHz) 11.42 (q), 19.99 (q), 20.85 (q), 51.68 (q), 52.42 (t), 66.19 (d), 114.27 (d), 119.69 (s), 122.52 (s), 127.02 (d, 2C), 127.65 (t), 129.88 (d, 2C), 133.99 (s), 136.65 (s), 137.38 (s), 140.28 (s), 143.55 (s), 149.03 (s), 164.90 (s). (Found: 402.1397 $[M+H]^+$. Calcd for $C_{21}H_{24}O_5NS$: 402.1375.) λ_{max} (0046 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 264 (3.20), 270 (3.14).

Methyl 2-methyl-3-(5-methylfuran-2-yl)-3-(4-methylphenyl sulfonamido)propanoate (**5**): In a flame dried flask, compound **4a** (349 mg, 100 μmol) was dissolved in 8 mL of dry dichloromethane. Crabtree's Catalyst (8.04 mg, 10.0 μmol) was then added to the solution and the mixture was flooded with hydrogen gas. The crude reaction mixture was stirred for 10 h under a hydrogen atmosphere. The solvent was removed under reduced pressure and the residue was separated on silica gel (eluent: PE/EE/DCM: 6/1/1) to afford **5**: Yield: 328 mg (934 μmol, 93%). R_f 0.27 (PE/EE/DCM: 6/1/1). δ_H ($CDCl_3$, 300 MHz) 1.15 (d, *J* 7.2, 3H), 1.17 (d, *J* 7.2, 3H), 2.03 (s, 3H), 2.36 (s, 3H), 2.82–2.96 (m, 1H), 3.59 (s, 3H), 3.63 (s, 3H), 4.50–4.57 (m, 1H), 5.47 (d, *J* 9.8, 1H), 5.60 (d, *J* 9.8, 1H), 5.63 (m, 1H), 5.78 (t, *J* 3.4, 1H), 7.16 (d, *J* 8.3, 2H), 7.59 (d, *J* 8.3, 2H). δ_C ($CDCl_3$, 75 MHz) 13.13 (q), 13.17 (q), 14.16 (q), 14.55 (q), 21.40 (q), 43.64 (d), 44.05 (d), 51.88 (q), 51.92 (q), 53.84 (d), 54.01 (d), 105.85 (d), 105.88 (d), 108.43 (d), 108.71 (d), 126.94 (d, 2C), 126.98 (d, 2C), 129.12 (d, 2C), 129.17 (d, 2C), 137.55 (s), 137.83 (s), 142.83 (s), 142.94 (s), 148.73 (s), 149.29 (s), 151.53 (s), 151.59 (s), 173.63 (s), 174.51 (s). *m/z* (GC-MS: EI^+) R_t 21.869 min: 351 $[M]^+$, 320 $[M-CH_3O]^+$, 196 $[M-C_7H_7O_2S]^+$. R_t 22.143 min: 351 $[M]^+$, 320 $[M-CH_3O]^+$, 196 $[M-C_7H_7O_2S]^+$.

Methyl-2-methyl-3-(5-methylfuran-2-yl)-3-{[(4-methylphenyl)sulfonyl](prop-2-in-1-yl)amino}propanoate (**6**): Yield: 351 mg (909 μmol, 90%), R_f 0.36 (PE/EE/DCM: 6/1/1).

ν_{max} (KBr)/cm^{-1} 3250, 1735, 1435, 1448, 1348, 1327, 1273, 1164, 1134, 1093, 1047, 886, 810, 787, 682, 665, 576, 561, 550, 540. δ_H ($CDCl_3$, 500 MHz) 1.09 (d, *J* 6.9, 3H), 1.46 (d, *J* 6.9, 3H), 1.85 (t, *J* 2.4, 1H), 1.94 (s, 3H), 2.45 (t, *J* 2.4, 1H), 2.12 (s, 3H), 2.38 (s, 3H), 2.41 (s, 3H), 3.28 (m, 1H), 3.35 (m, 1H), 3.58 (s, 3H), 3.69 (s, 3H), 4.04 (dd, *J* 18.6, *J* 2.4, 2H), 5.10 (d, *J* 11.1, 1H), 5.23 (d, *J* 11.1, 1H), 5.72 (d, *J* 3.1, 1H), 5.78 (d, *J* 3.1, 1H), 5.92 (d, *J* 3.1, 1H) 6.04 (d, *J* 3.1, 1H), 7.21 (d, *J* 8.1, 2H), 7.26 (d, *J* 8.1, 2H), 7.74 (d, *J* 8.1, 2H), 7.77 (d, *J* 8.1, 2H). δ_C ($CDCl_3$, 125 MHz) 13.14 (q), 13.40 (q), 15.07 (q), 16.04 (q), 21.01 (q), 21.07 (q), 33.62 (t), 34.08 (t), 41.36 (d), 41.82 (d), 51.94 (q), 52.02 (q), 57.17 (d), 57.52 (d), 71.55 (d), 71.98 (d), 78.43 (s), 78.65 (s), 105.97 (d), 106.15 (d), 110.03 (d), 110.16 (d), 127.91 (d, 2C), 127.93 (d, 2C), 127.94 (d, 2C), 128.12 (d, 2C), 128.13 (d, 2C), 128.18 (d, 2C), 128.90 (d, 2C), 128.97 (d, 2C), 129.15 (d, 2C), 129.21 (d, 2C), 137.01 (s), 137.15 (s), 143.17 (s), 143.28 (s), 147.46 (s), 148.21 (s), 151.93 (s), 151.99 (s), 173.72 (s), 174.68 (s). (Found: 389.1294 $[M]^+$. Calcd for $C_{20}H_{23}NO_5S$: 389.1297.) λ_{max} (0.11 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 266 (2.95), 274 (2.59).

