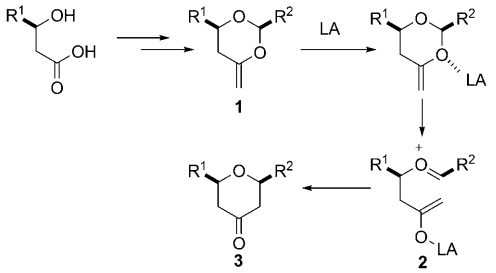
DOI: 10.1002/chem.201002918

Gold(I)-Catalyzed Access to Tetrahydropyran-4-ones from 4-(Alkoxyalkyl)oxy-1-butynes: Formal Catalytic Petasis–Ferrier Rearrangement

Hyo Jin Bae, Wook Jeong, Ji Hyung Lee, and Young Ho Rhee*[a]

Tetrahydropyran-4-ones are an important structural motif found in numerous bioactive natural products.[1] The Lewis acid mediated rearrangement of vinyl acetal **1** (Scheme 1),



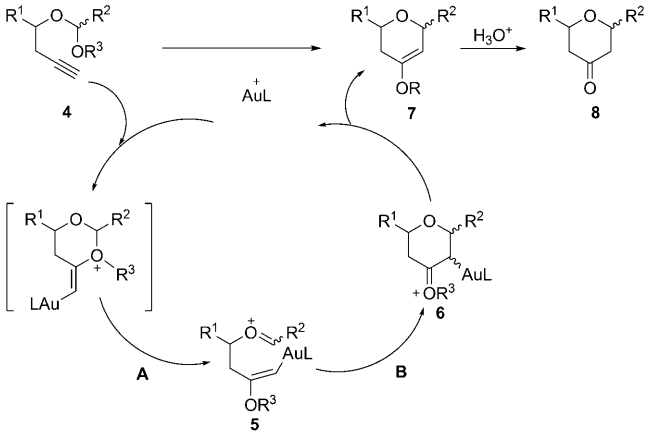
Scheme 1. The Petasis–Ferrier rearrangement; LA = Lewis acid.

named the Petasis–Ferrier rearrangement, has recently been developed for the synthesis of the tetrahydropyran-4-one moiety.[2,3] In this approach, formation of the key intermediate **2** is promoted by the coordination of the Lewis acid to the *cis*-vinyl acetal **1**. Although this reaction provides a unique access to *cis*-2,6-tetrahydropyran-4-ones **3**, a stoichiometric amount of strong Lewis acid is usually needed. Moreover, preparation of the vinyl acetal precursor **1** requires a multistep transformation that is generally performed under harsh conditions. Thus, a more efficient version of this reaction that overcomes the aforementioned limitations is highly desirable.

[a] H. J. Bae, W. Jeong, J. H. Lee, Prof. Dr. Y. H. Rhee
Department of Chemistry
POSTECH (Pohang University
of Science and Technology)
Pohang, 790-784 (Korea)
Fax: (+82) 54-279-3399
E-mail: yhrhee@postech.ac.kr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002918.

Based upon our experience in a related area,[4,5] we envisioned that a gold-catalyzed cycloisomerization of 4-(alkoxyalkyl)oxy-1-butyne **4** could offer a potential solution to this problem (Scheme 2). In this scenario, the initial alkoxycycli-

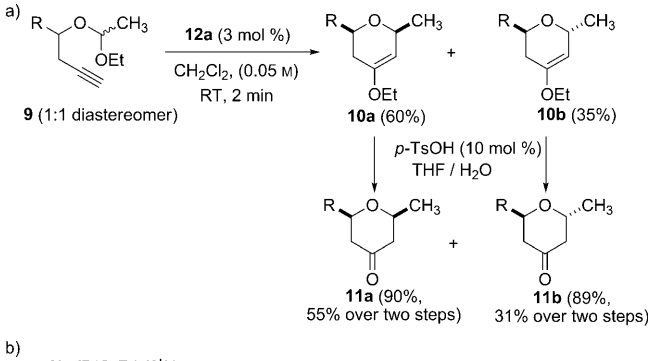


Scheme 2. Proposed mechanism for the gold(I)-catalyzed formation of tetrahydropyran-4-one.

