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The Condensation of Carbonyl Compounds with Electron-Rich Arenes: Mercury, Thallium, Gold or a Proton?

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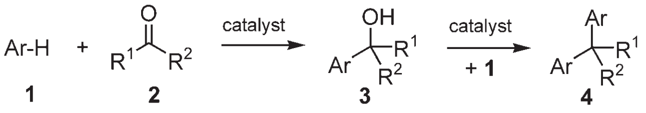
Abstract: Gold(III) chloride, mercury(II) perchlorate, thallium(III) perchlorate and p-toluenesulfonic acid were found to efficiently catalyze the condensation of two furans with aldehydes or acetone. The olefinic unit of α,β-unsaturated carbonyl compounds reacts faster than the carbonyl group, other olefins do not react selectively. The first (addition) step is rate-limiting, the second (substitution) step is much faster.

Keywords: arylation; furans; gold; mercury; thallium; ytterbium

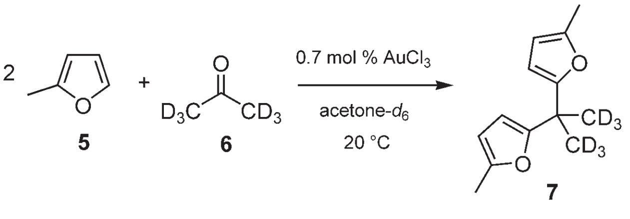
The reaction of electron-rich aromatic compounds **1** with aldehydes or ketones **2** is catalyzed by acid under relatively harsh conditions, prominent examples are the synthesis of Bakelite[1] or furanophanes.[2] Overall, a two-fold reaction is observed – in these condensation reactions one equivalent water is produced as a by-product. Thus any alternative and potentially milder method not dependent on Brønstedt acids must use water-tolerant Lewis acids. Since in the first step benzyl alcohols **3** are produced, the second step in which the latter reacts with a second molecule of the electron-rich arene is closely related to an iron-catalyzed reaction reported by Beller et al.[3] this year. Other activated alcohols recently shown to undergo similar reactions are propargylic alcohols, here Uemura et al.[4] investigated ruthenium catalysts and Toste et al.[5] rhenium catalysts.[6]

Here we report our results on the comparison of mercury, thallium and gold compounds with p-toluenesulfonic acid.



Scheme 1.

Starting point was the gold-catalyzed hydroarylation of α,β-unsaturated ketones.[7–11] When the reaction of 2-methylfuran **5** with methyl vinyl ketone was conducted not in acetonitrile but in acetone as solvent, a product of the type **4** was obtained as a significant side-product. Monitoring the reaction of **5** without α,β-unsaturated ketone in hexadeuteroacetone **6** with 0.7 mol % $AuCl_3$ as the catalyst in a NMR tube by ^{1}H NMR revealed three facts (Figure 1): a) The reaction was very selective, no side-products were observed; from the starting materials (furyl signals at 6.3 and 7.3 ppm) only **7** is formed (signals at 2.2, 6.0 and 6.2 ppm). b) No relevant concentration of a species of type **3** was built up during the reaction (a transient peak was not observed), which clearly shows that in this case the initial step leading to intermediate **3** was rate-limiting and the subsequent conversion of **3** to **4** was a much easier step (especially if one takes into account the high concentration of ketone **6**, which as the solvent should significantly accelerate the first step). c) The water set free as a by-product (broad peak at 3.2 ppm) quickly exchanged H versus D with the solvent, thus the peak disappeared again and a peak for partially deuterated acetone simultaneously appeared at 2.1 ppm. The time/concentration profile of these species was obtained by integration of the spectra and is shown in Figure 2.



Scheme 2.

Another Lewis acid, known to be water-tolerant, is $Yb(OTf)_3$. With the same amount of this catalyst after 2 days only 5% conversion to **7** were observed. Since we had good experience with $Hg(ClO_4)_2$ as a catalyst,[12,13] we tested the reaction of **5** and **6** with 1 mol % of this catalyst, too. Again **7** was formed selec-

