

Gold-Catalyzed Synthesis of Chroman, Dihydrobenzofuran, Dihydroindole, and Tetrahydroquinoline Derivatives

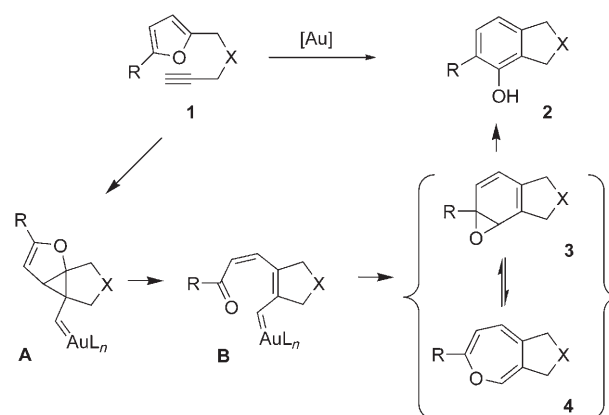
A. Stephen K. Hashmi,^{*,[a]} Matthias Rudolph,^[b] Jan W. Bats,^[c] Wolfgang Frey,^[b] Frank Rominger,^[a] and Thomas Oeser^[a]

Abstract: Different furans containing an ynamide or alkynyl ether moiety in the side chain were prepared. The gold-catalyzed transformation of these compounds delivered dihydroindole, dihydrobenzofuran, chroman, and tetrahydroquinoline derivatives at room temperature through very fast reactions. Furthermore, the stabilizing effect of the heteroatom directly attached to the intermediate arene oxides led to highly selective reactions, even in the case of only mono-substituted furans, which is quite different from previous results obtained with non-heteroatom-substituted alkynes.

Keywords: alkynes • arenes • gold • heterocycles • homogeneous catalysis

Introduction

The importance of gold catalysis as a powerful tool for organic synthesis is continuously increasing,^[1] the cyclization of enynes is playing a major role.^[2a,b] In our group, we developed a gold-catalyzed phenol synthesis (Scheme 1), in which the first step, like all the other ene-yne cyclizations, probably involves a cyclopropyl carbenoid (**A**) or an electronically related structure, but then due to the additional enol ether substructure follows a different pathway (via **B** and the valence tautomers **3/4**) to ultimately form the aromatic phenols **2**.^[3] This methodology has proven to be a powerful tool for the synthesis of various heterocycles, such as dihydro-



Scheme 1. Gold-catalyzed phenol synthesis.

[a] Prof. Dr. A. S. K. Hashmi, Dr. F. Rominger, Dr. T. Oeser*
Organisch-Chemisches Institut, Ruprecht-Karls-Universität
Heidelberg Im Neuenheimer Feld 270
69120 Heidelberg (Germany)
Fax (+49) 6221-544205
E-mail: hashmi@hashmi.de

[b] Dipl.-Chem. M. Rudolph, Dr. W. Frey*
Institut für Organische Chemie, Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)

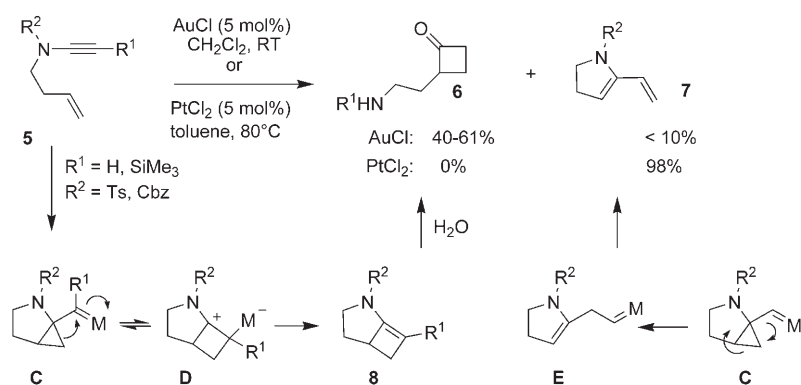
[c] Dr. J. W. Bats*
Institut für Organische Chemie und Chemische Biologie
Johann Wolfgang Goethe-Universität Frankfurt
Marie-Curie-Str. 11, 60439 Frankfurt (Germany)

[*] Crystallographic investigation.

Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

isoindoles,^[3a-c,f,h,i,k,l] tetrahydroisoquinolines,^[3a,f,i-l,n] dihydroisobenzofurans,^[3a,m] and isochromans.^[3m] All of these heterocycle syntheses are based on a propargylic moiety connected to the heteroatom in the tether of the substrate **1**. Herein, we report on our efforts to use alkynyl moieties directly connected to the heteroatom as reactive units in the side chain of the furans, namely alkynyl amides and alkynyl ethers. This should provide access to other types of heterocycles, such as dihydroindoles, dihydrobenzofurans, chromans, and tetrahydroquinolines.

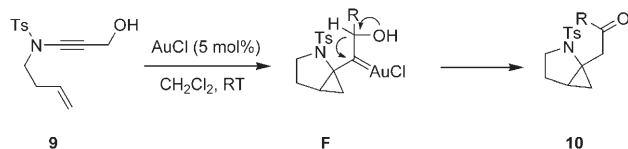
So far only very few examples of the gold-catalyzed eneynamide^[4a] and ene-ydol ether^[5] cyclizations have been reported. The gold-catalyzed cyclization of 1,6-ene-ynamides **5** developed by Cossy et al. delivered cyclobutanones **6** as



Scheme 2. Pathways for metal-catalyzed enyne cyclization of ynamides. Ts = tosyl; Cbz = benzyloxycarbonyl.

major products,^[4a] whereas similar substrates in platinum-catalyzed reactions delivered exclusively formal metathesis products **7** (Scheme 2).^[4b,c] The different chemoselectivity can be explained by the milder reaction conditions of the gold-catalyzed reactions. Here a ring expansion of the primary cyclopropyl carbenoid **C**, leads to a cyclobutyl cation **D** (stabilized by the neighbouring heteroatom). After elimination of the metal and addition of water to cyclobutene **8**, products **6** are formed. A double cleavage of the primary carbenoid complex **C** in the platinum-catalyzed reaction delivers carbenoid **E**, which finally results in products **7** after elimination of the metal.

By the use of substrate **9**, which contains a propargylic alcohol moiety, the cyclopropyl carbenoid **F** could be trapped by a 1,2-hydride shift to deliver the ketone **10** (Scheme 3).^[4]



Scheme 3. A third pathway for gold-catalyzed enyne cyclization of ynamides.

The products formed by the gold-catalyzed cyclization of siloxy enynes **11**, reported by Kozmin et al.,^[5] are also influenced by a stabilizing effect of the attached heteroatom. After the initial formation of the cyclopropylcarbenoid **G**, ring expansion, leading to cyclobutyl cations **H**, and a subsequent skeletal rearrangement via **I** to carbenoid **J**, could explain the shift of the silyl ether group in the final products **12** or **13** (depending on the substitution pattern, Scheme 4).

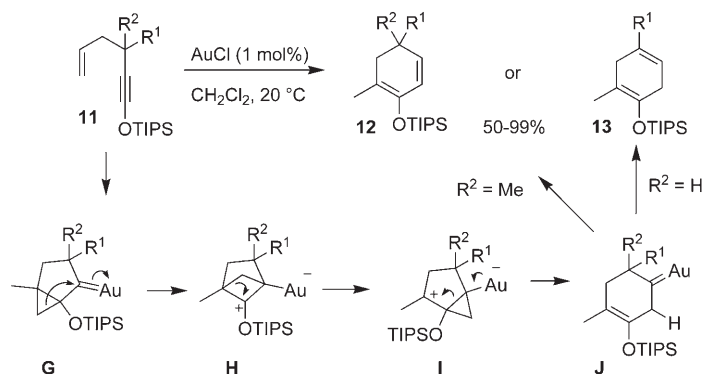
Results and Discussion

The introduction of the side chain for the dihydrobenzofuran syntheses was achieved by the addition of lithiated furans **14** to oxiranes **15**.^[3m] The corresponding three-carbon-atom chain for chroman synthesis was introduced by Michael ad-

