EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402983

Synthesis of Furans through Silver-Catalyzed Propargyl–Claisen Rearrangement Followed by Cyclocondensation

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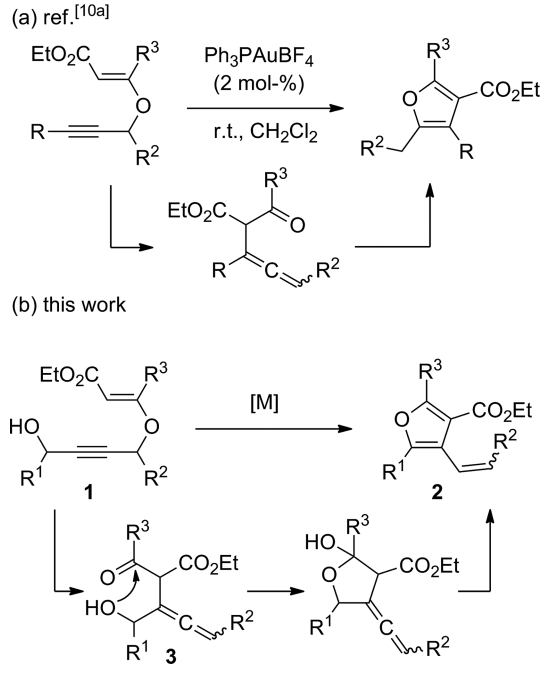
Keywords: Homogeneous catalysis / Silver / Rearrangement / Domino reactions / Oxygen heterocycles

The generation of highly substituted furans from propargyl vinyl ethers bearing a free hydroxy group was investigated. In the presence of catalytic amounts of $AgBF_4$, a formal [3,3] sigmatropic rearrangement takes place in the first stage of the sequence. The resulting allenyl carbonyl intermediates then undergo cyclocondensation, which upon double-bond isomerization leads directly to the five-membered heterocyclic products. This domino reaction allows the synthesis of various tri- and tetrasubstituted furan products; an example leading to pyrroles in an analogous way is also described.

Introduction

The development of methods for the synthesis of substituted furans is a major playground in contemporary chemistry: Furans can be found as structural units in many naturally occurring and biologically active compounds, and they have been recognized as important building blocks in organic synthesis and materials sciences.[1,2] In consequence, it comes as no surprise that a plethora of highly efficient methods for the synthesis of furans and their derivatives have been reported in the past,[3,4] and the development of novel methodologies is still in constant demand. A particular focus was recently put on the use of transition-metal catalysts for a range of furan-forming cycloadditions and cycloisomerizations.[5]

Over the last decade, noble-metal catalysts, and in particular gold catalysts, have, as a result of their carbophilic character, become the most prominent tools for the synthesis of furans through cyclization onto unsaturated C–C bonds;[6] various types of substrates including allenyl ketones,[7] alkynyl ketones,[8] and alkynyl alcohols[9] have been successfully cyclized. In this context, we[10] and others[11] studied the capability of propargyl vinyl ethers for the flexible synthesis of furans and related heterocycles (Scheme 1, a).[12] The domino reaction begins with a silver- or gold-catalyzed Claisen-type rearrangement[13] that rapidly leads to a skipped allenyl carbonyl intermediate; subsequent 5-*exo* cyclization followed by isomerization then provides the furan core.



Scheme 1. Synthesis of furans from propargyl vinyl ethers.

Herein, we show that propargyl vinyl ethers **1** having an additional hydroxy group are also great precursor compounds for the synthesis of furans (Scheme 1, b). In the presence of silver catalysts, a propargyl–Claisen rearrangement takes place first to provide allene **3**;[13] then, a classical cyclocondensation[14] followed by double-bond isomerization is believed to produce furans **2**.[15]

Results and Discussion

We began our studies by investigating the conversion of propargyl vinyl ether **1a** in the presence of several noble-

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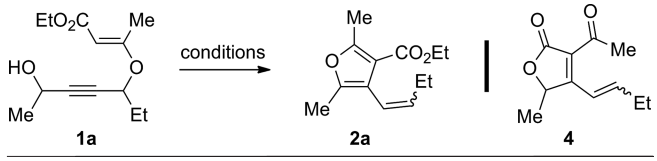
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402983.

