DOI: 10.1002/ejoc.200600546

Gold Catalysis: Observation of a Two-Fold Intermolecular Hydroarylation of Unactivated C–C Triple Bonds

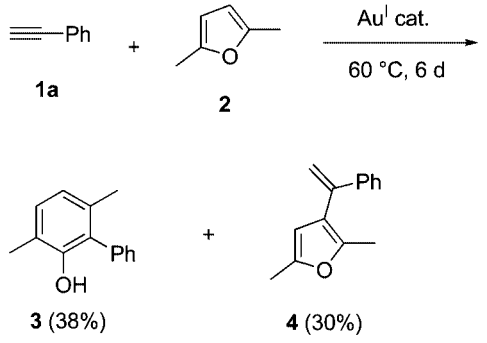
A. Stephen K. Hashmi,*[a] and M. Carmen Blanco[a]

Keywords: Alkynes / Furans / Gold / Homogeneous catalysis / Hydroarylation

The cationic binuclear catalyst $[(Mes_3PAu)_2Cl]BF_4$ enables the reaction of 2-methyl- or 2-pentylfuran with phenylacetylene, 1-pentyne or 1-heptyne to yield the products of a twofold hydroarylation of the alkyne.

Introduction

In the field of gold catalysis[1] several examples of hydroarylation have been reported. After initial reports on the hydroarylation of allenyl ketones and α,β-unsaturated ketones by electron-rich furans[2] and related arenes,[3] subsequent work of Arcadi on the hydroarylation of indoles[4] and 7-azaindoles,[5] of Reetz on the hydroarylation of phenylacetylenes and propiolates,[6] of He on the hydroarylation of propiolates and α,β-unsaturated ketones,[7] and domino sequences of hydrorarylation and cycloisomerization from our group[8] investigated that aspect of gold catalysis. All these *intermolecular* reactions were performed with *activated* alkynes, only in a few *intramolecular* cases *unactivated* alkynes have so far been reported to undergo hydroarylation.[2,9] Until today the *intermolecular* gold-catalyzed hydroarylation of *unactivated* alkynes has not been investigated.[10] Our starting point was the *intermolecular* reaction of furans with alkynes. Recently we have reported that phenylacetylene **1a** and 2,5-disubstituted furan **2** delivers both the product of the intermolecular phenol synthesis **3** and the product of the *intermolecular* hydroarylation **4**[9c] (Scheme 1). Here we report our observations when using 2-monosubstituted furans.



Scheme 1. *Intermolecular* reaction of 2,5-disubstituted furans with *activated* alkynes.

Results and Discussion

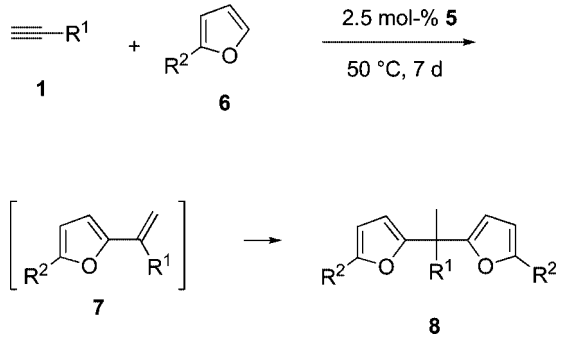
This investigation bases on the Schmidbaur–Bayler[11] salt $[(Mes_3PAu)_2Cl]BF_4$ (**5**) as the catalyst, which proved to be superior for the *intermolecular* reactions described in our previous investigation.[9c] The first explorative reactions were conducted with 2-substituted furans **6**; in order to change only one parameter at a time, again the *activated* alkyne **1a** was used as reaction partner. Unlike **2**, **6** can react with electrophiles at the more reactive 5-position of the furan ring, thus we hoped to get a more effective hydroarylation. Indeed, with a 1:1 stoichiometry of the reactants, a hydroarylation was observed – but even after long reaction times only 10–20% of **8**, the product of a twofold addition, was obtained. Having previously experienced the sensitivity of both furans and vinylfurans in reactions with such long reaction times, this was not surprising.[2,3a,8,9c] The reaction with 2.5 mol-% of catalyst **5** with **1a** and two equivalents of 2-methylfuran (**6a**) or 2-pentylfuran (**6b**) after a reaction time of seven days at 50 °C delivered significant better yields of products **8a** or **8b** (Table 1, entries 1 and 2). We could not detect or isolate the intermediate **7**, presumably like in related twofold reactions of furans with carbonyl compounds,[12] the second addition is faster than the first one, which allows only the formation of a small stationary concentration of **7** (Scheme 2).