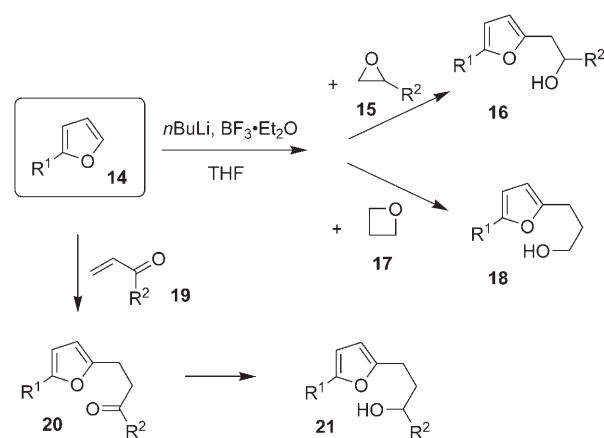
dition of furans **14** to enones **19** and subsequent reduction of the carbonyl group of **20** to the alcohol **21**.^[6-8] Alternatively, a boron trifluoride etherate mediated addition of lithiated furan to oxetane **17** provided direct access to the alcohol **18** in good yield (Scheme 5).^[9]

The resulting alcohols **16**, **18** and **21** were transformed into the dichlorovinyl ethers **23a-d** (Table 1) by following a protocol of Greene et al.^[10] The addition of the alcohols to trichloroethene in THF provided **23a-d** in yields of 66–80%. The addition of decanol (**22**) to trichloroethene yielded the alkyl vinyl ether **23e** in 70% yield.

The starting points for the ynamide syntheses were the toluenesulfonamides **24a-d** (Table 2), which were prepared by literature procedures from the corresponding amines.^[31,n] Toluene sulfonamides **24e/24g**, containing a three-carbon-atom unit were synthesized from the corresponding alcohols



Scheme 4. Reactions of alkynyl ethers in gold-catalyzed reactions. TIPS = triisopropylsilyl.



Scheme 5. Synthesis of furans with hydroxy groups in the side chain.

Table 1. Formation of the dichlorovinyl ethers **23**.

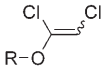
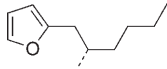
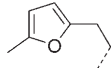
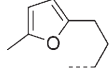
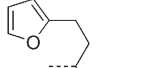
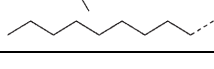
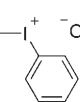
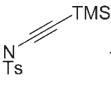
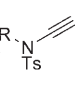
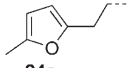
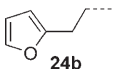
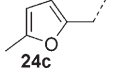
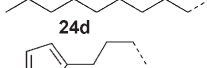
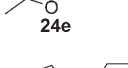
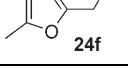
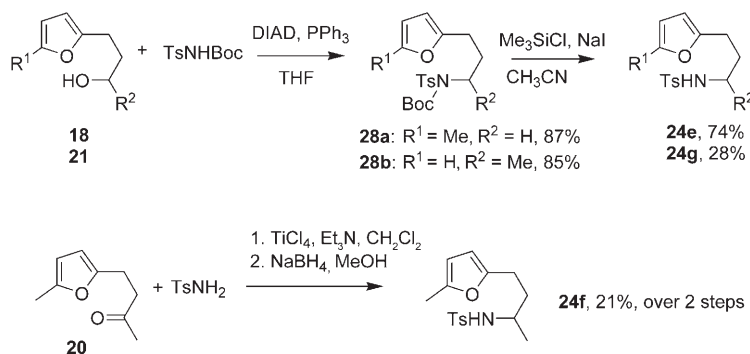
R-OH + 		NaH, THF 16h, RT	
16, 18, 21, 22			23
Entry	16,18,21	R	Product (yield [%])
1	16a		23a (79)
2	16b		23b (80)
3	18a		23c (66)
4	21a		23d (75)
5	22		23e (70)

Table 2. Synthesis of compounds **27** via alkynylidonium salts.^[a]

R-NHTs + 		$n\text{BuLi}$, toluene		TBAF, THF	
24	25		26		27
Entry	R	Reaction time	26 (yield [%])		yield of 27 [%]
1		3 d	26a (65)		27a (100)
2		16 h	26b (65)		27b (100)
3		16 h	26c (43)		27c (99)
4		2 d	26d (48)		27d (99)
5		2 d	slow decomposition		–
6		2 d	slow decomposition		–

[a] TMS = trimethylsilyl; TBAF = tetrabutylammonium fluoride



Scheme 6. Different routes to tosylamides **24**. DIAD = diisopropyl azodicarboxylate.