metal catalysts as summarized in Table 1. Regarding the formation of desired furan **2a**, soluble silver catalysts were in general superior to gold catalysts in terms of yield if using dichloromethane at room temperature. In complete accordance with our previous results that silver salts are ideal catalysts for the propargyl–Claisen rearrangement, whereas simple Brønsted acids are less effective,[10d] hidden Brønsted acids[16] can be ruled out to trigger the overall furan-forming sequence (Table 1, entries 6 and 7): The initial propargyl–Claisen rearrangement appears to be catalyzed best by silver, but the final cyclocondensation might be possible through the action of either the silver salts or trace amounts of protons. The highest yields were obtained by using $AgBF_4$ (10 mol-%) in dichloromethane at 35 °C (Table 1, entry 9); higher temperatures led to slightly diminished yields owing to decomposition. Although product formation was observed in low yields under simple heating conditions (Table 1, entry 8),[11e–11g] only decomposition was found upon adding Brønsted acids at elevated temperatures. Of note, we never found a dihydrofuran product formed through a sequence in which activated allene **3** was attacked by the secondary hydroxy upon propargyl–Claisen rearrangement.[17] Instead, trace amounts of lactone **4** were observed in some cases by analysis of the crude mixtures by GC, albeit in negligible yields (<5%).

Table 1. Screening of the catalysts and the conditions.



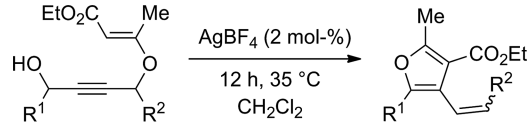
1a 2a 4

Entry	Catalyst (10 mol-%)	Conditions	Yield [%][a]
1	AuCl	CH_2Cl_2, 3 h, r.t.	23
2	$(Ph_3P)AuNTf_2$[b]	CH_2Cl_2, 24 h, r.t.	32
3	AgOTf[c]	CH_2Cl_2, 24 h, r.t.	76
4	$AgSbF_6$	CH_2Cl_2, 24 h, r.t.	74
5	$AgBF_4$	CH_2Cl_2, 24 h, r.t.	88
6	*p*TsOH[d]	CH_2Cl_2, 24 h, r.t.	trace
7[e]	AgOTf	*t*BuCl, CH_2Cl_2, 24 h, r.t.	9
8	–	$ClCH_2CH_2Cl$, 24 h, 90 °C	12
9	$AgBF_4$	CH_2Cl_2, 1 h, 35 °C	91
10	$AgBF_4$	$ClCH_2CH_2Cl$, 30 min, 70 °C	83
11[f]	$AgBF_4$	CH_2Cl_2, 24 h, 35 °C	87

[a] Yield of isolated product after column chromatography. Compound **2a** was isolated as a mixture of *E*/*Z* isomers (entries 1 and 4, *Z*/*E* = 7:2; entry 2, *Z*/*E* = 5:1; entry 3, *Z*/*E* = 4:1; entries 5 and 9–11, *Z*/*E* = 3:1; entries 6–8, *Z*/*E* not determined). [b] $(Ph_3P)AuNTf_2$ = [bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold(I). [c] AgOTf = silver trifluoromethanesulfonate. [d] *p*TsOH = *p*-toluenesulfonic acid. [e] Conditions for hidden Brønsted acids as introduced by Hintermann et al.[16] [f] Catalyst (2 mol-%).

With the optimized conditions [$AgBF_4$ (2 mol-%), CH_2Cl_2 (0.1 M), 35 °C], we then investigated the scope of the reaction. Table 2 demonstrates that R^1 and R^2 can be aryl, alkyl, or hydrogen if R^3 = Me. Products **2** were formed in varying yields ranging from 31 to 75%. Typically, the furans were obtained as mixtures of diastereoisomers, for which the *Z* isomer was the major isomer. To simplify the purification and the analysis of the furan products, several furans **2** were, without purification, directly submitted to hydrogenation [H_2 (101.3 kPa), Pd/C, r.t., MeOH/EtOAc (2:1)]. Table 3 shows a range of furans **5** that were easily obtained through this two-step procedure consisting of furan formation and hydrogenation. Reactions of starting substrates containing methyl, phenyl, or hydrogen at R^3 were possible; sterically demanding substituents at R^2 were found to have no influence on the course of the reaction.

Table 2. Scope of the silver-catalyzed furan formation.

