CHEMISTRY
A EUROPEAN JOURNAL

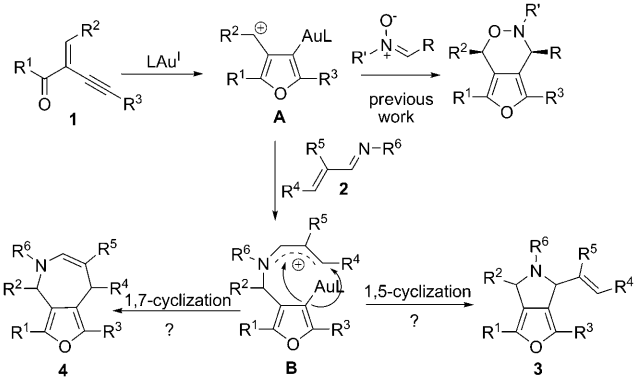
DOI: 10.1002/chem.200901813

Highly Substituted Furo[3,4-*c*]azepines by Gold(I)-Catalyzed Diastereoselective Tandem Double Heterocyclizations and 1,2-Alkyl Migration

Hongyin Gao,[a] Xiaoli Zhao,[a] Yihua Yu,[b] and Junliang Zhang*[a]

Transition-metal-catalyzed domino reactions[1] are unrivaled in their ability to provide rapid access to architecturally complex molecules from relatively simple starting materials. In the context of our ongoing efforts to develop cascade reactions for the synthesis of heterocyclic compounds,[2] we now report a novel approach to fused heterobicyclic furo-[3,4-*c*]azepines by a gold-catalyzed[3] highly diastereoselective tandem double heterocyclization[4] and 1,2-alkyl migaration.[5] Despite the numerous methods towards furans[6] or azepines[7] from acyclic precursors developed in past few years, there are no reports on the synthesis of fused heterobicyclic furo[3,4-*c*]azepines. Furthermore, as far as we know, no gold-catalyzed domino reaction consisting of tandem double heterocyclizations and 1, 2-alkyl migration has been described.

Recently, gold-catalyzed heterocyclization of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles leading to trisubstituted furans was reported by Larock and co-workers.[8] Very recently, we also developed a novel approach to fused heterobicyclic compounds by a highly diastereoslective gold(I)-catalyzed tandem heterobicyclization of 2-(1-alkynyl)-2-alken-1-ones with nitrones.[2f] These reactions are believed to proceed via furanyl gold intermediates **A**. We envisaged that the nucleophilic α, β-unsaturated imines might attack the carbocation of intermediates **A** to produce furanyl gold intermediates **B** tethered with an allylic iminium ion. Subsequent nucleophilc attack of furanyl gold to the iminium ion would give two different heterobicycylic compounds **3** or **4** via regioselective 1,5- or 1,7-cyclizations (Scheme 1).



Scheme 1. Proposed reaction pattern of ketones **1** with α, β-unsaturated imines **2**.

We began our research by examining the cyclization of ketone **1a** and *N*-4-methoxyphenyl imine **2a** in the presence of various metal catalysts (see the Supporting Information). This cyclization reaction was later found to proceed smoothly under the catalysis of 5 mol% of $Ph_3PAuOTf$ (generated from a 1/1 mixture of [Ph_3AuCl] and AgOTf) at room temperature in CH_2Cl_2 in the presence of 4 Å molecular sieves. However, to our surprise, we found that the product was 5,7-fused **5aa** rather than the expected fused 5,5-heterobicyclic **3aa** or 5,7-heterobicyclic **4aa** [Eq. (1)]. The structure of **5aa** was confirmed by single-crystal X-ray diffraction (Figure 1),[9] indicating that the reaction undergoes a novel unexpected reaction pathway. Other commonly used catalysts in cyclization reactions such as AuCl, $AuCl_3$, picolinic acid derived gold catalyst ($PicAuCl_2$), IPrAuOTf, $PtCl_2$, $Yb(OTf)_3$, $Sc(OTf)_3$ as well as silver catalysts give the product in low yields. Other solvents such as 1,2-dichloroethane (DCE), toluene, CH_3CN and THF also give lower product yields.