zation,[4,6] followed by the scission of the C–O bond generates an oxocarbenium ion intermediate **5** (step **A**, Scheme 2), which is analogous to the intermediate **2** in the classical Petasis–Ferrier reaction shown in Scheme 1. Sequential recombination of **5** via **6** provides the cycloisomerization product **7** (step **B**, Scheme 2). Final hydration of **7** would easily generate the tetrahydropyranone **8**. Notably, the unique catalytic activity of gold complexes allows the use of alkynes as substrates, thereby substantially improving the step and atom efficiency of the classical Petasis–Ferrier reaction. Unlike the vinyl acetal **1**, the acyclic precursor **4** is most likely obtained as a mixture of diastereomers in the proposed catalytic cycle. Moreover, little is known about the addition of the oxocarbenium ion onto the alkoxyvinylgold species. Thus, our main interest in designing the proposed

catalytic cycle was to establish the diastereoselectivity of the alkyl substituents at the 2- and 6-positions.

We began our study by using the mixed acetal **9** as a substrate, which was obtained as an equimolar mixture of two diastereomers from the homopropargylic alcohol precursor (Scheme 3). When the electrophilic gold complex **12a**[7]

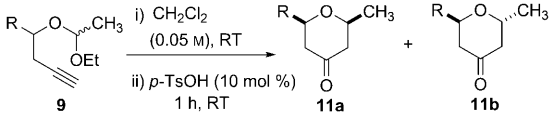


Scheme 3. a) A preliminary study using catalyst **12a**; b) structures of catalysts **12a–f**, $X^- = SbF_6^-$.

(3 mol%) was used, the reaction was complete within 2 minutes to give two enol ether products **10a** and **10b** isolated in 60 and 35% yield, respectively. The structure of the major *cis* isomer **10a** was confirmed by conversion to the *cis*-ketone **11a** in 90% yield by using a catalytic amount of *para*-toluene sulfonic acid (*p*-TsOH, 10 mol%). Under the same conditions, the *trans*-enol ether **10b** was converted into the *trans*-ketone **11b** in 89% yield with no apparent formation of **11a**.

Even though the preliminary study confirms the viability of the proposed reaction, the gold(I)-catalyzed cycloisomerization shows only moderate selectivity towards the *cis*-enol ether **10a**. In view of this result, we reasoned that the phosphine ligand might play a crucial role because the key event involves an intramolecular addition of the oxocarbenium ion onto the vinyl-gold species (step **B** in Scheme 2).[8] Thus, we investigated various gold complexes for the formation of ketone **11a** by using the two-step protocol established in Scheme 3. Interestingly, by using a less electrophilic complex **12b**, the cycloisomerization step was slower than with ligand **12a**, and the selectivity for the *cis*-tetrahydropyran-4-one **11a** was improved (Table 1, entry 1).[9] Further enhancement of the diastereoselectivity was observed when ligand **12c** was used (Table 1, entry 2). Thus, the electronic factor seems to be crucial in optimizing the diastereoselectivity. However, switching to bulkier (e.g., compound **12d**) or more compact trialkylphosphine ligands (e.g., compound **12e**) caused a significant decrease in the conversion of the cycloisomerization (Table 1, entries 3 and 4), even though the selectivity was slightly higher than in the previous examples. As shown in Table 1, entry 5, the commercially available catalyst **12f** gave the optimal result. In this case, 8:1 selectivity was assigned by NMR spectroscopic analysis of the crude reaction mixture. After purification, the *cis*-tetrahydropyranone **11a** was isolated in 72% yield.[10]

Table 1. Optimization of **11a**.