18a/21a by a Mitsunobu reaction with *N*-*tert*-butoxycarbonyl-*p*-toluenesulfonamide^[11] and subsequent deprotection of **28a/28b** with trimethylsilyl iodide (Scheme 6).^[12] A deprotection under acidic conditions led to decomposition of the starting materials. Alternatively, TiCl₄-mediated tosylation and reduction delivered amide **24f** in moderate overall yield (Scheme 6). To introduce the alkyne moiety, we used a procedure published by Witulski's group.^[13] Addition of deprotonated amides in toluene to trimethylsilyl ethynylphenyliodonium triflate^[14] **25** and deprotection with tetrabutylammonium fluoride delivered ynamides **27a–d** in moderate overall yields (Table 2). A partial loss of product might result from problems during purification. Unfortunately, amides **24e** and **24f** containing a three-carbon-atom unit did not react—only a slow decomposition could be detected by TLC.

As a consequence, we switched to a protocol of Brückner et al. (Table 3).^[15] Our intention was the direct introduction of the tosylated nitrogen under Mitsunobu conditions. The necessary alcohols **28** are easily available. A Mitsunobu reaction of *N*-formyl toluenesulfonamide **29** delivered mixtures of *N*- and *O*-alkylated products **30/31**, which—without purification—were directly converted to the dichlorovinyl amides **32a–c** in moderate to good overall yields (depending on the steric demand of the alcohols **28**, which led to different *N*/*O* ratios of the intermediate products **30** and **31** that were formed by substitution of the ambident formamide nucleophile). Chloride elimination with *n*BuLi led to ynamides **33a–c** in excellent yields.

For the gold-catalyzed formation of oxygen heterocycles we used two different procedures (methods A and B as described in Scheme 7). Elimination to **34** with *t*BuLi at –78 °C delivered cleaner crude alkynyl ethers than elimination with *n*BuLi. The isolated alkynyl ethers **34a–e** were used for gold catalysis without further purification. Both solvents CH₃CN and CHCl₃ were suitable for the gold-catalyzed transformations. When CH₃CN was used, a competitive addi-

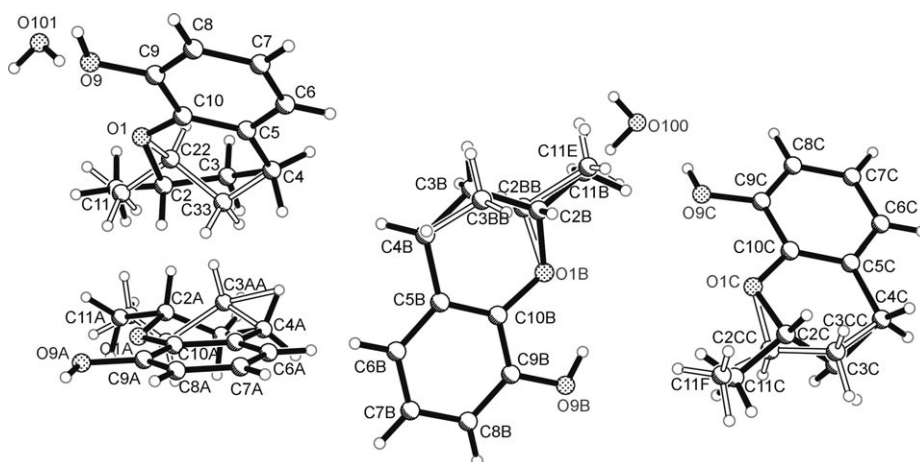
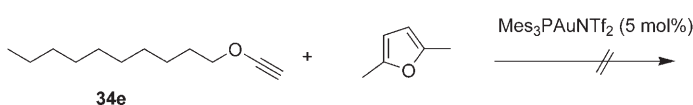


Figure 2. Solid state structure of **35d**.



Scheme 9. No efficient intermolecular phenol synthesis was observed with the alkynyl ether **3e**. Mes = mesityl; Tf = triflate.