[a] H. Gao, Prof. Dr. X. Zhao, Prof. Dr. J. Zhang
Shanghai Key Laboratory of Green Chemistry and Chemical Processes
Department of Chemistry, East China Normal University
3663 N. Zhongshan Road, Shanghai 200062 (China)
Fax: (+86) 21-6223-5039
E-mail: jlzhang@chem.ecnu.edu.cn

[b] Prof. Y. Yu
Shanghai Key Laboratory of Magnetic Resonance
Department of Physics, East China Normal University (China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901813.

WILEY InterScience DISCOVER SOMETHING GREAT
© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

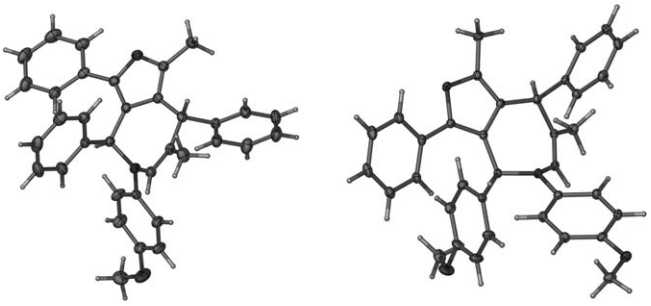
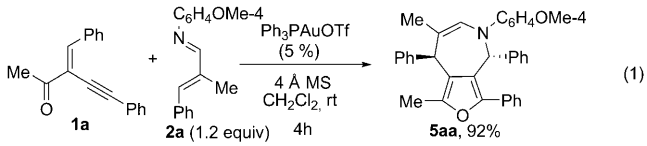


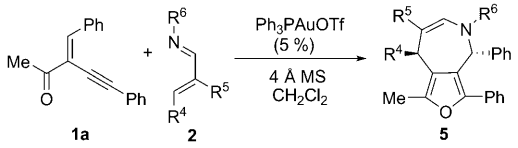
Figure 1. X-ray structures of **5aa** (left) and **5ba** (right).



(1)

Having established the standard conditions, we examined the scope of this gold-catalyzed cascade reaction (Table 1). The reaction is highly tolerant of various substituents at all three positions of the unsaturated imine component **2**. For example, conjugation with aryl or aliphatic groups (R^4 and R^5) and *N*-aryl or *N*-benzyl groups (R^6) had little impact on the product yield (Table 1, entries 1–8). For example, the reaction of imine **2h** with **1a** affords **5ah** in 63% yield albeit with higher catalyst loading (Table 1, entry 7). Furthermore, it is noteworthy that all the products were obtained as a single diastereoisomer (>20:1), as determined by checking the ^{1}H NMR spectrum of the crude product.

Table 1. Diastereoselective synthesis of highly substituted furo[3,4-*c*]azepines by variation of imine **2**[a].

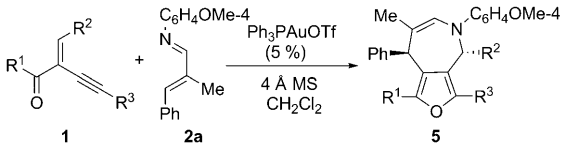


Entry	Imine **2** $R^4/R^5/R^6$	Temp	Time [h]	Yield of **5**[b] [%]
1	Ph/Me/Ph (**2b**)	rt	12	**5ab** (85)
2	Ph/Me/4-ClPh (**2c**)	rt	12	**5ac** (80)
3	Ph/Me/4-$NO_2C_6H_4$ (**2d**)	rt	12	**5ad** (86)
4	Ph/Ph/4-$MeOC_6H_4$ (**2e**)	reflux	10	**5ae** (88)
5	4-$MeOC_6H_4$/Me/4-$MeOC_6H_4$ (**2f**)	reflux	10	**5af** (86)
6	4-$NO_2C_6H_4$/Me/4-$MeOC_6H_4$ (**2g**)	reflux	10	**5ag**(75)
7[c]	Me/Me/4-$MeOC_6H_4$ (**2h**)	reflux	10	**5ah** (63)
8	Ph/Me/Bn (**2i**)	reflux	12	**5ai** (77)

[a] All reactions were carried out using **1** (0.5 mmol) under standard conditions. [b] Yield of the isolated product as a single diasteroisomer (>20:1). [c] 20 mol% of [Ph_3PAuCl]/AgOTf were employed, otherwise a by-product was formed from the reaction of **1a** with 4-methoxyphenylamine generated from the decomposition of unstable imine **2h**.