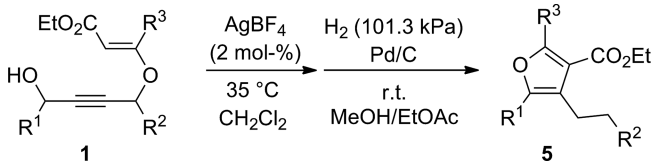


1 2

Entry	R^1	R^2	Product	Yield [%][a]
1	Ph	H	**2b**	36
2	Et	H	**2c**	43
3	Ph	Me	**2d**	31[b]
4	Et	Me	**2e**	56[b]
5	Ph	Et	**2f**	34[b]
6	H	Et	**2g**	45[c]
7	H	Ph	**2h**	70
8	*i*Bu	Ph	**2i**	75[d]

[a] Yield of isolated product after column chromatography. [b] *Z*/*E* = 3:1. [c] *Z*/*E* = 6:1. [d] *Z*/*E* = 2:1.

Table 3. Scope of silver-catalyzed furan formation including subsequent hydrogenation.



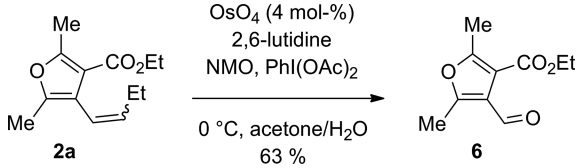
1 5

Entry	R^1	R^2	R^3	Product	Yield [%][a]
1	Me	Et	Me	**5a**	72
2	Me	*n*Pr	Me	**5j**	68
3	Me	*t*Bu	Me	**5k**	66
4	Me	Ph	Me	**5l**	78
5	*i*Bu	Et	Me	**5m**	64
6	*i*Bu	Ph	Me	**5i**	60
7	Ph	Et	Me	**5f**	30
8	Ph	Ph	Me	**5n**	65
9	Me	Et	H	**5o**	33
10	Me	Et	Ph	**5p**	68
11	H	Et	Me	**5g**	53
12	H	Ph	Me	**5h**	60

[a] Yield of isolated product after column chromatography. The reaction time for the silver-catalyzed step was 12 h in all cases.

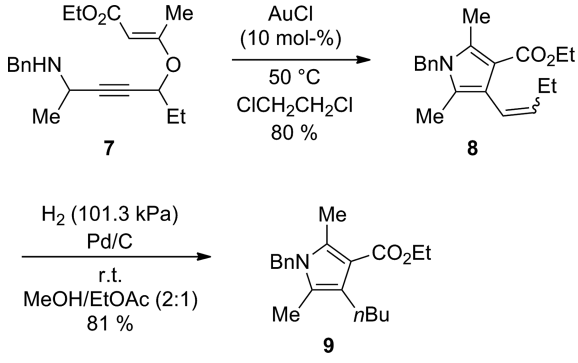
To further explore how to synthesize furans with different substitution patterns, we briefly studied the oxidative cleavage of the olefinic moiety generated in the course of this domino strategy. As exemplified for furan **2a**, the alde-

hyde functionality was smoothly introduced in 63% yield by using conditions developed by Nicolaou and co-workers [Equation (1), NMO = *N*-methylmorpholine *N*-oxide].[18]



(1)

We finally envisioned to access pyrroles (rather than furans) through the same process consisting of propargyl–Claisen rearrangement and subsequent cyclocondensation. To this end, amine **7** was subjected to various noble-metal catalysts: In the presence of silver salts only trace amounts of desired pyrrole **8** were obtained, but the use of gold(I) chloride in 1,2-dichloroethane at 50 °C was found to be highly efficient to produce the pyrrole core in 80% yield [Equation (2)].



(2)

Conclusions

In conclusion, we reported a silver-catalyzed route to highly substituted furans through a domino sequence involving Claisen-type rearrangement and cyclocondensation. We also showed that this strategy is applicable for the synthesis of pyrroles. Further work is currently underway to expand this strategy to the synthesis of thiophenes.

Experimental Section

Synthesis of Ethyl 4-(But-1-en-1-yl)-2,5-dimethylfuran-3-carboxylate (2a) as a Representation of General Procedure A: Under a N_2 atmosphere, $AgBF_4$ (0.8 mg, 4.16 μmol) was added to a solution of propargyl vinyl ether **1a** (50.5 mg, 0.208 mmol) in dry CH_2Cl_2 (2.1 mL, 0.1 M). The mixture was heated to 35 °C for 12 h. After filtration through Celite and concentration, the crude product was purified by flash chromatography (cyclohexane/EtOAc = 95:5) to obtain the product (40.9 mg, 0.184 mmol, 87%) as a mixture of *E*/*Z* isomers.