The gold-catalyzed dihydroindole formation with substituted furan **27a** delivered the product **39a** in good yield and with a very short reaction time (short reaction time relative to other substrates in the phenol synthesis in which a heteroatom is not directly attached to the alkyne, Table 4) by using 5 mol % AuCl_3 as the catalyst. Single crystals for XRD analysis could be obtained (Figure 3). An intramolecular hydrogen bond between the phenolic hydrogen atom and the oxygen atom is observed. Problems occurred for unsubstituted substrate **27b**. In this case, the reaction was very unselective for gold(I) complexes and only the pyridine–gold(III) complexes **40**^[19] and **41** delivered a small amount of product **39b**. During preparation of complex **41**, single crystals were

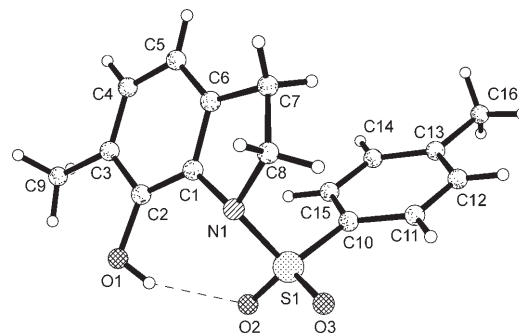


Figure 3. Solid state structure of **39a**.

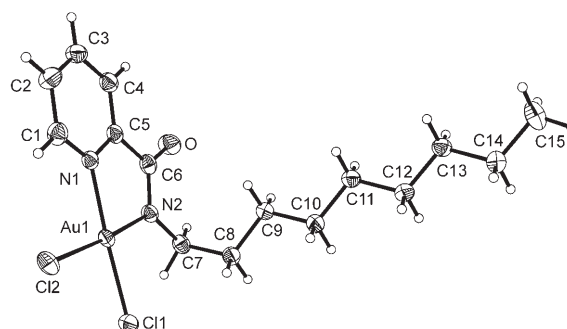
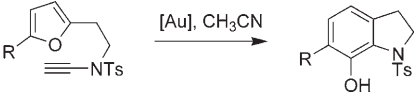
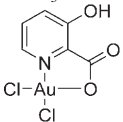
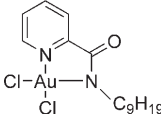
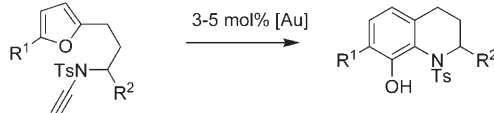


Figure 4. Solid state structure of catalyst **41**.

Table 4. Gold-catalyzed conversion of the ynamines **27**.

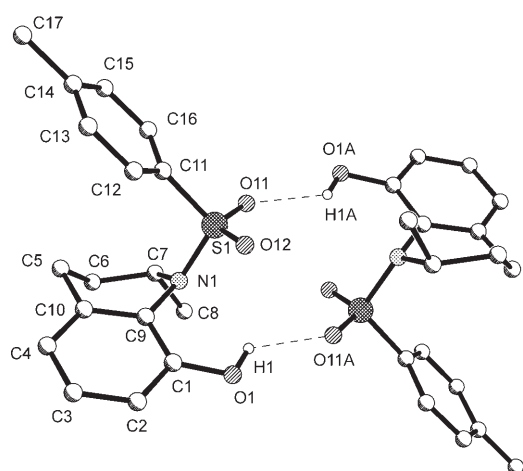
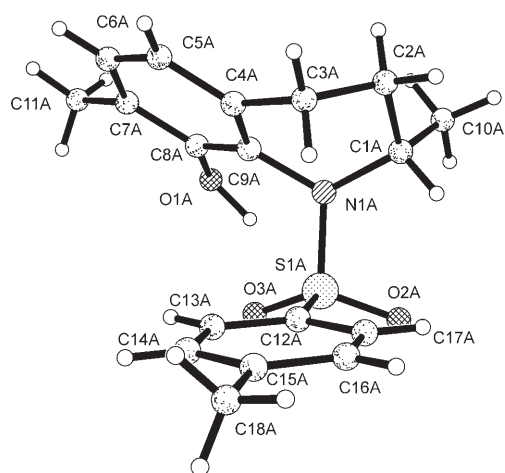
					