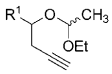
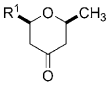
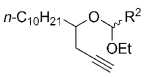
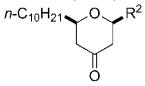
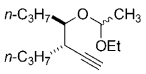
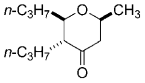
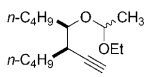
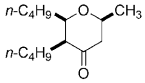
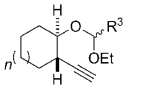
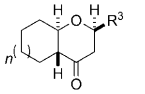


	Catalyst (3 mol%)[a]	*t* [min][b]	Conversion [%]	Ratio **11a**/**11b**[c]	Yield [%] **11a**[d]
1	**12b**	5	100	5:1	63
2	**12c**	15	100	7:1	69
3	**12d**	60	77	8:1	55
4	**12e**	60	75	9:1	46
5	**12f**	15	100	8:1	72

[a] All the catalysts were generated in situ except for catalyst **12f**. [b] Reaction time for the gold(I)-catalyzed cycloisomerization. [c] The ratio of crude product was determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [d] Yield of isolated product **11a**.

With the optimized conditions determined, we tested an array of substrates for the *cis*-2,6-tetrahydropyran-4-one synthesis using the catalyst **12f** (Table 2). Introduction of a

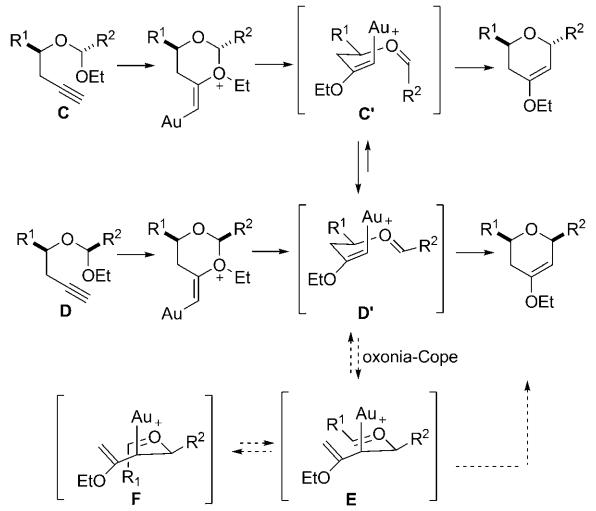
Table 2. Examples of tetrahydropyran-4-one formation.[a]

	Substrate		Method[b]	Product		Yield [%][c,d]
						
1	$R^1 = C_{10}H_{21}$	**9**	A	$R^1 = C_{10}H_{21}$	**11a**	72
2	$R^1 = c\text{-}C_6H_{11}$	**13**	A	$R^1 = c\text{-}C_6H_{11}$	**14**	70
3	$R^1 = Ph(CH_2)_2$	**15**	A	$R^1 = Ph(CH_2)_2$	**16**	73
						
4	$R^2 = n\text{-}C_9H_{19}$	**17**	A	$R^2 = n\text{-}C_9H_{19}$	**18**	68
5	$R^2 = c\text{-}C_6H_{11}$	**19**	A	$R^2 = c\text{-}C_6H_{11}$	**20**	78
6	$R^2 = (CH_2)_8CH{=}CH_2$	**21**	A	$R^2 = (CH_2)_8CH{=}CH_2$	**22**	71
7	$R^2 = (CH_2)_5CO_2Et$	**23**	A	$R^2 = (CH_2)_5CO_2Et$	**24**	71
8		**25**	B		**26**	51
9		**27**	B		**28**	58
						
10	$n = 1$, $R^3 = CH_3$	**29**	B	$n = 1$, $R^3 = CH_3$	**30**	68
11	$n = 1$, $R^3 = CH_2C(CH_3)_3$	**31**	B	$n = 1$, $R^3 = CH_2C(CH_3)_3$	**32**	69
12	$n = 2$, $R^3 = CH_3$	**33**	B	$n = 2$, $R^3 = CH_3$	**34**	69

[a] Typical procedure: The substrate was treated with catalyst **12f** in CH_2Cl_2 (0.05 M) and *p*-TsOH (10 mol%) was added. [b] Method A: catalyst **12f** (3 mol% loading); Method B: catalyst **12f** (5 mol% loading) [c] Yield of isolated product [d] In all examples, 5–8% of the *trans*-tetrahydropyran-4-one isomer was obtained.