Synthesis of Ethyl 4-Butyl-2,5-dimethylfuran-3-carboxylate (5a) as a Representation of General Procedure B: Under a N_2 atmosphere, $AgBF_4$ (0.6 mg, 3.32 μmol) was added to a solution of propargyl vinyl ether **1a** (40 mg, 0.166 mmol) in dry CH_2Cl_2 (1.6 mL, 0.1 M). The mixture was heated to 35 °C for 12 h. After filtration through Celite and concentration, the residue was dissolved in dry MeOH/EtOAc (2:1, 1.1 mL, 0.15 M), and Pd/C (10.6 mg, 4.98 μmol, 5 mol-%) was added. The mixture was stirred at room temperature for 1 h under a H_2 atmosphere. After filtration through Celite and concentration, the crude product was purified by flash chromatography (cyclohexane/EtOAc = 95:5) to obtain the product (26.8 mg, 0.120 mmol, 72%). R_f = 0.74 (cyclohexane/EtOAc = 4:1) [UV/CAM]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.27 (q, J = 7.1 Hz, 2 H), 2.53–2.45 (m, 5 H), 2.16 (s, 3 H), 1.48–1.41 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.33–1.28 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 165.0, 157.6, 146.0, 119.6, 113.3, 59.7, 33.0, 24.2, 22.7, 14.4, 14.3, 14.1, 11.2 ppm. MS (EI): *m*/*z* (%) = 224.1 (53) [M^+], 195.1 (16) [M^+ – Et], 182.0 (100) [M^+ – *n*Pr], 167.0 (18) [M^+ – *n*Bu], 153.0 (88), 137.0 (58). HRMS (ESI): calcd. for $C_{13}H_{21}O_3$ [M + H^+] 225.1485; found 225.1485.

Supporting Information (see footnote on the first page of this article): Experimental procedures, analytical data, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

Support of this research by the Deutsche Forschungsgemeinschaft (DFG) through grant KI 1289/1-3 is gratefully acknowledged. The authors thank RockwoodLithium for the kind donation of chemicals. A. P. thanks the Deutscher Akademischer Austausdienst (DAAD) for a Ph. D. fellowship.

[1] a) X. L. Hou, Z. Yang, H. N. C. Wong, *Progress in Heterocyclic Chemistry* (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, UK, **2003**, vol. 15, p. 167–205; b) B. A. Keay, P. W. Dibble, *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier, Oxford, UK, **1997**, vol. 2, p. 395–436.

[2] B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795.

[3] Reviews: a) 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; b) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076; c) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; d) G. Balme, D. Bouyssi, N. Monteiro, *Heterocycles* **2007**, *73*, 87.

[4] Selected works: a) A. Sniady, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2005**, *7*, 1769; b) C.-K. Jung, J.-C. Wang, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4118; c) S. Kramer, J. L. H. Madsen, M. Rottländer, T. Skrydstrup, *Org. Lett.* **2010**, *12*, 2758; d) K.-D. Umland, A. Palisse, T. T. Haug, S. F. Kirsch, *Angew. Chem. Int. Ed.* **2011**, *50*, 9965; *Angew. Chem.* **2011**, *123*, 10140; e) Z. Chen, G. Huang, H. Jiang, H. Huang, X. Pan, *J. Org. Chem.* **2011**, *76*, 1134; f) A. Blanc, K. Tenbrink, J.-M. Weibel, P. Pale, *J. Org. Chem.* **2009**, *74*, 4360; g) X. Du, H. Chen, Y. Chen, J. Chen, Y. Liu, *Synlett* **2011**, 1010; h) H. Tsuhi, K.-i. Yamagata, Y. Ueda, E. Nakamura, *Synlett* **2011**, 1015; i) R. B. Dateer, K. Pati, R.-S. Liu, *Chem. Commun.* **2012**, *48*, 7200.

[5] a) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084; b) S. F. Kirsch, *Synthesis* **2008**, 3183; c) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395.