Then we switched to the *unactivated* alkynes **1b** and **1c**, and even with the latter a hydroarylation was observed. The reaction of **1b** with **6a** gave **8c** (entry 3), **1b** and **6b** yielded **8d** (entry 4), **1c** and **6a** gave **8e** (entry 5), **1c** and **6b** delivered **8f** (entry 6). The reactions were still slow and not unexpectedly slightly lower yields were obtained compared with the

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: +49-711-685-64321
E-Mail: hashmi@hashmi.de

Table 1. Two-fold hydroarylation of alkynes **1** with furans **6** with 2.5 mol-% of catalyst **5**.

Entry	**1**	R^1	**6**	R^2	**8**	Yield (%)
1	**1a**	Ph	**6a**	Me	**8a**	53
2	**1a**	Ph	**6b**	*n*-C_5H_{11}	**8b**	58
3	**1b**	*n*-C_3H_7	**6a**	Me	**8c**	39
4	**1b**	*n*-C_3H_7	**6b**	*n*-C_5H_{11}	**8d**	47
5	**1c**	*n*-C_5H_{11}	**6a**	Me	**8e**	42
6	**1c**	*n*-C_5H_{11}	**6b**	*n*-C_5H_{11}	**8f**	44



Scheme 2.

activated alkyne; in addition the formation of oligo- and polymeric material was observed. All reactions followed the usual Markovnikov regioselectivity known for gold-catalyzed nucleophilic additions to alkynes.[13] The MS data clearly support the 2:1 assembly of the two starting materials in the product. The NMR and IR spectra show no alkyne signals and in the NMR spectra no alkene but a new methyl signal and a quaternary alkyl carbon signal is visible. The ^{1}H NMR are in accordance with the assumption of 2,5-disubstituted furan rings, the typical resonances of the protons at the 5-position of the furan ring have disappeared. Peaks for the other groups are unchanged.

Control experiments (at 50 °C) with the Lewis acid BF_3·Et_2O (1 mol-%) and the Brønsted acid HOTs (1 mol-%) as possible catalysts[3a,12] gave only black tary residues. The sensitive furan ring decomposes under the acidic conditions. At lower temperatures and with smaller amounts of catalyst no siginificant reaction can be detected.

Conclusions

The formation of the 2:1 products **8** documents the ability of catalyst **5** to also hydroarylate unactivated alkynes in intermolecular gold-catalyzed reactions. Although the overall yields under these reaction conditions and with this catalyst are not very good, the yield corresponds to up to 76% for each hydroarylation step of the twofold hydroarylation. This is a promising basis for future investigations.