27a : R = Me 27b : R = H		39a 39b			
Entry	27	Catalyst	Loading [mol %]	Reaction time	39 (yield [%])
1	27a		5	5 min	39a (62)
2	27b		3	5 min	39b (13)
3	27b		3	1 h	39b (9)

ing to pyridine complexes **40** and **41** (Table 5) in CD_3CN . Fortunately, single crystals for **42a** could be obtained. The X-ray crystal structure (Figure 5) unambiguously shows the position of the oxygen atom at the 8-position of the tetrahydroquinoline structure. Two intermolecular hydrogen bonds between the phenolic hydroxyl group and the oxygen atom of the tosyl group are observed. The X-ray crystal structure of product **42b** shows two different conformers, which are stabilized by two intermolecular hydrogen bonds (Figure 6). Compound **42c** also gave crystals suitable for XRD analysis

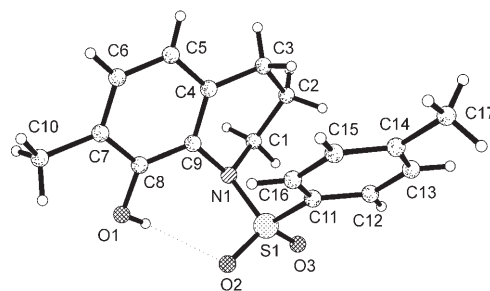
Table 5. Gold-catalyzed conversion of the ynamines **33**.


33a: R¹ = H, R² = Me **42a**
33b: R¹ = Me, R² = Me **42b**
33c: R¹ = Me, R² = H **42c**

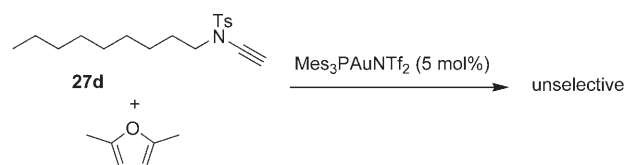
Entry	33	Catalyst	Loading [mol %]	T [°C]	Solvent	Reaction time	42 (yield [%])
1	33a	AuCl ₃	3	0	CDCl ₃	5 min	42a (17)
2	33a	40	5	RT	CD ₃ CN	1 h	42a (26)
3	33a	41	5	RT	CD ₃ CN	16 h	42a (37)
4	33b	AuCl ₃	3	0	CDCl ₃	5 min	42a (88)
5	33c	AuCl ₃	3	0	CDCl ₃	5 min	42a (67)

Figure 5. Solid state structure of product **42a**.Figure 6. Solid state structure of product **42b**.

(Figure 7). The molecule shows an intramolecular hydrogen bond between the phenolic hydrogen atom and the oxygen atom of the tosyl group. The intermolecular reaction of **27d** with dimethylfuran turned out to be unselective

Figure 7. Solid state structure of product **42c**.

(Scheme 10). Compound **27c**, with only one carbon atom in the side chain, also did not produce a selective reaction.

Scheme 10. No selective intermolecular phenol synthesis was observed with **27d**.

Conclusion

The routes presented here, allow an efficient access to chromans, dihydrobenzofurans, dihydroindoles, and tetrahydroquinolines from furans by two simple steps and a subsequent gold-catalyzed reaction of the substrates containing an ynamide and ynol ether moiety in the side chain. In contrary to the reported gold-catalyzed reactions, no ring expansion of the primary cyclopropyl carbenoids could be observed. This indicates a very fast ring opening of the strained cyclopropyl carbenoid **A**, to form the monocyclic carbenoid **B**. Furthermore, due to the stabilizing effect of the heteroatom, which was directly attached to the intermediate pentadienyl cation, selectivity problems were not observed for unsubstituted furans. Relative to other, previously described substrate types for the phenol synthesis, the donor-substituted alkynes reacted very quickly.

Acknowledgement

We thank Umicore AG & Co KG, Hanau (Germany) for the donation of gold salts.

- [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.* **2003**, *36*, 3–9; c) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65; d) N. Krause, A. Hoffmann-Röder, *Org. Biomol. Chem.* **2005**, *3*, 387–391; e) A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150–7154; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990–6993; f) A. S. K. Hashmi, G. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; g) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211.