[6] [Au]: a) J. Muzart, *Tetrahedron* **2008**, *64*, 5815; b) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; c) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657; d) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994; e) D. Garayalde, C. Nevado, *Beilstein J. Org. Chem.* **2011**, *7*, 767; f) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2011**, *47*, 6536; [Ag]: g) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*,

3149; [Cu]: h) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054.
[7] Selected works: a) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; *Angew. Chem.* **2000**, *112*, 2382; b) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169; c) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; d) A. S. Dudnik, Y. Xia, Y. Li, V. Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 7645; e) C.-Y. Zhou, P. W. H. Chang, C.-M. Che, *Org. Lett.* **2006**, *8*, 325.
[8] Selected works: a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553; c) J. A. Marshall, C. A. Sehon, *J. Org. Chem.* **1995**, *60*, 5966; d) A. W. Sromek, A. V. Kel'in, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2280; *Angew. Chem.* **2004**, *116*, 2330; e) M. Hoffmann, S. Miaskiewicz, J.-M. Weibel, P. Pale, A. Blanc, *Beilstein J. Org. Chem.* **2013**, *9*, 1774.
[9] Selected works: a) A. S. K. Hashmi, T. Häffner, M. Rudolph, F. Rominger, *Eur. J. Org. Chem.* **2011**, 667; b) X. Zhang, Z. Lu, C. Fu, S. Ma, *J. Org. Chem.* **2010**, *75*, 2589; c) A. Arcadi, M. Alfonsi, M. Chiarini, F. Marinelli, *J. Organomet. Chem.* **2009**, *694*, 576; d) A. Aponick, C.-Y. Li, J. Malinge, E. F. Marques, *Org. Lett.* **2009**, *11*, 4624; e) M. Egi, K. Azechi, S. Akai, *Org. Lett.* **2009**, *11*, 5002.
[10] a) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925; b) J. T. Binder, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 2151; c) H. Menz, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 4795; d) T. Harschneck, S. F. Kirsch, *J. Org. Chem.* **2011**, *76*, 2145.
[11] Selected works: a) B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132; b) H. Cao, H. Jiang, W. Yao, X. Liu, *Org. Lett.* **2009**, *11*, 1931; c) H. Jiang, W. Yao, H. Cao, H. Huang, D. Cao, *J. Org. Chem.* **2010**, *75*, 5347; d) H. Cao, H. Jiang, R. Mai, S. Zhu, C. Qi, *Adv. Synth. Catal.* **2010**, *352*, 143; e) D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428; f) D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Eur. J. Org. Chem.* **2010**, 6582; g) D. Tejedor, L. Cotos, F. García-Tellado, *Org. Lett.* **2011**, *13*, 4422; h) A. Saito, T. Konishi, Y. Hanzawa, *Org. Lett.* **2010**, *12*, 372; i) X. Xin, D. Wang, X. Li, B. Wan, *Angew. Chem. Int. Ed.* **2012**, *51*, 1693; *Angew. Chem.* **2012**, *124*, 1725; j) H. Cao, H. Zhan, J. Cen, J. Lin, Y. Lin, Q. Zhu, M. Fu, H. Jiang, *Org. Lett.* **2013**, *15*, 1080.
[12] Review: Z.-B. Zhu, S. F. Kirsch, *Chem. Commun.* **2013**, *49*, 2272.
[13] a) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978; b) J. W. Grissom, D. Klingberg, D. Huang, B. J. Slattery, *J. Org. Chem.* **1997**, *62*, 603; c) M. E. Krafft, K. M. Hallal, D. V. Vidhani, J. W. Cran, *Org. Biomol. Chem.* **2011**, *9*, 7535; d) rhodium catalysis: D. V. Vidhani, M. E. Krafft, I. V. Alabugin, *Org. Lett.* **2013**, *15*, 4462.
[14] a) V. Amarnath, K. Amarnath, *J. Org. Chem.* **1995**, *60*, 301; b) H. S. P. Rao, S. Jothilingam, *J. Org. Chem.* **2003**, *68*, 5392; c) G. Minetto, L. F. Raveglia, A. Sega, M. Taddei, *Eur. J. Org. Chem.* **2005**, 5277.
[15] A related acid-catalyzed cycloisomerization of but-2-yne-1,4-diols: S. R. Mothe, S. J. L. Lauw, P. Kothandaraman, P. W. H. Chan, *J. Org. Chem.* **2012**, *77*, 6937.
[16] T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353.
[17] A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957.
[18] K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Org. Lett.* **2010**, *12*, 1552.

Received: July 23, 2014
Published Online: September 26, 2014