Experimental Section

Synthesis of 8a: To a mixture of 2-methylfuran (205 mg, 2.50 mmol) and phenylacetylene (128 mg, 1.25 mmol) the catalyst **5** (40 mg, 31 μmol, 2.5 mol-%) was added. The reaction mixture was stirred for 7 d at 50 °C. Then the residue was purified by flash chromatography on silica gel (petroleum ether ether) to yield **8a** (176 mg, 53%) as a yellow oil. R_f (petroleum ether/ethyl acetate/dichloromethane, 6:1:0.5) = 0.56. IR (film): $\tilde{\nu}$ = 2985, 2921, 2358, 2339, 2038, 1555, 1446, 1218, 1021, 781, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (d, J = 1.0 Hz, 3 H), 2.19 (s, 6 H), 5.79 (d, J = 3.0 Hz, 2 H), 5.82 (dq, J = 3.0 Hz, 1.0 Hz, 2 H), 7.02 (m, 2 H), 7.15 (m, 1 H), 7.20 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.7 (q, 2C), 25.9 (q), 46.2 (s), 105.8 (d, 2C), 107.7 (d, 2C), 126.5 (d), 127.1 (d, 2C), 128.0 (d, 2C), 145.7 (s), 151.3 (s, 2C), 156.7 (s, 2C). MS (EI): *m*/*z* (%): 266 (40) [M$^+$], 251 (100), 189 (30), 165 (10), 84 (15), 43 (30). HRMS (70 eV): $C_{18}H_{18}O_2$: calcd. 266.1307; found: 266.1307.

Synthesis of 8b: To a mixture of 2-pentylfuran (300 mg, 2.17 mmol) and phenylacetylene (110 mg, 1.08 mmol) the catalyst **5** (35 mg, 27 mmol, 2.5 mol-%) was added. This reaction mixture was stirred for 7 d at 50 °C. Then the mixture was purified by flash chromatography on silica gel (petroleum ether) to give **8b** (239 mg, 58%) as a yellow oil. R_f (petroleum ether) = 0.86. IR (film): $\tilde{\nu}$ = 2954, 2927, 2858, 1685, 1600, 1554, 1494, 1461, 1376, 1175, 1014, 961, 780, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (m, 6 H), 1.22 (m, 8 H), 1.52 (m, 4 H), 1.90 (s, 3 H), 2.49 (t, J = 7.5 Hz, 4 H), 5.78 (d, J = 3.1 Hz, 2 H), 5.81 (dm, J = 3.1 Hz, 2 H), 7.08 (m, 2 H), 7.22 (m, 1 H), 7.28 (m, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (q, 2C), 22.4 (t, 2C), 25.8 (q), 27.8 (t, 2C), 28.0 (t, 2C), 31.3 (t, 2C), 46.3 (s), 104.9 (d, 2C), 107.3 (d, 2C), 126.3 (d), 127.1 (d, 2C), 128.3 (d, 2C), 145.9 (s), 155.7 (s, 2C), 156.5 (s, 2C). MS (EI): *m*/*z* (%): 378 (7) [M$^+$], 363 (100), 187 (12). HRMS (70 eV): $C_{26}H_{34}O_2$: calcd. 378.2559; found: 378.2554.

Synthesis of 8c: To a mixture of 2-methylfuran (102 mg, 1.24 mmol) and 1-pentyne (42.2 mg, 620 μmol) catalyst **5** was added (20 mg, 16 μmol, 2.5 mol-%). The reaction mixture was stirred for 7 d at 50 °C. Then the mixture was purified by flash chromatography on silica gel (petroleum ether/diethyl ether/dichloromethane, 20:0.5:1) to provide **8c** (56.2 mg, 39%) as a yellow oil. R_f (petroleum ether/ethyl acetate, 5:1) = 0.62. IR (film): $\tilde{\nu}$ = 2957, 2360, 1558, 1452, 1378, 1220, 1110, 1021, 941, 780, 631 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.2 Hz, 3 H), 1.11 (m, 2 H), 1.47 (s, 3 H), 1.86 (m, 2 H), 2.26 (d, J = 1.0 Hz, 6 H), 5.77 (dq, J = 3.0 Hz, J = 1.0 Hz, 2 H), 5.80 (d, J = 3.0 Hz, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.6 (q), 14.5 (q, 2C), 17.7 (t), 23.0 (q), 40.9 (s), 41.4 (t), 105.2 (d, 2C), 105.6 (d, 2C), 150.4 (s, 2C), 158.0 (s, 2C). MS (EI): *m*/*z* (%): 232 (15) [M$^+$], 190 (15), 189 (100), 84 (10), 43 (10). HRMS (70 eV): $C_{15}H_{20}O_2$: calcd. 232.1463; found 232.1464.