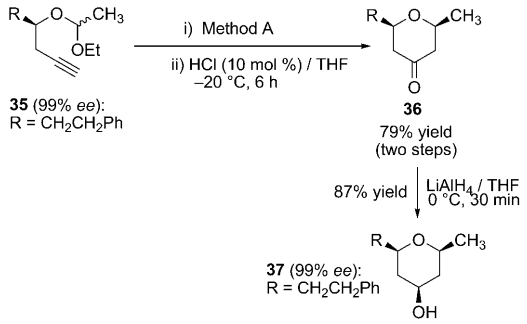
bulkier cyclohexyl group at the bis-homopropargylic position gave a similar result to **11a** (Table 2, entry 2). A phenethyl group also had no negative effect (Table 2, entry 3). Next, we explored the effect of the alkyl group at the acetal position.[11] Introduction of a longer alkyl group (Table 2, entry 4) provided the ketone **18** in 68% yield, whereas introduction of a cyclohexyl group increased the yield of ketone **20** to 78% (Table 2, entry 5). Significant chemoselectivity was noted. Thus, substrates that had a terminal olefin (Table 2, entry 6) or an ester group (entry 7) also showed good reactivity with no significant loss in yield. Next, we explored the structural effect of the homopropargylic position. Acyclic substrates with an alkyl substituent at the propargylic position (Table 2, entries 8 and 9) required a higher catalyst loading (5 mol%) for complete conversion into the corresponding tetrahydropyranones and were isolated in lower yields than in previous examples. However, cyclic substrates were converted into the corresponding *cis*-tetrahydropyranones in good yields (Table 2, entries 10–12).[12]

Although the origin of the diastereoselectivity awaits further studies, there seems to be a direct correlation between the electronic effect of the phosphine ligands and the diastereoselectivity. As depicted in Scheme 4, the initial heterocyclization–fragmentation of mixed acetal diastereomers **C** and **D** should generate two isomeric oxocarbenium ions **C′** and **D′**. The inherent preference of the cycloisomerization step towards the *cis*-enol ether strongly suggests that the oxocarbenium ion **C′** is the less stable, and easily isomerizes to the more stable ion **D′**.[13] Under these conditions, the cyclization of **C′** should be slower to increase the selectivity for the formation of the *cis*-enol ether. This analysis is in good agreement with the experimental data on the rate of the cycloisomerization, as shown in Table 1.



Scheme 4. Mechanistic proposal for the stereoselectivity of the reaction.

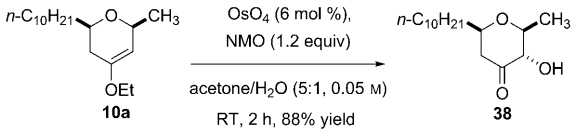
The mechanistic aspect of the proposed reaction could be further complicated by a competing oxonia-Cope pathway (Scheme 4).[14] This undesirable pathway may lead to deleterious racemization during the cycloisomerization (by isomerisation of intermediates **E** and **F**) and should be more pronounced when the cyclization of the oxocarbenium ion is slow.[15] Because of this concern, our next task was to investigate the enantioenriched substrate **35** for the tetrahydropyranone formation.[16] By using the optimized conditions, this compound was converted into the corresponding ketone **36** in good yield (Scheme 5).



Scheme 5. Preparation of enantioenriched **37**.

The complete conversion of enantiomeric excess (*ee*) in this step was confirmed by the stereoselective reduction (over 10:1 diastereosomeric ratio (d.r.)) of **36** with $LiAlH_4$, which generated *cis*-2,6-dialkyl-4-hydroxytetrahydropyran **37** in 87% yield. Although the possibility of the oxonia-Cope pathway could not be verified by experiments at this stage, the result shown in Scheme 5 firmly establishes the viability of the current method in tetrahydropyran synthesis.