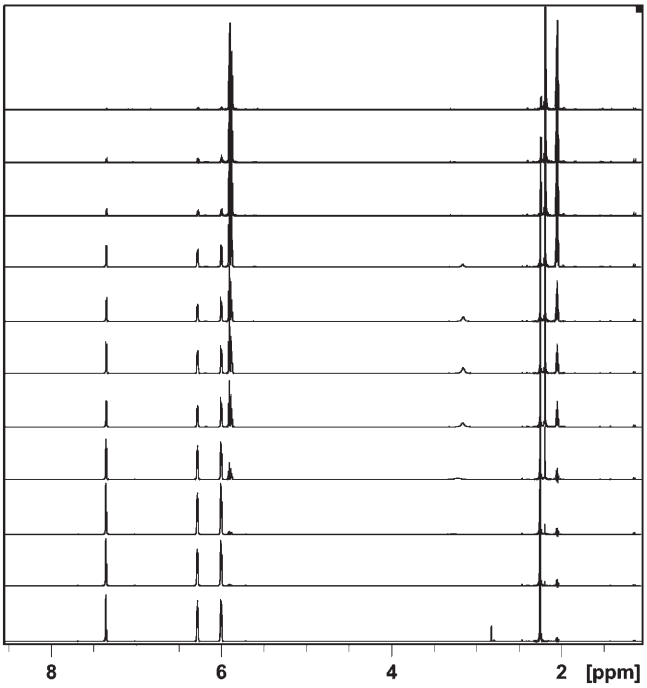


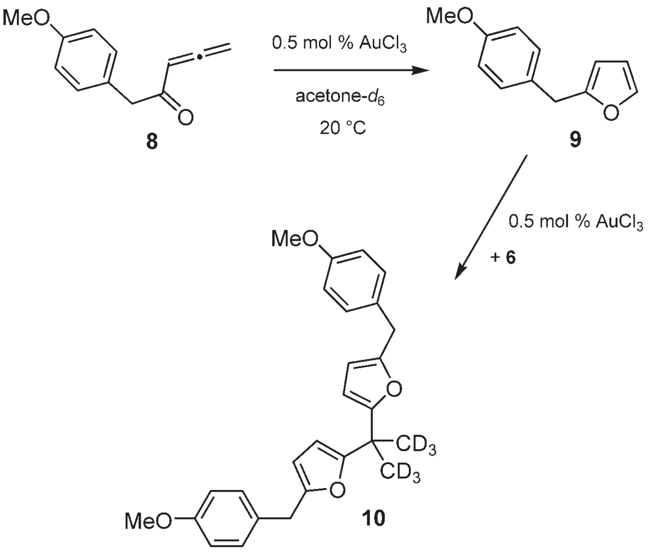
Figure 1. ^{1}H NMR spectra taken during the gold-catalyzed conversion of **5** and **6** to **7**.

tively, after 14 hours at 20 °C the reaction was complete. A similar behaviour was observed with 1 mol % $Tl(ClO_4)_3$ as the catalyst, after only 5 hours at room temperature the conversion was complete. Finally, $InCl_3$ was tested, only with 33 mol % of this catalyst and at 70 °C did a slow and less selective reaction take place.

As Brønsted acids, 11 mol % of $HClO_4$ and 1 mol % of TsOH were tested, both gave a clean reaction to **7**, too.

A similar behaviour was observed when the cycloisomerization of allenyl ketone **8** was conducted in acetone. Marshall et al.[14,15] have reported the cycloisomerization of such allenyl ketones with silver(I) catalysts in acetone, the related cycloisomerization/dimerization is usually conducted in acetonitrile with palladium[13,16–19] or gold[7] catalysts. Different from the silver-catalyzed reactions in acetone, with the $AuCl_3$ catalyst in acetone even after a short reaction time of only 2 h at room temperature a 23% yield of **10** was observed (after this short time the cycloisomerization is finished, **9** is still the major product). After two days all **9** was consumed and in a clean reaction converted to **10**.

Next we tested the more reactive aldehyde group. In the reaction with two equivalents of **5** the aldehyde **11** with as little as 0.3 mol % of $AuCl_3$ in acetonitrile instead of acetone at room temperature a quantitative yield of the known compound **12** was obtained.



Scheme 3.