After examination the scope of imine **2**, we turned our attention to studying the scope of the ketone component of this gold-catalyzed transformation (Table 2). The ketone substituent R^1, which can be either aromatic or aliphatic groups, has little impact on the yield of transformation (Table 2, compare entries 1 and 10). The alkyne substituent R^3 can also be aromatic or aliphatic groups, but aliphatic ones give relatively lower yields of the cycloadducts (Table 2, entries 5, 8, and 9). It seems that the olefin substituent R^2 needs to be aromatic group to obtain a reasonable product yield. The structure of **5ba** was also further confirmed by single-crystal X-ray diffraction (Figure 1).[9] 2-D NMR spectra analysis (H,H-NOESY, HSQC, HMBC) of selected compounds **5aa**, **5ae**, **5fa**, **5ai**, and **5ia** showed that they are consistent with each other. For example, there are H,H-NOESY signals between the protons of CH_3 and the CH (R^4) for **5aa**, **5ae**, **5ai**, and **5ia** and the protons of CH_2-(C_3H_7) and CH(R^2) of **5fa**.

Table 2. Diastereoselective synthesis of highly substituted furo[3,4-*c*]azepines by variation of ketone **1**.



Entry	Ketone **1** $R^1/R^2/R^3$	Temp	Time [h]	Yield of **5**[a] [%]
1	Me/4-$MeOC_6H_4$/Ph (**1b**)	rt	12	**5ba** (81)
2	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1c**)	reflux	24	**5ca** (79)
3	Me/Ph//1-Naphthyl (**1d**)	rt	24	**5da** (82)
4	Me/4-$MeOC_6H_4$/1-Naphthyl (**1e**)	rt	36	**5ea** (76)
5	Me/Ph/*n*Bu (**1f**)	reflux	12	**5fa** (58)
6[b]	Me/Ph/4-$MeOC_6H_4$ (**1g**)	rt	24	**5ga** (78)
7	Me/Ph/4-$NO_2C_6H_4$ (**1h**)	reflux	18	**5ha** (84)
8[c]	Ph/Ph/*n*Bu (**1i**)	rt	24	**5ia** (79)
9[d]	Ph/Ph/1-cyclohexenyl (**1j**)	rt	24	**5ja** (81)
10	Ph/Ph/Ph (**1k**)	rt	24	**5ka** (96)

[a] Unless otherwise specified, the diastereoselectivity is >20:1, the number in parentheses is the isolated yield of the major isomer. [b] d.r. = 8.0:1. [c] d.r. = 4.1:1. [d] d.r. = 6.1:1.

We next examined the reaction of **1a** with heteroaryl imine **6a** under the catalysis of $Ph_3PAuOTf$ [Eq. (2)]. Surprisingly, the 2-D NMR spectra of the product are not consistent with those of **5aa**. For example, there is a H,H-NOESY signal between the protons of CH_3 and C*H*(Ph) rather than C*H*(NTs), indicating that the reaction might not undergo the same migration pathway.[10] This hypothesis was further confirmed by the X-ray structure analysis of **7ab** (Figure 2).[9]

A proposed mechanism that accounts for this gold-catalyzed cascade transformation is depicted in Scheme 2. Gold-catalyzed cyclization of ketone **1** afforded a furanyl gold intermediate **A**. The addition of imine **2** to the cabocation via the nitrogen atom would afford intermediate **B** with an allylic iminium ion, which would undergo intramolecular 2,7-cyclization leading to a spirobicyclic oxonium ion **C** rather