- [2] a) L. Zhang, J. Sun, S. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; b) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206–209; *Angew. Chem. Int. Ed.* **2006**, *45*, 200–203.
- [3] a) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, *3*, 3769–3771; c) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Catal. Today* **2002**, *72*, 19–27; d) A. S. K. Hashmi, L. Ding, P. Fischer, J. W. Bats, W. Frey, *Chem. Eur. J.* **2003**, *9*, 4339–4345; e) A. S. K. Hashmi, L. Grundl, *Tetrahedron* **2005**, *61*, 6231–6236; f) A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem.* **2004**, *116*, 6707–6709; *Angew. Chem. Int. Ed.* **2004**, *43*, 6545–6547; g) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfe, W. Frey, J. W. Bats, *Angew. Chem.* **2005**, *117*, 2858–2861; *Angew. Chem. Int. Ed.* **2005**, *44*, 2798–2801; h) A. S. K. Hashmi, J. P. Weyrauch, E. Kurpejovic, T. M. Frost, B. Miehl, W. Frey, J. W. Bats, *Chem. Eur. J.* **2006**, *12*, 5806–5810; i) A. S. K. Hashmi, M. C. Blanco, E. Kurpejovic, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713; j) A. S. K. Hashmi, P. Haufe, C. Schmid, A. Rivas Nass, W. Frey, *Chem. Eur. J.* **2006**, *12*, 5376–5382; k) A. S. K. Hashmi, R. Salathé, W. Frey, *Chem. Eur. J.* **2006**, *12*, 6991–6996; l) S. Carretin, M. C. Blanco, A. Corma, A. S. K. Hashmi, *Adv. Synth. Catal.* **2006**, *348*, 1283–1288; m) A. S. K. Hashmi, M. Wölfe, F. Ata, M. Hamzic, R. Salathé, W. Frey, *Adv. Synth. Catal.* **2006**, *348*, 2501–2508; n) A. S. K. Hashmi, F. Ata, E. Kurpejovic, J. Huck, M. Rudolph, *Top. Catal.* **2007**, *44*, 245–251.
- [4] a) S. Couty, C. Meyer, J. Cossy, *Angew. Chem.* **2006**, *118*, 6878–6882; *Angew. Chem. Int. Ed.* **2006**, *45*, 6726–6730; b) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807; c) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509–1511.
- [5] F. Marion, J. Coulomb, A. Servais, C. Courillon, L. Fensterbank, M. Malacria, *Tetrahedron* **2006**, *62*, 3856–3871.
- [6] H.-J. Wu, S.-H. Lin, *Heterocycles* **1994**, *38*, 1507–1518.
- [7] R. Franke, *Liebigs Ann. Chem.* **1979**, 3–8.
- [8] 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.
- [9] M. J. Eis, J. E. Wrobel, B. Ganem, *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.
- [10] A. Moyano, F. Charbonnier, A. E. Greene, *J. Org. Chem.* **1987**, *52*, 2919–2922.
- [11] B. R. Neustadt, *Tetrahedron Lett.* **1994**, *35*, 379–380.
- [12] R. S. Lott, V. S. Chauhan, C. H. Stammer, *J. Chem. Soc. Chem. Commun.* **1979**, 495–496.
- [13] B. Witulski, T. Stengel, *Angew. Chem.* **1998**, *110*, 495–498; *Angew. Chem. Int. Ed.* **1998**, *37*, 489–492.
- [14] *Modern Acetylene Chemistry*, (Eds.: P. J. Stang, F. Dieterich), VCH, Weinheim, **1995**, 67–98.
- [15] D. Brückner, *Synlett* **2000**, *10*, 1402–1404.
- [16] CCDC-676361 (**35b**), 676362 (**35d**), 676304 (**39a**), 676363 (**41**), 676364 (**42a**), 676305 (**42b**), and 676306 (**42c**) contain the supplementary 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.
- [17] A. S. K. Hashmi, M. Rudolph, H.-U. Siehl, M. Tanaka, J. W. Bats, W. Frey, *Chem. Eur. J.* **2008**, *14*, 3703–3708.
- [18] A. S. K. Hashmi, M. C. Blanco, *Eur. J. Org. Chem.* **2006**, 4340–4342.
- [19] A. Dar, K. Moss, S. M. Cottrill, R. V. Parisch, C. A. McAuliffe, R. G. Pritchard, B. Beagley, J. Sandbank, *J. Chem. Soc. Dalton Trans.* (1972–1999), **1992**, 1, 1907–1913.

Received: February 1, 2008

Please note: Minor changes have been made to this publication in Chemistry—A European Journal Early View. The Editor.

Published online: June 23, 2008