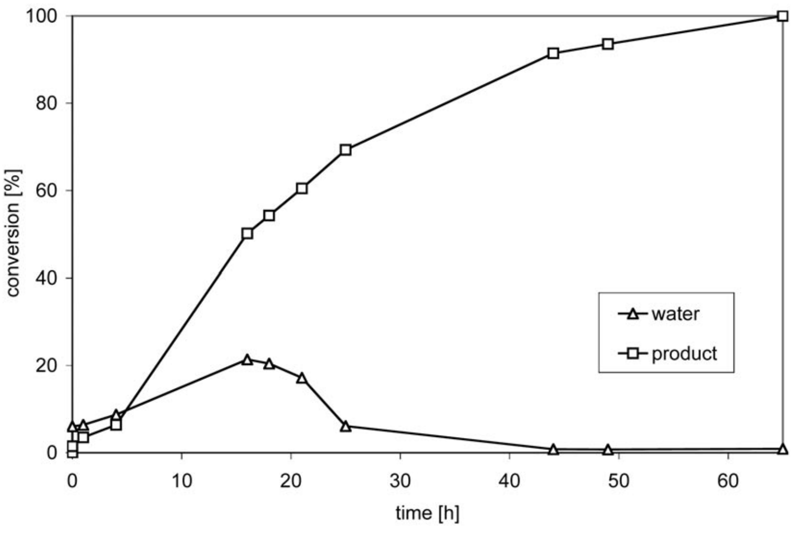
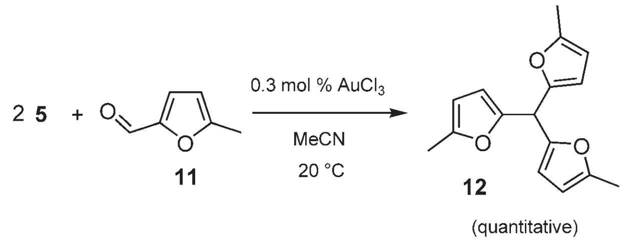
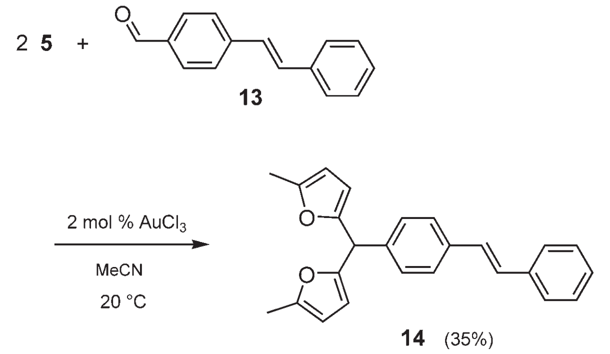


Figure 2. Time-concentration profile of the gold-catalyzed conversion of **5** and **6** to **7**.



Scheme 4.



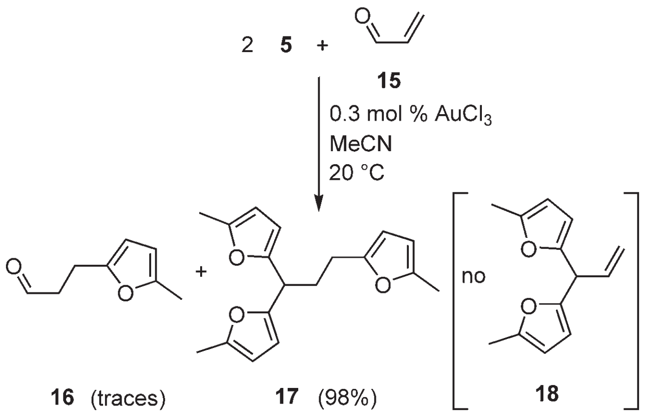
Scheme 5.

With the more sensitive stilbene aldehyde **13** and two equivalents of **5** under the similar conditions only a 35% yield of **14** was achieved. Presumably, some unselective side-reactions at the olefinic, styryl-like unit take place.

Finally, we investigated the α,β-unsaturated aldehyde acrolein **15**. With 1 mol % of $AuCl_3$ and three equivalents of **5** a highly selective reaction to **17** was observed, the ^{1}H NMR spectra taken during the reaction indicated that first in a very fast step the hydroarylation product **16** is formed, which subsequently reacts with two more molecules of **5** as indicated for the other aldehydes **11** and **13**. The absence of **18** and the survival of the double bond in **14** are in accord with the observation that unactivated alkenes in gold-catalyzed reactions react at higher temperatures in non-coordinating solvents only;[20] if **5** would react with the aldehyde group of **15** first, it should be possible to isolate or at least observe **18**.