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

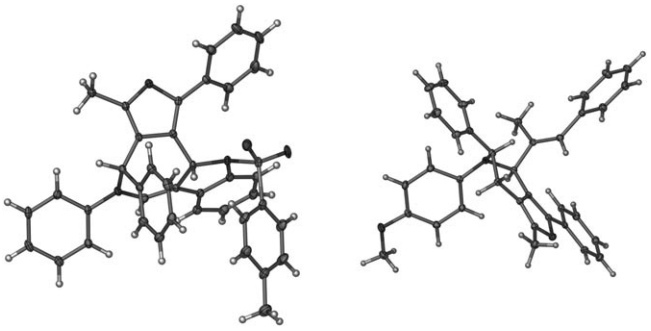
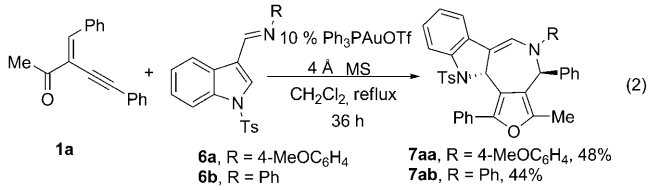
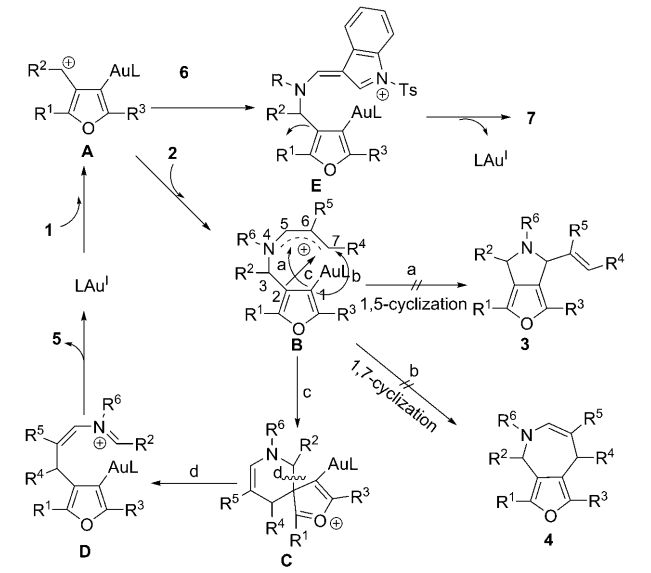


Figure 2. X-ray structures of **7ab** (left) and **9** (right).



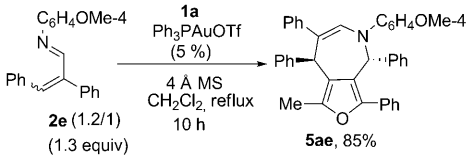
(2)



Scheme 2. Plausible mechanism.

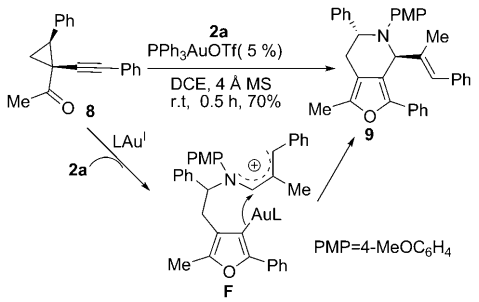
than the direct 1,5- or 1,7-cyclization. The definite reason is unclear but the configuration of the intermediate **B** may not favor the direct 1,5-or 1,7-cyclizations. Subsequent regioselective C–C bond cleavage via path d in Scheme 2 would give a furanyl gold intermediate **D** with an iminium ion followed by cyclization to produce the final product and regenerate the gold catalyst. In contrast, when heteroaryl imines **6** were used as the heterodiene component, the reaction of heteroaryl imine **6** with intermediate **A** produced a furanyl gold intermediate **E** with an iminium ion. Subsequent direct cyclization of intermediate **E** gave the product **7** without any migration. The reason why the intermediate **E** undergoes the direct cyclization is not very clear, but the highly reactive iminium ion may readily react with the vinyl gold. To our surprise, the oxonium ion **C** did not undergo the expected 1,2-alkyl migration from 3- to 2-positions of the furan ring, which was discovered by Kirsch and co-workers in the Au^{III}- or Pt^{II} -catalyzed tandem hetherocyclization and 1,2-alkyl migration reaction of alkynyl carbonyl compounds.[5a]

It is not surprising to find that the reaction of the imine (*Z*, *E*)-**2e** with **1a** gave the same product, *trans*-**5ae**, in 85 % yield [Eq. (3)], since the reaction was believed to proceed via the same allylic iminium ion **B** as those *E*,*E*-heterodienes.