Finally, it should be noted that the scope of the products accessed by the gold(I)-catalyzed cycloisomerization can be easily expanded to more densely functionalized tetrahydropyranones because cyclic enol ethers are involved as an intermediate. For example, catalytic dihydroxylation of the cycloisomerized intermediate **10a** gave 3-hydroxytetrahydropyran-4-one **38** in 88% yield as a single diastereomer (Scheme 6).[17] This highlights a unique additional advantage of the proposed catalytic cycloisomerization reaction.



Scheme 6. Catalytic dihydroxylation of **10a** to give substituted tetrahydropyranone **38**; NMO = *N*-methylmorpholine-*N*-oxide.

In summary, we have developed a new method to access highly substituted tetrahydropyran-4-ones, using a gold(I)-catalyzed cycloisomerization of the 4-(alkoxyalkyl)oxy-1-ynes as the key transformation. Of particular note is the unique effect of the phosphine ligand on the stereoselectivity of the tetrahydropyranone formation. Detailed mechanistic studies, as well as their application in the total synthesis

of bioactive natural products are currently ongoing in our laboratory and will be reported in due course.

Experimental Section

Preparation of 11a: A solution of **9** (80 mg, 0.28 mmol) in CH_2Cl_2 (5.6 mL, 0.05 M) was added to the catalyst **12f** (6.6 mg, 0.0085 mmol) in a flask equipped with a septum. The resulting solution was stirred at room temperature for 15 min. When the reaction was complete (monitored by TLC), triethylamine (0.1 mL) was added and the solution was stirred for 10 min. The reaction mixture was passed through a pad of celite and concentrated under reduced pressure. The residual oil was diluted with THF (5.6 mL) followed by *para*-toluene sulfonic acid monohydrate (*p*-TsOH·H_2O, 5.4 mg, 0.028 mmol) and the resulting solution was stirred at room temperature for 1 h. Triethylamine (0.2 mL) was then added and the solution was stirred for 10 min. The resulting reaction mixture was filtered through a pad of silica gel and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane/ether 90:10) to give **11a** as a yellow oil (52 mg, 0.20 mmol, 72% yield). $R_f = 0.21$ (hexane/ether 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.87 (t, $J = 6.7$ Hz, 3H), 1.17–1.55 (m, 20H), 1.56–1.74 (m, 1H), 2.13–2.27 (m, 2H), 2.29–2.41 (m, 2H), 3.48–3.62 (m, 1H), 3.70 ppm (ddq, $J = 11.3$, 6.1, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$, 22.3, 22.9, 25.5, 29.5, 29.7, 29.7, 29.8, 32.1, 36.7, 47.8, 49.7, 73.4, 77.3, 208.0 ppm; IR: $\tilde{\nu} =$ 2925, 2852, 1666, 1155 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{16}H_{30}O_2$: 254.2246 found; 254.2249.

Acknowledgements

This work was supported by the National Research Foundation of Korea, which is funded by the Korean Government (nos.: 2010–0009458 and 2008–0061957 from the NRF). The authors also thank the BK21 program for the graduate fellowship.

Keywords: diastereoselectivity · gold · isomerization · Petasis–Ferrier reaction · tetrahydropyranones

[1] a) V. Baliah, R. Jeyaraman, L. Chandrasekaran, *Chem. Rev.* **1983**, *83*, 379–423; b) M. J. Cloninger, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 1092–1093; c) K. N. Cossey, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217; d) S. Das, L.-S. Li, S. C. Sinha, *Org. Lett.* **2004**, *6*, 123–126; e) W. Tu, L. Liu, P. E. Floreancig, *Angew. Chem.* **2008**, *120*, 4252–4255; *Angew. Chem. Int. Ed.* **2008**, *47*, 4184–4187; f) W. J. Morris, D. W. Custar, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 1113–1116.

[2] a) N. A. Petasis, S.-P. Lu, *Tetrahedron Lett.* **1996**, *37*, 141–144; b) A. B. Smith III, R. J. Fox, T. M. Razler, *Acc. Chem. Res.* **2008**, *41*, 675–687.