In analogy to our recent report,[8] the conversions leading to **12**, **14** and **16** can also be conducted with Brønsted acids with non-nucleophilic counterions.

While mercury and thallium salts due to their toxicity are not an alternative to Brønsted acids with non-nucleophilic counterions, and ytterbium salts suffer from activity problems, the mild conditions of the gold catalysis are an interesting synthetic alternative. This investigation furthermore showed that in α,β-unsaturated carbonyl compounds the olefin reacts faster than the aldehyde group, while other alkenes remain intact. The first reaction of the carbonyl group with the electron-rich arene is the rate-limiting-step, the reaction of the benzylic alcohol is much faster.



Scheme 6.

Experimental Section

Synthesis of 1,1,1,3,3,3-Hexadeutero-2,2-bis-(5-methylfuran-2-yl)propane (7)

2-Methylfuran (183 mg, 2.23 mmol) was dissolved in acetone-d_6 (2.00 g), then $AuCl_3$ (2.4 mg, 0.7 mol %) in acetone-d_6 (250 mg) was added, after one day the starting material was consumed and no further conversion was observed. The solvent was removed and the crude product was purified by column chromatography (hexanes/ethyl acetate, 20:1) to afford **7**; yield: 213 mg (91%). R_f (hexanes/ethyl acetate, 20:1)$=$0.50; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=2.26$ (d, $J=0.9$ Hz, 6H), 5.84–5.89 (m, 4H); ^{1}H NMR (250 MHz, acetone-d_6): $\delta=2.18$ (d, $J=0.9$ Hz, 6H), 5.86–5.90 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=13.42$ (q, 2C), 25.65 (m, CD_3, 2C), 37.21 (m, C), 104.31 (d, 2C), 105.53 (d, 2C), 150.34 (s, 2C), 158.45 (s, 2C); IR (NaCl, film): $\nu=3106$, 2924, 2231, 1612, 1559, 1448, 1220, 1045, 1023, 952, 781 cm^{-1}; anal. calcd. for $C_{13}H_{10}D_6O_2$ (210.30): H 7.90, C 74.25; found: H 7.76, C 74.00.

2,2-Bis-[5-(4-methoxybenzyl)furan-2-yl]propane (10)

Compound **8** (298 mg, 1.60 mmol) was dissolved in acetone (4.00 g), then $AuCl_3$ (1.2 mg, 0.5 mol %) in acetone (125 mg) was added at room temperature. After 2 days the reaction was complete, the acetone was removed under reduced pressure and the residue was purified by column chromatography (hexanes:ethyl acetate, 10:1) to furnish 20.9 mg (7%) of **9**[17] and 263 mg (79%) of **10**.

Product **10**: R_f (hexanes/ethyl acetate, 5:1)$=$0.30; mp 60 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=1.60$ (s, 6H), 3.79 (s, 6H), 3.87 (s, 4H), 5.79–5.81 (m, 2H), 5.86 (d, $J=3.1$ Hz, 2H), 6.81–6.86 (m, 4H), 7.11–7.17 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=26.30$ (q, 2C), 33.54 (t, 2C), 37.25 (s), 55.09 (q, 2C), 104.43 (d, 2C), 106.17 (d, 2C), 113.68 (d, 4C), 129.54 (d, 4C), 130.38 (s, 2C), 153.40 (s, 2C), 158.03 (s, 2C), 158.88 (s, 2C); IR (film): $\nu=3104$, 2975, 2935, 2907, 2835, 1611, 1554, 1512, 1462, 1299, 1247, 1176, 1103, 1034, 968, 788 cm^{-1}; MS (EI, 70 eV): *m/z* (%)$=$416 (34) [M^+], 401 (100), 121 (37); anal. calcd. for $C_{27}H_{28}O_4$ (416.52): H 6.78, C 77.86; found: H 6.90, C 77.67.

Tris(5-methylfuran-2-yl)methane (12)

2-Methylfuran (800 mg, 9.74 mmol) and 5-methylfurfural (390 mg, 4.87 mmol) were dissolved in acetonitrile (4 mL) and 4.4 mg (0.3 mol %) $AuCl_3$ were added. After two days the conversion was quantitative, the usual work-up afforded the known **12**;[21] yield: 98%. ^1H NMR (300 MHz, CD_3CN): $\delta = 2.24-2.27$ (m, 9H), 5.43 (s, 1H), 5.99–6.01 (m, 6H).