(3)

Interestingly, cyclization of 1-(1-alkynyl)cyclopropyl ketone **8**, an analogue of 2-(1-alkynyl)-2-alken-1-one **1**, with imine **2a** provided the fused 5,6-heterobicyclic compound **9** in 70 % yield under the standard conditions (Scheme 3). The



Scheme 3. Tandem double heterocyclization of **8** with **2a** and the proposed reaction pathway.

structure was also confirmed by single-crystal X-ray diffraction (Figure 2).[9] The reaction is believed to proceed via the 1,6-cyclization of furanyl gold intermediate **F** tethered with an allylic iminium ion, a longer tethered chain than intermediate **B**. The reason that intermediate **F** did not undergo similar cyclization and subsequent migration is unclear, but the configuration of intermediate **F** may favor the nucleophilic attack of vinyl gold to the iminium ion to form a six-membered ring.

In summary, we have developed a novel cationic Au^{I}-catalyzed tandem reactions under mild conditions, providing a rapid, efficient and stereoselective access to highly substituted furo[3,4-*c*]azepines from the simple, readily available 2-(1-alkynyl)-2-alken-1-ones and heterodienes. The nature of the heterodienes will control the reaction pathway. Furthermore, the substituent of the product could be easily varied

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

by changing the substituent pattern of the corresponding starting materials. Further studies including mechanism, scope and synthetic application are being ongoing in this laboratory.

Experimental Section

Synthesis of fused heterobicyclic compound 5aa [Eq. (1)]: To a solution of [Ph_3PAuCl] (12.4 mg, 0.025 mmol) in CH_2Cl_2 (2 mL) was added AgOTf (6.4 mg, 0.025 mmol) under an Ar atmosphere, and the mixture was stirred for 10 min at room temperature. Then 4 Å molecular sieves (200 mg), ketone **1a** (123 mg, 0.50 mmol), imine **2a** (150.6 mg, 0.60 mmol), and CH_2Cl_2 (3 mL) under Ar at room temperature was added to this mixture. The resulting mixture was stirred for 12 h after which time the reaction was complete as determined by TLC analysis. The mixture was passed through a short silica gel column and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the pure product **5aa** (228.8 mg) in 92% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 7.5$ Hz, 2H), 7.41–7.29 (m, 9H), 7.28–7.15 (m, 4H), 6.93–6.82 (m, 4H), 6.68 (s, 1H), 5.56 (s, 1H), 4.34 (s, 1H), 3.80 (s, 3H), 1.98 (s, 3H), 1.70 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 152.42$, 148.78, 145.42, 145.05, 142.07, 141.99, 131.07, 128.90, 128.62, 128.30, 128.26, 128.15, 128.06, 127.80, 127.03, 126.73, 126.04, 125.28, 122.41, 120.23, 114.87, 114.63, 56.93, 55.63, 47.81, 21.92, 12.61 ppm; MS (EI) *m/z* (%): 497 [M^+] (23.17), 375 (100); HRMS calcd for $C_{35}H_{31}NO_2$: 497.2355, found: 497.2357. For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

Acknowledgements

Financial support from 973 Program (2009CB825300), NSFC (20702015) and Science and Technology Commission of Shanghai Municipality (08dj1400100), Shanghai Shuguang Program (07SG27) are greatly appreciated. X. Zhao thanks NSFC for financial support (20801018). Y. Yu thanks STCSM for financial support (07DZ22937).