Crystal data and structure refinement for **6**: colourless crystal (polyhedron), dimensions $0.49 \times 0.14 \times 0.12$ mm^3, crystal system monoclinic, space group $P2_1$, *Z* 2, *a* 9.2273(8) Å, *b* 10.8698(9) Å, *c* 10.4509(8) Å, α 90°, β 110.996(2)°, γ 90°, *V* 978.62(14) Å^3, ρ 1.322 g cm^{-3}, *t* 200(2) K, θ_{max} 28.30°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 10 282 reflections measured, 4723 unique (*R*(int) 0.0242), 4579 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.20 mm^{-1}, T_{min} 0.91, T_{max} 0.98, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 249 parameters refined, hydrogen atoms were treated using appropriate riding models, Flack absolute structure parameter 0.22(6), goodness of fit 1.11 for observed reflections, final residual values $R_1(F)$ 0.036, $wR(F^2)$ 0.090 for observed reflections, residual electron density −0.28 to 0.45 e Å^{-3}.

Methyl-2-{4-hydroxy-5-methyl-2-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-isoindol-1-yl}propanoat (**7**): Yield: 45.0 mg (116 μmol, 91%). R_f 0.25 (PE/EE: 3/1), mp 172°C. ν_{max} (KBr)/cm^{-1} 3432, 3028, 2951, 1719, 1597, 1458, 1347, 1216, 1162, 817, 715, 664, 593, 549. δ_H ((D_6)DMSO, 300 MHz) 0.94 (d, *J* 7.0, 3H), 1.16 (d, *J* 7.0, 3H), 2.18 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 2.88–2.92 (m, 1H), 3.54–3.59 (m, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 4.57–4.72 (m, 2H), 5.41 (s, 1H), 5.51 (s, 1H), 6.41 (d, *J* 7.7, 1H), 6.60 (d, *J* 7.7, 1H), 6.94 (d, *J* 7.7, 1H), 6.98 (d, *J* 7.7, 1H), 7.23 (d, *J* 8.2, 2H), 7.28 (d, *J* 8.2, 2H), 7.72 (d, *J* 8.2, 2H), 7.77 (d, *J* 8.2, 2H). δ_C ($CDCl_3$, 75 MHz) 9.19 (q), 10.85 (q), 15.15 (q), 15.19 (q), 20.98 (q), 21.41 (q), 45.35 (d), 46.60 (d), 51.81 (q), 51.93 (q), 52.14 (t), 52.44 (t), 66.98 (d), 67.76 (d), 114.00 (d), 114.74 (d), 122.81 (s), 122.92 (s), 122.96 (s), 127.35 (d, 2C), 127.41 (d, 2C), 129.64 (d, 2C), 129.73 (d, 2C), 129.82 (s), 130.81 (d), 130.85 (d), 134.15 (s), 134.47 (s), 135.93 (s), 138.38 (s), 143.52 (s), 143.68 (s), 148.76 (s), 148.83 (s), 171.29 (s), 173.91 (s), 174.00 (s). (Found: 390.1362 $[M + H]^+$. Calcd for $C_{20}H_{24}O_5NS$: 390.1375.) λ_{max} (0.107 mg mL^{-1} in CH_2Cl_2)/nm (log ε) 266 (3.15), 276 (3.07).

Crystal data and structure refinement for **7**: yellow crystal (polyhedron), dimensions $0.30 \times 0.16 \times 0.09$ mm^3, crystal system monoclinic, space group $P2_1$, *Z* 8, *a* 10.2465(12) Å, *b* 15.8242(19) Å, *c* 24.008(3) Å, α 90°, β 93.935(3)°, γ 90°, *V* 3883.5(8) Å^3, ρ 1.332 g cm^{-3}, *t* 200(2) K, θ_{max} 22.01°, radiation $Mo_{K\alpha}$, λ 0.71073 Å, 0.3° Ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 15 782 reflections measured, 15 782 unique (*R*(int) 0.0000), 12 882 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using *SADABS*[8] based on the Laue symmetry of the reciprocal space, μ 0.20 mm^{-1}, T_{min} 0.94, T_{max} 0.98, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the *SHELXTL-PLUS (6.10)* software package,[9] 986 parameters refined, hydrogen atoms were treated using appropriate riding models, Flack absolute structure parameter 0.34(15), goodness of fit 2.11 for observed reflections, final residual values $R_1(F)$ 0.071, $wR(F^2)$ 0.113 for observed reflections, residual electron density −0.34 to 0.37 e Å^{-3}.

Accessory Publication

CCDC 724873 (**1a**), 724874 (**1b**), 724875 (**1c**), 724876 (**2a**), 724877 (**4a**), 724878 (**4b**), 724879 (**4c**), 724880 (**4d**), 724881 (**6**), 724882 (**7**), and 724883 (isocupreidin) contain the Accessory Publication 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. The Accessory Publication is also available on the Journal's website.

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