Synthesis of 2-Methyl-5-[(5-methylfuran-2-yl)(4-styrylphenyl)methyl]furan (14)

To *trans*-4-stilbenecarboxaldehyde (73.0 mg, 350 μmol) and **5** (78.0 mg, 708 μmol) in acetonitrile (0.5 mL) $AuCl_3$, (2.1 mg, 7.0 μmol, 2 mol %) was added. After 24 h the solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate, 20:1) to afford **14**; yield: 44.0 mg (35%). R_f (petrol ether/ethyl acetate, 20:1) = 0.30; mp 108 °C; IR (film): $\nu =$ 3020, 1214, 1021, 962, 748, 668, 629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.16$ (s, 6H), 5.25 (s, 1H), 5.80 (s, 4H), 7.00 (d, $J = 1.1$ Hz, 2H), 7.14–7.17 (m, 3H), 7.24–7.27 (m, 2H), 7.36–7.38 (m, 2H), 7.40–7.42 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 13.7$ (q, 2C), 45.0 (d), 106.2 (d, 2C), 108.3 (d, 2C), 126.6 (d, 2C), 126.7 (d, 2C), 127.7 (d), 128.5 (d), 128.6 (d), 128.8 (d, 2C), 128.9 (d, 2C), 136.2 (s), 137.5 (s), 139.6 (s), 151.6 (s, 2C), 152.8 (s, 2C); MS (70 eV): *m/z* (%) = 355 (47) $[M+H^+]$, 354 (100) $[M^+]$, 312 (84), 311 (100), 272 (32), 178 (45), 175 (80); HRMS (EI 70 eV): *m/z* = 354.1620; calcd. for $C_{25}H_{22}O_2$: 354.1620;.

Synthesis of 1,1,3-Tris(5-methylfuran-2-yl)propane (17)

To acrolein (110 mg, 2.00 mmol) and **5** (492 mg, 6.00 μmol) in 1.00 g MeCN, $AuCl_3$ (1.8 mg, 0.3 mol%) in 49 mg MeCN was added. Purification of the crude product by column chromatography (hexanes/ethyl acetate, 10:1), afforded **17**; yield: 557 mg (98%).

In addition traces of **16** were obtained (less than 1 mg), with an excess of acrolein, **16** was prepared independently.

Product: **16**: R_f (hexanes/ethyl acetate, 5:1) = 0.20; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.24$ (s, 3H), 2.73–2.79 (m, 2H), 2.90–2.96 (m, 2H), 5.83–5.85 (m, 1H), 5.88–5.89 (m, 1H), 9.82 (t, $J = 1.4$ Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.24$ (q), 20.66 (t), 41.82 (t), 105.80 (d), 105.94 (d), 150.65 (s), 151.79 (s), 201.05 (d); IR (NaCl, film): $\nu = 3105$, 2949, 2923, 2828, 2726, 1726 (C=O), 1616, 1570, 1436, 1387, 1218, 1162, 1021, 941, 784 cm^{-1}; MS (80 eV): *m/z* (%) = 138 (30) $[M^+]$, 95 (100), 82 (58); anal. calcd. for $C_8H_{10}O_2$ (136.16): H 7.30, C 69.55; found H: 7.27, C 75.74.

Product **17**: R_f (hexanes/ethyl acetate, 5:1) = 0.56; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.22-2.31$ (m, 2H), 2.25 (s, 9H), 2.55–2.61 (m, 2H), 3.99 (t, $J = 7.6$ Hz, 1H), 5.83–5.88 (m, 4H), 5.96 (d, $J = 3.0$ Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.32$ (q), 13.40 (q, 2C), 25.73 (t), 31.06 (t), 38.12 (d), 105.48 (d), 105.60 (d), 105.75 (d, 2C), 106.26 (d, 2C), 150.13 (s), 150.63 (s, 2C), 153.28 (s, 2C), 153.49 (s); IR (NaCl, film): $\nu = 3104$, 2947, 2922, 2884, 1616, 1568, 1452, 1357, 1219, 1131, 1020, 958, 779 cm^{-1}; anal. calcd. for $C_{18}H_{20}O_3$ (284.35): H 7.09, C 76.03; found: H 7.26, C 69.77.

Acknowledgements

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