[3] For selected applications of the Petasis–Ferrier rearrangement in the total synthesis of natural products, see: a) A. B. Smith III, T. Bosanac, K. Basu, *J. Am. Chem. Soc.* **2009**, *131*, 2348–2358; b) A. B. Smith III, V. Simov, *Org. Lett.* **2006**, *8*, 3315–3318; c) A. B. Smith III, E. F. Mesaros, E. A. Meyer, *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299.

[4] a) H. J. Bae, B. Baskar, S. E. An, J. Y. Cheong, D. T. Thangadurai, I.-C. Hwang, Y. H. Rhee, *Angew. Chem.* **2008**, *120*, 2295–2298; *Angew. Chem. Int. Ed.* **2008**, *47*, 2263–2266; b) C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath, Y. H. Rhee, *J. Am. Chem. Soc.* **2009**, *131*, 14660–14661; c) C. Kim, W. Lim, Y. H. Rhee, *Bull. Korean Chem. Soc.* **2010**, *31*, 1465–1466.

[5] For recent reviews of gold-catalyzed reactions, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; d) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; e) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; f) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075–6089; g) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

[6] For selected examples of the tandem gold(I)-catalyzed reaction by using a cyclization–fragmentation strategy, see: a) P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062–12063; b) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; c) S. E. An, J. Jeong, B. Baskar, J. Lee, J. Seo, Y. H. Rhee, *Chem. Eur. J.* **2009**, *15*, 11837–11841; d) H.-S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J.-E. Lee, S. S. Lee, S. Shin, *Angew. Chem.* **2010**, *122*, 1655–1658; *Angew. Chem. Int. Ed.* **2010**, *49*, 1611–1614.

[7] For synthesis of the gold complex **12a**, see: S. Shin, *Bull. Korean Chem. Soc.* **2005**, *26*, 1925–1926.

[8] For selected examples that address the ligand effect on divergent pathways in gold-catalyzed reactions, see: a) M. Alcarazo, T. Stork, A. Anoop, W. Thiel, A. Fürstner, *Angew. Chem.* **2010**, *122*, 2596–2600; *Angew. Chem. Int. Ed.* **2010**, *49*, 2542–2546; b) A. Z. González, F. D. Toste, *Org. Lett.* **2010**, *12*, 200–203; c) B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605–2607.

[9] By using ^{1}H NMR spectroscopy, it was confirmed that the ratio of **10a** to **10b** (after the cycloisomerization step) was comparable to the ratio of **11a** to **11b**.

[10] When **9** was treated with strong oxophilic Lewis acids, such as BF_3OEt_2, neither **10** nor **11** was obtained in any significant amount.

[11] All the mixed acetal substrates were prepared by the coupling of the homopropargylic alcohol with the enol ether precursor in good yields. For a detailed procedure of the coupling reaction, see the Supporting Information.

[12] Unlike the terminal alkynes, internal alkynes (both methyl- and phenyl-substituted) were unreactive under the reaction conditions.

[13] For a discussion on the configurational stability of oxocarbenium ions, see: a) D. Cremer, J. Gauss, R. F. Childs, C. Blackburn, *J. Am. Chem. Soc.* **1985**, *107*, 2435–2441; b) L. Liu, P. E. Floreancig, *Angew. Chem.* **2010**, *122*, 6030–6033; *Angew. Chem. Int. Ed.* **2010**, *49*, 5894–5897.

[14] For studies on the competition between the Prins pathway and the oxonia-Cope pathway in the tetrahydropyran synthesis, see: a) R. Jasti, C. D. Anderson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945; b) L. D. M. Lolkema, C. Semeyn, L. Ashek, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 7129–7140; c) W. R. Roush, G. J. Dilley, *Synlett* **2001**, 0955–0959.

[15] a) For an in-depth discussion of racemization in the related Prins reaction in tetrahydropyran synthesis, see: R. Jasti, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2006**, *128*, 13640–13648; b) for a recent review on the Prins cyclization in tetrahydropyran synthesis, see: C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron* **2010**, *66*, 413–445.

[16] A detailed synthetic procedure of **35** can be found in the Supporting Information.

[17] The structure of compound **38** was determined by using ^{1}H NMR spectroscopy.

Received: October 10, 2010
Published online: January 12, 2011