Synthesis of 8d: To a mixture of 2-methylfuran (205 mg, 2.50 mmol) and 1-heptyne (120 mg, 1.25 mmol) catalyst **5** (40 mg, 31 μmol, 2.5 mol-%) was added. The reaction mixture was stirred for 7 d at 50 °C. Then the mixture was purified by flash chromatography on silica gel (petroleum ether/diethyl ether/dichloromethane, 5:1:0.5) to deliver **8d** (153 mg, 47%) as a yellow oil. R_f (petroleum ether/ethyl acetate/dichloromethane 5:1:0.5) = 0.71. IR (film): $\tilde{\nu}$ = 2924, 2861, 1611, 1557, 1220, 1020, 850, 645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.28 (m, 6 H), 1.57 (s, 3 H), 1.97 (m, 2 H), 2.27 (d, J = 1.0 Hz, 6 H), 5.86 (dq, J = 3.0 Hz, 1.0 Hz, 2 H), 5.90 (d, J = 3.0 Hz, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.6 (q, 2C), 14.0 (q), 22.5 (t), 23.0 (q), 24.0 (t), 32.2 (t), 39.0 (t), 40.9 (s), 105.2 (d, 2C), 105.7 (d, 2C), 150.4 (s, 2C), 158.6 (s, 2C). MS (EI): *m*/*z* (%): 260 (10) [M$^+$], 190 (20), 189 (100), 84 (10), 43 (10). HRMS (70 eV): $C_{17}H_{24}O_2$: calcd. 260.1776; found 260.1777.

Synthesis of 8e: To a mixture of 2-pentylfuran (300 mg, 2.17 mmol) and 1-pentyne (73.6 mg, 1.08 mmol) catalyst **5** (35 mg, 27 μmol,

2.5 mol-%) was added. The reaction mixture was stirred for 7 d at 50 °C. Then the mixture was purified by flash chromatography on silica gel (petroleum ether) to yield **8e** (156 mg, 42%) as a yellow oil. R_f (petroleum ether) = 0.34. IR (film): $\tilde{\nu}$ = 2956, 2929, 2860, 1556, 1465, 1378, 1220, 1175, 1111, 1015, 780, 629 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (m, 9 H), 1.20 (m, 2 H), 1.34 (m, 8 H), 1.56 (s, 3 H), 1.61 (m, 4 H), 1.95 (m, 2 H), 2.58 (t, J = 7.6 Hz, 4 H), 5.86 (d, J = 3.0 Hz, 2 H), 5.89 (d, J = 3.0 Hz, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (q, 2C), 14.5 (q), 17.8 (t), 22.4 (t, 2C), 23.1 (q), 27.7 (t, 2C), 27.8 (t, 2C), 31.3 (t, 2C), 41.1 (s), 41.7 (t), 104.7 (d, 2C), 104.9 (d, 2C), 154.9 (s, 2C), 157.8 (s, 2C). MS (EI): *m*/*z* (%): 344 (10) [M^+], 301 (100), 187 (10), 84 (10), 28 (10). HRMS (70 eV): $C_{23}H_{36}O_2$: calcd. 344.2715; found: 344.2715.