Keywords: cyclization · domino reactions · gold · heterobicycles · rearrangement

[1] For recent reviews, see: a) "Metal-Catalyzed Cascade Reactions": *Topics in Organometallic Chemistry, Vol. 19* (Ed.: T. J. J. Müller), Springer, Berlin, **2006**; b) D. M. D′Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; c) S. K. Bur, A. Padwa, *Adv. Heterocycl. Chem.* **2007**, *94*, 1–105; d) S. F. Kirsch, *Synthesis* **2008**, 3183–3204.

[2] Our group's work, see: a) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929–1932; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903–1906; b) X. Yu, H. Ren, Y. Xiao, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 8481–8485; c) L. Fan, W. Zhao, W. Jiang, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 9139–9142; d) Y. Xiao, J. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 617–629; e) Y. Xiao, J. Zhang, *Chem. Commun.* **2009**, 3594–3596; f) F. Liu, J. Zhang, *Angew. Chem.* **2009**, *121*, 5613–5616; *Angew. Chem. Int. Ed.* **2009**, *48*, 5505–5508.

[3] For reviews on gold-catalyzed reactions since **2008**, see: a) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; b) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; e) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442; f) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391; g) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885–3903; h) A. S. K. Hashmi, *Angew. Chem.* **2008**, *120*, 6856–6858; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754–6756; i) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776–1782; j) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775; k) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181.

[4] For examples on gold-catalyzed tandem double heterocyclizations, see: a) 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; b) S. Antoniotti, E. Genin, V. Michelet, J.-P. Genêt, *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977; c) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814–1815; d) J. Meng, Y. L. Zhao, C. Q. Ren, Y. Li, Z. Li, Q. Liu, *Chem. Eur. J.* **2009**, *15*, 1830–1834.

[5] For examples of gold-catalyzed domino heterocyclization/1,2-alkyl migration, see: a) S. F. Kirsch, J. T. Binder, C, Liébert, H. Menz, *Angew. Chem.* **2006**, *118*, 6010–6013; *Angew. Chem. Int. Ed.* **2006**, *45*, 5878–5880; b) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287–5289; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195–5197; c) A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel′in, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452; d) X.-Z. Shu, X.-Y. Liu, K.-G. Ji, H.-Q. Xiao, Y.-M. Liang, *Chem. Eur. J.* **2008**, *14*, 5282–5289; e) for a recent highlight, see: B. Crone, S. F. Kirsch, *Chem. Eur. J.* **2008**, *14*, 3514–3522.

[6] For recent reviews of furan synthesis, see: a) X. L. Hou, Z. Yang, K.-S. Y, H. N. C. Wong, *Prog. Heterocycl. Chem.* **2008**, *19*, 176; b) A. Jeevanandam, A. Ghule, Y.-C. Ling, *Curr. Org. Chem.* **2002**, *6*, 841; c) R. C. D. Brown, *Angew. Chem.* **2005**, *117*, 872–874; *Angew. Chem. Int. Ed.* **2005**, *44*, 850–852; d) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076–2080; e) D. M. D′Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; f) N. T. Patil, Y. Yamamoto, *ARKIVOC* **2007**, (*x*), 121; g) G. Balme, D. Bouyssi, N. Monteiro, *Heterocycles* **2007**, *73*, 87–124.

[7] For recent reviews on azepine synthesis, see: a) J. B. Bremner, *Heterocycl. Chem.* **2005**, *17*, 389; b) M. D. Surman, R. H. Hutchings, *Sci. Synth.* **2004**, *17*, 749; c) J.-C. Quirion, E. Leclerc, P. Jubault, *Sci. Synth.* **2007**, *33*, 659; d) *Chemistry of Heterocyclic Compounds: Azepines, Part 2, Vol. 43* (Ed.: A. Rosowsky), Wiley-Intersience, New York, **2008**; e) for gold-catalyzed azepine synthesis, see: N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244–9245.

[8] a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679–7685; c) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531–4534.

[9] CCDC-736346 (**5aa**), CCDC-725115 **(5ba)**, CCDC-748437 (**7ab**), CCDC-732510 **(9)** 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.

[10] We acknowledge one reviewer's suggestion to run 2D NMR spectra, which led us to find the different reaction pathway between imines **2** and **7.**

Received: July 1, 2009
Revised: September 29, 2009
Published online: November 27, 2009

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim