Cyclizations

DOI: 10.1002/anie.201103961

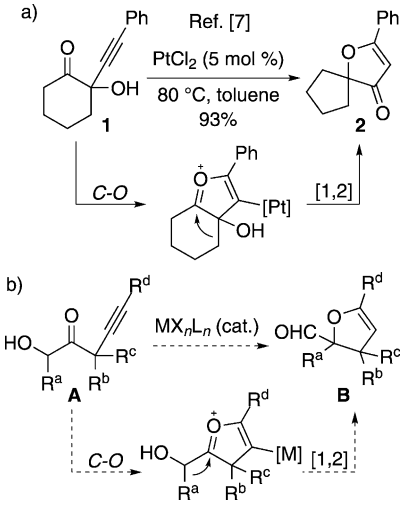
Domino Reactions Consisting of Heterocyclization and 1,2-Migration—Redox-Neutral and Oxidative Transition-Metal Catalysis**

*Klaus-Daniel Umland, Adeline Palisse, Timm T. Haug, and Stefan F. Kirsch**

Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

Domino reactions, in which two (or more) distinct reactions are performed in a single operation without isolation of the reaction intermediates, possess significant economic and ecological benefits and have thus emerged as powerful tools for the creation of architecturally complex structures from relatively simple starting compounds.[1] A major class of domino reactions is based on cationic cyclizations; these include reactions in which the cascade terminates with a pinacol rearrangement—a particularly useful approach for the creation of products with challenging quaternary stereogenic centers.[2,3]

Recently, carbophilic Lewis acids have been recognized to activate π systems including alkenes, allenes, and alkynes toward intermolecular and intramolecular nucleophilic attack.[4] On the basis of this expedient reactivity, we launched a program focusing on domino reactions that start with catalytic alkyne activation and terminate with a pinacol-type 1,2-alkyl migration.[5,6] For example, in 2006 we constructed valuable 3(2*H*)-furanones **2** by combining an initial 5-*endo* heterocyclization with a pinacol-type rearrangement.[7] To this end, carbonyl substrates **1** were designed incorporating both a tertiary hydroxy and an alkynyl substituent at the α-position (**1**→**2**, Scheme 1a). Inspired by this intriguing reactivity,[8,9] we then expected that alkynone **A**, which generates an oxonium ion intermediate in which the hydroxy group is outside the cycle, could be induced to undergo 1,2-migration of R^a (Scheme 1b). If the envisaged domino process is feasible, synthetically challenging 2,3-dihydrofurans should be accessible through a pathway that departs from traditional approaches to dihydrofurans;[10] this would significantly expand the value of pinacol-terminated domino reactions. Herein we report a novel method for the diastereoselective



Scheme 1. Catalyzed domino reactions with alkynones. a) Synthesis of 3(2*H*)-furanones through a cyclization/1,2-shift strategy. b) Projected route to 2,3-dihydrofurans.

construction of bicyclic 2,3-dihydrofurans starting from 5-hydroxyalkyn-4-ones, and illustrate how oxidative conditions with copper catalysts are prerequisite to the realization of this goal: Both alkyne activation and alcohol oxidation are triggered by copper catalysis. This unique and unexpected finding is complemented by the observation that the same starting compounds can be efficiently transformed into furans through an alternative alkyl shift by replacing oxidative copper catalysis with redox-neutral platinum catalysis.

In analogy to related heterocyclizations,[11] we reasoned that the direct cyclization of alkyn-4-ones to give simple furans must be blocked to facilitate the transformation **A**→**B**. On the basis of this hypothesis, we anticipated that 5-hydroxyalkyn-4-ones with a quaternary center at C3 (R^b,$R^c \neq H$) could serve as a potentially useful class of substrates since the corresponding cyclic oxonium ion intermediates cannot undergo competing aromatization or double-bond isomerization. Accordingly, starting 6-hydroxycyclohexanones **1a**–**n** having 2-alkynyl side chains were prepared as detailed in the Supporting Information. When conducting first experiments with these compounds to test their ability to undergo cyclization–pinacol cascades with carbophilic Lewis acids, we found that subjecting alkynone **1a** to typical conditions for $(Ph_3P)Au^+$-catalyzed reactions

[*] K.-D. Umland, A. Palisse, T. T. Haug, Prof. Dr. S. F. Kirsch[+]
Department Chemie, Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
E-mail: stefan.kirsch@ch.tum.de

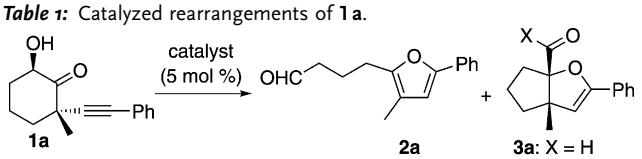
[+] New address: Bergische Universität Wuppertal
Fachbereich C – Organische Chemie
Gaußstraße 20, 42119 Wuppertal (Germany)
E-mail: sfkirsch@uni-wuppertal.de

[**] The authors thank Deutsche Forschungsgemeinschaft (DFG) and Fonds der Chemischen Industrie (FCI) for generous support. A.P. thanks the DAAD for a PhD fellowship. Support from the TUM Graduate School is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103961.

resulted in traces of the unexpected furan **2a** (Table 1, entry 1). Changing the ligand from PPh_3 to numerous other ligands led only to the formation of the furan in varying yields; not even traces of the desired aldehyde **3a** were detected. We subsequently examined several platinum com-

Table 1: Catalyzed rearrangements of **1a**.

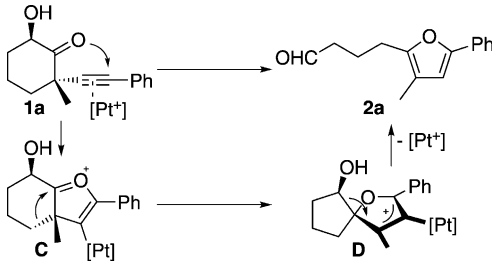


Entry	Catalyst	Conditions	Yield[a] [%]
1	$(Ph_3P)AuCl/AgSbF_6$	23 °C, 1 h, CH_2Cl_2	traces (**2a**)[b]
2	$(Me_3P)AuCl/AgSbF_6$	23 °C, 1 h, CH_2Cl_2	54 (**2a**)
3	$(Me_3P)AuCl/AgSbF_6$	100 °C, 1 h, toluene	68 (**2a**)
4	$PtCl_2$	100 °C, 5 h, toluene	74 (**2a**)
5	$PtCl_4$	100 °C, 2 h, toluene	77 (**2a**)
6	**$PtCl_4$**	***i*PrOH, 100 °C, 0.5 h, toluene**	**83 (2a)**
7	HBF_4	23 °C, 5 h, CH_2Cl_2	0[c]
8[d]	$Cu(OTf)_2$	air, 80 °C, 4 h, (wet) DMF	62 (**4a**)

[a] Yield of isolated product after complete consumption of **1a**. [b] Identified by gas chromatography. [c] No conversion of **1a** was detected. [d] 10 mol% of catalyst was used.

plexes and were pleased to find that $PtCl_4$ (5 mol%) catalyzed the formation of furan **2a** in toluene at 100 °C in 77% yield (Table 1, entry 5). To our delight, the addition of *i*PrOH markedly decreased the time required for full conversion (Table 1, entry 6). Although we did not find conditions for the direct formation of bicyclic aldehyde **3a**, we finally found that the reaction of cyclohexanone **1a** with 10 mol% of $Cu(OTf)_2$ in wet DMF at 80 °C in an open flask provided acid **4a**, which has the desired carbon core, in 62% yield (Table 1, entry 8). Of primary importance, either **2a** or **4a** was obtained as the exclusive product under the conditions tested.

Since they are ubiquitous in bioactive substances, polysubstituted furans are important target structures, and thus countless synthetic routes toward furans having a specific substitution pattern have been designed.[12] However, the title reaction converting cyclohexanone **1a** into furan **2a** differs significantly from other cycloisomerization routes to furans since the catalyzed ring closure is invariably accompanied by the opening of the six-membered ring system to install the aldehyde-containing side chain. The mechanism depicted in Scheme 2 explains the furan formation. The domino reaction starts with the activation of the alkyne moiety in **1a** through coordination of the transition-metal catalyst. Nucleophilic attack of the carbonyl group produces the cyclic oxonium ion **C**, which, after a ring-contracting 1,2-shift, rearranges to the spirocyclic intermediate **D**.[13] Grob-type fragmentation[14] of this rather stabilized cation gives rise to the furan heterocycle and installation of the C_4 side chain containing the aldehyde group. The protodemetalation step required for the regeneration of the catalytic species appears to be facilitated by the

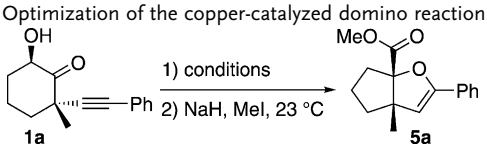


Scheme 2. Plausible mechanism for the formation of **2a**.

presence of stoichiometric amounts of *i*PrOH as an external proton source.

We next examined the intriguing copper-catalyzed reaction that provides access to complex 2,3-dihydrofurans having two adjacent quaternary stereogenic centers. When studying the conversion of cyclohexanone **1a** into dihydrofuran **4a**, we encountered major experimental problems with regard to product purity and reaction reproducibility. Attempts to isolate the free carboxylic acid **4a** resulted in substantial decomposition; therefore, the intermediate carboxylic acids were transformed in situ into their methyl esters, which could be readily purified. In light of our preliminary reaction conditions (10 mol% of $Cu(OTf)_2$, 80 °C, wet DMF), we continued our investigations by testing various solvents under open-flask conditions (Table 2, entries 1–5). While complete decomposition of **1a** was observed in toluene, dioxane, and

Table 2: Optimization of the copper-catalyzed domino reaction.



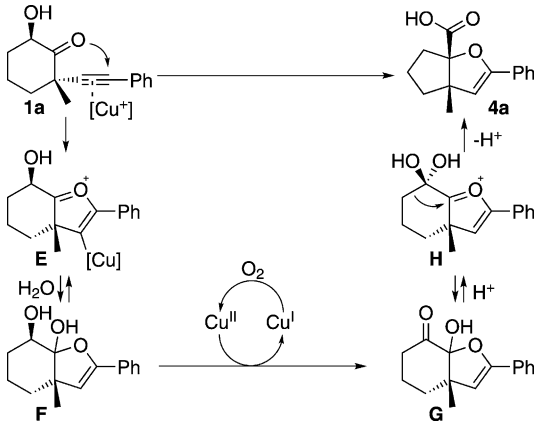
Entry	Catalyst (mol%)	Conditions	Yield[a] [%]
1	$Cu(OTf)_2$ (10)	air, 80 °C, DMF	60
2	$Cu(OTf)_2$ (10)	air, 80 °C, DMPU	73
3	$Cu(OTf)_2$ (10)	air, 80 °C, toluene	0[b]
4	$Cu(OTf)_2$ (10)	air, 80 °C, dioxane	0[b]
5	$Cu(OTf)_2$ (10)	air, 80 °C, CH_3CN	0[b]
6	$Cu(OTf)_2$ (10)	Ar, 80 °C, DMPU	<10
7	$Cu(OTf)_2$ (10)	O_2, 80 °C, (anhydrous) DMPU	traces
8	$CuSO_4$ (10)	air, 80 °C, DMPU	32
9	$CuCl_2/AgSbF_6$ (10/5)	air, 80 °C, DMPU	50
10	CuOTf (10)	air, 80 °C, DMPU	78
11	**CuCl (10)**	**air, 80 °C, DMPU**	**82**

[a] Yield of isolated product after complete consumption of **1a** and subsequent ester formation by addition of NaH and MeI to the reaction mixture at room temperature. Unless otherwise indicated, all reactions were run under open-flask conditions. [b] Decomposition only.

acetonitrile, the substrate was fully consumed in the reaction in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), affording methyl ester **5a** in 73% yield. We found that the presence of both oxygen and water[15] was essential, since the use of either argon atmosphere or rigorously dried solvents resulted in only trace amounts of product (Table 2, entries 6 and 7). Gratifyingly, this domino reaction also took

place when copper(I) salts were employed as precatalysts. The use of CuCl as an inexpensive and nontoxic copper source improved the yield of ester **5a** to 82%, and thus our optimal reaction conditions (10 mol% CuCl, 80°C, air, wet DMPU; Table 2, entry 11) are of great practicability.[16]

The transformation of alkynone **1a** into 2,3-dihydrofuran **4a** comprises three distinct steps: 1) oxidation (of the hydroxy-bearing carbon), 2) C–O bond formation (between the alkyne carbon and carbonyl oxygen atoms), and 3) 1,2-alkyl migration (in a pinacol-type manner with ring contraction). Since a mechanism via aldehyde intermediate **3a** and subsequent oxidation can be ruled out,[17] we propose the mechanism outlined in Scheme 3 for this reaction. By coordinating to the cationic $Cu^{I/II}$ species, alkyne **1a** is activated for intramolecular nucleophilic attack. The

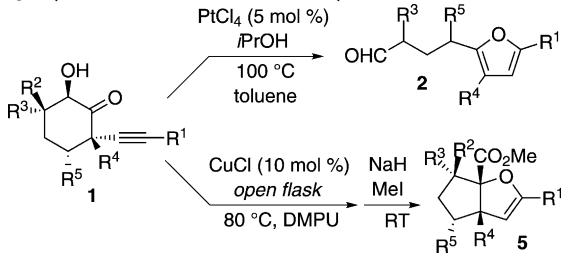


Scheme 3. Plausible mechanism for the formation of **4a**.

domino reaction then commences, passing through cyclic oxonium ion **E** which presumably equilibrates with cyclic hemiacetal **F**. Crucial for the selective dihydrofuran formation is that oxonium ion **E** does not rearrange to a spirocyclic intermediate analogous to **D**, possibly because the electron back-donation capability of copper atoms are weaker than that of platinum. Instead, oxidation promoted by Cu^{II} results in the formation of carbonyl compound **G**. If the addition of water to the carbonyl moiety gives hydrate **H**, it can rearrange by ring contraction with conversion into the 2,3-dihydrofuran **4a**, which contains a free carboxylic acid. Therefore, this unique 1,2-alkyl migration resembles the classical benzilic acid rearrangement,[18] which, in this special case, does not proceed through the action of hydroxide anions. To our knowledge, the use of a benzilic acid type rearrangement as the pivotal step in domino reactions catalyzed by π acids has not been reported before.

Applying these optimized conditions, we examined the scope of the two domino reactions (Table 3). To probe the catalyzed furan formation, hydroxyalkynones **1** were allowed to react with 5 mol% of $PtCl_4$ in the presence of 1.5 equivalents of *i*PrOH at 100°C in toluene. The reaction outcome was predictable in all cases, and products **2** were typically obtained in good to excellent yields. In a few cases diminished yields presumably result from the somewhat limited stability

Table 3: Synthesis of furans **2** and 2,3-dihydrofurans **5**.



Entry	Substrate **1**		R^2	R^3	R^4	R^5	Yield[a] [%] **2**[b]	**5**[c]
1	**a**	Ph	H	H	Me	H	83	82
2	**b**	4-MeO-C_6H_4	H	H	Me	H	88	92
3	**c**	4-F_3CO-C_6H_4	H	H	Me	H	56	84
4	**d**	3-Cl-C_6H_4	H	H	Me	H	77	95
5	**e**	2-thienyl	H	H	Me	H	86	76
6	**f**	1-cyclohexenyl	H	H	Me	H	41	n.r.
7	**g**	cyclopropyl	H	H	Me	H	47	decomp.
8	**h**	*n*Pent	H	H	Me	H	65	56
9	**i**	*t*Bu	H	H	Me	H	n.r.	58
10	**j**	Ph	H	H	*n*Bu	H	63	n.r.
11	**k**	4-MeO-C_6H_4	H	H	*n*Bu	H	77	70
12	**l**	Ph	H	Me	Me	H	93	83[d]
13	**m**	Ph	Me	H	Me	H	n.r.	83[d]
14	**n**	Ph	H	H	Me	Me	78	65

[a] Yield of isolated product after complete consumption of **1**. [b] Conditions: $PtCl_4$ (5 mol%), *i*PrOH (1.5 equiv), 100°C, toluene (0.05 M). [c] Conditions: 1) CuCl (10 mol%), open-flask, 80°C, DMPU (0.3 M); 2) NaH, MeI, 23°C. [d] d.r. > 95:5. n.r. = experiment not run; decomp. = decomposition only.

of the furans under the reaction conditions (in the presence of Lewis acids) and aerobic purification conditions. When hydroxyalkynones **1** were treated with 10 mol% of CuCl under open-flask conditions at 80°C in DMPU, substrates with aryl substituents at the alkyne unit provided dihydrofurans **5** in good yields and as a single diastereoisomer.[19] Alkyl-substituted alkynes also participated in the domino reaction, but the yields were lower.[20] The most impressive feature of the copper-catalyzed domino reaction is that in all cases not even traces of furan products were detected.

In conclusion, two unprecedented domino reactions starting from 6-hydroxy-2-alkyl-2-alkynylcyclohexanones have been disclosed. In one, the starting substrates are transformed into substituted furans. This sequence is effectively catalyzed by $PtCl_4$ and most likely proceeds through a heterocyclization followed by a ring-contracting 1,2-shift and a Grob-type fragmentation. In the second domino reaction, identical starting compounds are submitted to catalytic amounts of CuCl under convenient open-flask conditions in hot DMPU to give 2,3-dihydrofurans with two adjacent quaternary stereogenic centers. Oxidative copper catalysis allows for heterocyclization and oxidation and, thus, opens the way for an alternative 1,2-shift analogous to the benzilic acid rearrangement. This is a striking example of how to determine the catalytic reaction pathway by simply switching between appropriate reaction parameters. Further work in our laboratory is devoted to extending the use of benzilic acid

rearrangements in transition-metal-catalyzed domino reactions.

Received: June 10, 2011
Published online: September 7, 2011

Keywords: copper · domino reactions · heterocycles · homogeneous catalysis · platinum

[1] For selected reviews, see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; b) L. F. Tietze, G. Brasche, G. Gericke in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; d) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; e) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; f) S. F. Kirsch, *Synthesis* **2008**, 3183; g) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; h) J. Zhou, *Chem. Asian J.* **2010**, *5*, 422.

[2] For a leading review, see: L. E. Overman, L. D. Pennington, *J. Org. Chem.* **2003**, *68*, 7143.

[3] For selected applications in natural product synthesis, see: a) N. Hanaki, J. T. Link, D. W. C. MacMillan, L. E. Overman, W. G. Trankle, J. A. Wurster, *Org. Lett.* **2000**, *2*, 223; b) A. D. Lebsack, L. E. Overman, R. J. Valentekovich, *J. Am. Chem. Soc.* **2001**, *123*, 4851; c) G. C. Hirst, T. O. Johnson, L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 2992; For related strategies, see: d) M. A. Beaulieu, C. Sabot, N. Achache, K. C. Guérard, S. Canesi, *Chem. Eur. J.* **2010**, *16*, 11224; e) L. E. Overman, J. P. Wolfe, *J. Org. Chem.* **2002**, *67*, 6421; f) A. Armstrong, Y. Bhonoah, S. E. Shanahan, *J. Org. Chem.* **2007**, *72*, 8019.

[4] For selected reviews on π activation with carbophilic Lewis acids, see: a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; b) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885; c) A. Corma, A. Leyva-Perez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657; d) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675; e) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; f) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; g) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; h) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612; i) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; j) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

[5] a) B. Crone, S. F. Kirsch, *Chem. Eur. J.* **2008**, *14*, 3514; b) A. Duschek, S. F. Kirsch, *Angew. Chem.* **2008**, *120*, 5787; *Angew. Chem. Int. Ed.* **2008**, *47*, 5703.

[6] a) S. F. Kirsch, J. T. Binder, B. Crone, A. Duschek, T. T. Haug, C. Liébert, H. Menz, *Angew. Chem.* **2007**, *119*, 2360; *Angew. Chem. Int. Ed.* **2007**, *46*, 2310; b) H. Menz, J. T. Binder, B. Crone, A. Duschek, T. T. Haug, S. F. Kirsch, P. Klahn, C. Liébert, *Tetrahedron* **2009**, *65*, 1880; c) B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605; d) A. Lange, W. Heydenreuther, H. Menz, S. F. Kirsch, *Synlett* **2009**, 2987; e) T. T. Haug, T. Harschneck, A. Duschek, C.-U. Lee, J. T. Binder, H. Menz, S. F. Kirsch, *J. Organomet. Chem.* **2009**, *694*, 510.

[7] a) S. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem.* **2006**, *118*, 6010; *Angew. Chem. Int. Ed.* **2006**, *45*, 5878; b) J. T. Binder, B. Crone, S. F. Kirsch, C. Liébert, H. Menz, *Eur. J. Org. Chem.* **2007**, 1636; c) B. Crone, S. F. Kirsch, *J. Org. Chem.* **2007**, *72*, 5435.

[8] For selected examples of carbocyclization combined with 1,2-migrations, see: a) E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 5578; *Angew. Chem. Int. Ed.* **2006**, *45*, 5452; b) J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708; c) J.-M. Tang, S. Bhunia, S. Md. A. Sohel, M.-Y. Lin, H.-Y. Liao, S. Datta, A. Das, R.-S. Liu, *J. Am. Chem. Soc.* **2007**, *129*, 15677; d) H.-S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J.-E. Lee, S. S. Lee, S. Shin, *Angew. Chem.* **2010**, *122*, 1655; *Angew. Chem. Int. Ed.* **2010**, *49*, 1611; e) X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 6398; f) V. N. Korotchenko, M. R. Gagné, *J. Org. Chem.* **2007**, *72*, 4877; g) S. G. Sethofer, S. T. Staben, O. Y. Hung, F. D. Toste, *Org. Lett.* **2008**, *10*, 4315; h) F. Kleinbeck, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 9178; i) L. Liu, J. Zhang, *Angew. Chem.* **2009**, *121*, 6209; *Angew. Chem. Int. Ed.* **2009**, *48*, 6093; j) M. Alcarazo, T. Stork, A. Anoop, W. Thiel, A. Fürstner, *Angew. Chem.* **2010**, *122*, 2596; *Angew. Chem. Int. Ed.* **2010**, *49*, 2542; k) A. S. K. Hashmi, W. Yang, F. Rominger, *Angew. Chem.* **2011**, *123*, 5882; *Angew. Chem. Int. Ed.* **2011**, *50*, 5762; l) S. M. Canham, D. J. France, L. E. Overman, *J. Am. Chem. Soc.* **2010**, *132*, 7876.

[9] For selected examples of heterocyclization combined with 1,2-migrations, see: a) C. R. Smith, E. M. Bunnelle, A. J. Rhodes, R. Sarpong, *Org. Lett.* **2007**, *9*, 1169; b) H. Gao, X. Zhao, Y. Yu, J. Zhang, *Chem. Eur. J.* **2010**, *16*, 456; c) W. Li, Y. Li, J. Zhang, *Chem. Eur. J.* **2010**, *16*, 6447; d) E. M. Bunnelle, C. R. Smith, S. K. Lee, W. S. Singaram, A. J. Rhodes, R. Sarpong, *Tetrahedron* **2008**, *64*, 7008; e) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260.

[10] For a leading reference, see: a) Q.-F. Wang, H. Hou, L. Hui, C.-G. Yan, *J. Org. Chem.* **2009**, *74*, 7403, and references therein; For a recent phosphine-induced approach to bicyclic 2,3-dihydrofurans, see: b) J. Ma, P. Xie, C. Hu, Y. Huang, R. Chen, *Chem. Eur. J.* **2011**, *17*, 7418.

[11] For furan syntheses through direct heterocyclization of alkyn-4-ones and related processes, see: a) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; b) S. Labsch, S. Ye, A. Adler, J.-M. Neudörfl, H.-G. Schmalz, *Tetrahedron: Asymmetry* **2010**, *21*, 1745; c) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164.

[12] For selected reviews, see: a) X. L. Hou, Z. Yang, H. N. C. Wong in *Progress in Heterocyclic Chemistry*, *Vol. 15* (Eds.: G. W. Gribble, T. L. Gilchrist, Pergamon, Oxford, **2003**, p. 167; b) H.-K. Lee, K.-F. Chan, C.-W. Hui, H.-K. Yim, X.-W. Wu, H. N. C. Wong, *Pure Appl. Chem.* **2005**, *77*, 139; c) R. C. D. Brown, *Angew. Chem.* **2005**, *117*, 872; *Angew. Chem. Int. Ed.* **2005**, *44*, 850; d) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076; e) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955.

[13] For processes proceeding through spirocyclic intermediates somewhat related to cation **D**, see references [8k, 9b,c]. In those works, a ring-enlarging rearrangement of spirocyclic oxonium ions was proposed.

[14] For a leading review, see: K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, *110*, 3741.

[15] Nearly identical yields for **5a** were obtained with DMPU/H_2O ratios ranging from 2:1 to 50:1. Most reactions were conducted with reagent-grade DMPU under open-flask conditions without added water.

[16] Reaction temperatures from 60 to 100 °C were found to be best for optimal conversion. Lower temperatures led to dramatically reduced yields while higher temperatures resulted in decomposition.

[17] A number of test reactions on the model substrate **1a** that support the proposed mechanism are detailed in the Supporting Information.

[18] a) S. Yamabe, N. Tsuchida, S. Yamazaki, *J. Org. Chem.* **2006**, *71*, 1777; b) A. Schaltegger, P. Bigler, *Helv. Chim. Acta* **1986**, *69*, 1666.

[19] The *cis* configuration was established by extensive NOE studies.

[20] Our attempts to react acyclic alkynones were not successful.