Synthesis of 8f: To a mixture of 2-pentylfuran (300 mg, 2.17 mmol) and 1-heptyne (104 mg, 1.08 mmol) catalyst **5** (35 mg, 27 μmol, 2.5 mol-%) was added. This reaction mixture was stirred for 7 d at 50 °C. Then the mixture was purified by flash chromatography on silica gel (petroleum ether) to yield **6** (177, 44%) as a yellow oil. R_f (petroleum ether) = 0.48. IR (film): $\tilde{\nu}$ = 2987, 2959, 1557, 1465, 1378, 1112, 1016, 947, 779, 629, 582 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (m, 9 H), 1.30 (m, 12 H), 1.56 (s, 3 H), 1.61 (m, 6 H), 1.96 (m, 2 H), 2.58 (t, J = 7.6 Hz, 4 H), 5.86 (d, J = 3.0 Hz, 2 H), 5.88 (d, J = 3.0 Hz, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (q, 2C), 22.4 (q), 23.1 (t), 24.1 (t), 26.4 (q), 27.7 (t, 2C), 27.8 (t, 2C), 28.0 (t, 2C), 31.3 (t, 2C), 32.3 (t), 39.2 (t), 41.1 (s), 104.7 (d, 2C), 105.0 (d, 2C), 154.9 (s, 2C), 157.8 (s, 2C). MS (EI): *m*/*z* (%): 372 (5) [M^+], 316 (20), 301 (100), 187 (10), 43 (10), 18 (10). HRMS (70 eV): $C_{25}H_{40}O_2$: calcd. 372.3028; found: 372.3028.

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie and by the AURICAT EU-RTN (HPRN-CT-2002-00174). Gold salts were kindly donated by Johnson Matthey.

[1] a) G. Dyker, *Angew. Chem.* **2000**, *112*, 4407–4409; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237–4239; b) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65; c) A. Arcadi, S. Di Giuseppe, *Curr. Org. Chem.* **2004**, *8*, 795–812; d) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387–391.

[2] A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382–2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288.

[3] a) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247–1252; b) A. S. K. Hashmi, R. Salathé, T. M. Frost, L. Schwarz, J.-H. Choi, *Appl. Catal. A* **2005**, *291*, 238–246.

[4] a) A. Arcadi, G. Bianchi, M. Chiarini, G. D'Anniballe, F. Marinelli, *Synlett* **2004**, 944–950; b) M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli, *J. Org. Chem.* **2005**, *70*, 2265–2273.

[5] M. Alfonsi, A. Arcadi, G. Bianchi, F. Marinelli, A. Nardini, *Eur. J. Org. Chem.* **2006**, 2393–2402.

[6] M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, *68*, 3465–3496.

[7] a) Z. Shi, C. He, *J. Org. Chem.* **2004**, *69*, 3669–3671; b) Z. Li, Z. Shi, C. He, *J. Organomet. Chem.* **2005**, *690*, 5049–5054.

[8] A. S. K. Hashmi, L. Grundl, *Tetrahedron* **2005**, *61*, 6231–6236.

[9] a) C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155–3164; b) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123–1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; c) A. S. K. Hashmi, M. C. Blanco, E. Kurpejovic, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713; d) A. S. K. Hashmi, P. Haufe, C. Schmid, A. Rivas Nass, W. Frey, *Chem. Eur. J.* **2006**, *12*, 5376–5382; e) A. S. K. Hashmi, J. P. Weyrauch, E. Kurpejovic, T. M. Frost, B. Miehlich, W. Frey, J. W. Bats, *Chem. Eur. J.* **2006**, *12*, 5806–5814.

[10] For related Pd^{II}- and Pt^{II}-catalyzed reactions, which exclusively use acceptor-substituted or phenyl-substituted and thus activated alkynes and thus are closely related to the results reported for gold-catalysts in ref.[6], see: a) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263; b) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992–1995.

[11] A. Bayler, A. Bauer, H. Schmidbaur, *Chem. Ber./Recueil* **1997**, *130*, 115–118.

[12] A. S. K. Hashmi, L. Schwarz, P. Rubenbauer, M. C. Blanco, *Adv. Synth. Catal.* **2006**, *348*, 705–708.

[13] a) R. O. C. Norman, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983–1987; b) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475–1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

Received: June 23, 2006
Published Online: August 22, 2006

