C–H Activation

DOI: 10.1002/anie.201000033

Structurally and Stereochemically Diverse Tetrahydropyran Synthesis through Oxidative C–H Bond Activation**

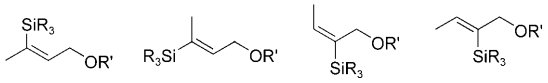
*Lei Liu and Paul E. Floreancig**

Dedicated to Professor Paul Grieco on the occasion of his 65th birthday

Tetrahydropyrans are core units within a multitude of biologically active natural products,[1] and methods to prepare these structures, which utilize C–H bond functionalization as a prelude to C–C bond-formation are desirable. This approach is both step[2] and atom[3] economical, because the substrate preparation and reactive intermediate generation employ unreactive C–H bonds, rather than conventional leaving groups. We have shown that heterocycles can be formed with high levels of diastereocontrol from benzylic and allylic ethers through the DDQ-mediated (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxocarbenium ion formation, and subsequent intramolecular nucleophilic addition.[4] This method is highly complementary to Prins-based methods in the preparation of tetrahydropyrans,[5] and has been validated through its application to natural product synthesis.[6] Additional strategic benefits of this approach include the tolerance of acid labile functional groups towards oxidative conditions,[7] the application of facile etherification reactions to form stable linkages in segment coupling reactions, and the access to versatile unsaturated products. We have shown that this unsaturation provides a route towards a range of structurally and stereochemically diverse tetrahydropyrans through post-cyclization manipulations. Vinylsilane- and alkyne-containing products serve as useful moieties for application in target- and diversity-oriented synthesis.

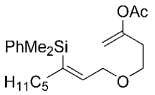
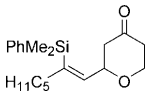
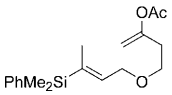
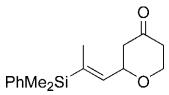
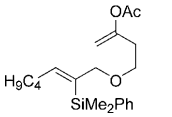
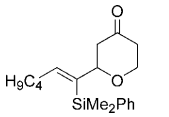
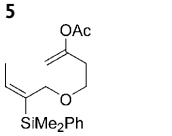
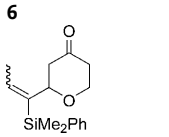
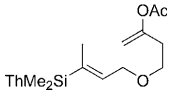
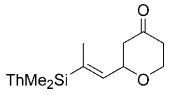
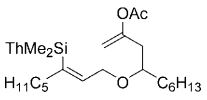
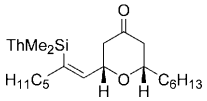
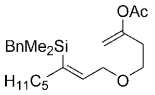
Vinylsilanes are outstanding precursors for functionally and stereochemically diverse structures because of their ability to engage in numerous transformations,[8] and their well-defined[9] conformational preferences. The cyclization substrates can be prepared by etherification reactions of the corresponding silylallylic alcohols.[10] This approach maximizes convergency by introducing the silyl group prior to the fragment coupling, and is therefore applicable in efficient natural product and other target-oriented syntheses. The class of silylated ether substrates that were prepared for this study are depicted in Scheme 1.

The results of the oxidative cyclization reactions for the silylallylic ethers are shown in Table 1. Both *Z*- and *E*-3-phenyldimethylsilanes **1** and **3** reacted smoothly, and formed tetrahydropyrones **2** and **4**, respectively (entries 1 and 2).



Scheme 1. Vinylsilane classes.

Table 1: Vinylsilane scope.[a]

Entry	Substrate	Product	*t* [h]	Yield [%][b]
1				
	1	**2**	18	73
2				
	3	**4**	17	94
3				
	5	**6**	6	82
4				
	7	**8**	24	69[c]
5				
	9	**10**	8	86
6				
	11	**12**	18	82
7		n.r.		
	13		36	–

[a] Representative procedure: DDQ (4 equiv) was added to a solution (0.1 M) of the substrate, $LiClO_4$ (0.2 equiv), and 2,6-dichloropyridine (2 equiv) in 1,2-dichloroethane. The reaction mixture was stirred at 45 °C. [b] Yields refer to isolated, purified material unless otherwise noted. [c] Yield of isolated product refers to a 1:1 mixture of alkene stereoisomers. Th = 2-thienyl, n.r. = no reaction.

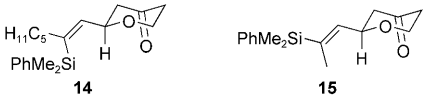
[*] L. Liu, Prof. Dr. P. E. Floreancig
Department of Chemistry, University of Pittsburgh
Pittsburgh, PA 15260 (USA)
Fax: (+1) 412-624-8611
E-mail: florean@pitt.edu

[**] We thank the National Institutes of Health (GM062924). We thank Dr. Steve Geib for crystallographic analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000033.

When 2-phenyldimethylsilanes **5** and **7** were employed, products **6** and **8** were afforded, respectively, in good yield (entries 3 and 4), however, alkene isomerization of the intermediate radical cation or oxocarbenium ion from **7** was faster than the cyclization, thus leading to a 1:1 mixture of alkene isomers. Hetero-arylsilanes are also suitable substrates for this process as demonstrated by the cyclization of 3-(2-thienyl)dimethylsilanes **9** and **11** to form **10** and **12**, respectively (entries 5 and 6). Consistent with previous studies,[4] vinylsilane substrates react exclusively to form the 2,6-*cis* isomers (entry 6). Benzylsilane **13** was not converted into the cyclized product (entry 7). This result could be a consequence of benzylsilane acting as a quenching agent for the radical cation intermediate, which is in accord with the known capacity of benzylsilanes to undergo facile single-electron oxidations.[11] The reactions, although efficient with respect to yield and stereocontrol, were substantially slower than reactions of similarly substituted trialkylallylic ethers, requiring heating to 45 °C and multiple hours for complete substrate consumption. These results were consistent with the observations of Kochi and co-workers,[12] in which sterically hindered arenes reacted with quinones at a slower rate than sterically unhindered arenes having similar oxidation potentials because the rate of electron transfer is dependent upon the ability of the quinone to approach the arene. The bulky trialkylsilyl groups block the approach of the quinone towards the alkene, thereby lowering the rate of the reaction.

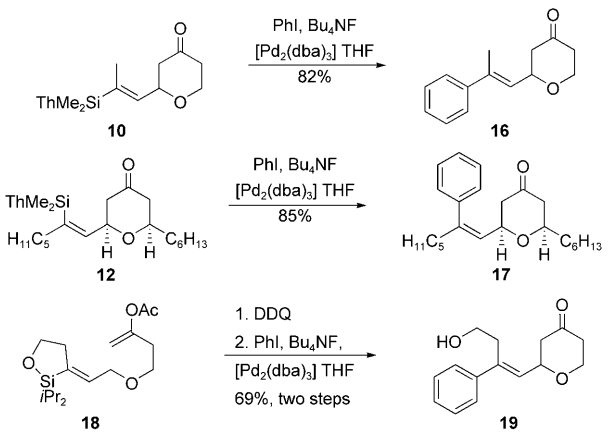
The successful cyclizations of *E*- and *Z*-vinylsilane substrates are significant for maximizing the range of products that can ultimately be accessed through this process. The 1,3-allylic strain[13] dictates that products **2** and **4** would strongly prefer to adopt conformations **14** and **15**, respectively (Scheme 2).[14] Conformational restriction will be important



Scheme 2. Conformational control through 1,3-allylic strain minimization.

for subsequent studies (see below) because it allows stereochemical complementary functionalization, through directed reagent delivery from the tetrahydropyranyl oxygen atom.

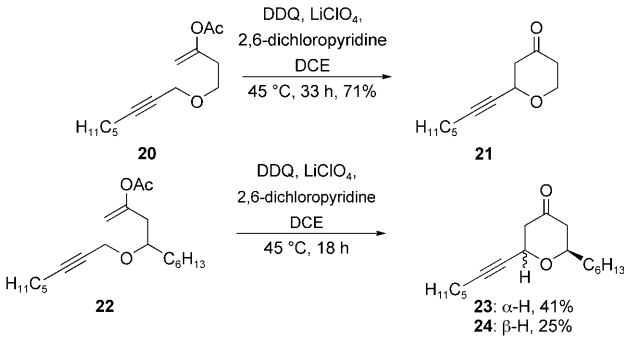
The capacity of vinylsilanes to engage in cross-coupling reactions[15] allows the products of the cyclization reactions to serve as precursors to other alkenes, thus showing that the products from this study will be useful for natural product and library syntheses (Scheme 3). The 2-thienyldimethylsilane group was selected for these reactions to ensure that the vinylsilane is not cleaved prior to coupling.[16] *E*-Vinylsilane **10** reacted smoothly with iodobenzene in the presence of Bu_4NF and $[Pd_2(dba)_3]$, thus affording **16** in 82% yield, whereas *Z*-vinylsilane **12** provided **17** in 85% yield. Heteroatom substitution on the silicon atom eliminates the concern of desilylation,[17] therefore vinylsiloxane **18** was prepared through a platinum-mediated intramolecular hydrosilylation[18] reaction, and served as a substrate for oxidative



Scheme 3. Vinylsilane products in cross-coupling reactions. dba = 1,5-diphenyl-1,4-pentadien-3-one.

cyclization. The resulting reaction mixture was treated with iodobenzene in the presence of Bu_4NF and $[Pd_2(dba)_3]$ to form **19** in 69% overall yield. Although, this study was not exhaustive, these results demonstrate the capacity to prepare diverse structures by combining the oxidative cyclization of vinylsilane substrates with cross-coupling reactions.

The potential for product diversification led us to explore propargylic ethers as substrates[10] because the alkynyl groups of propargylic ethers can be converted into numerous groups at a later stage in the synthetic sequence. Propargylic ethers (Scheme 4) were similar in reactivity to the vinylsilane substrates. For example, the DDQ-mediated cyclization of alkyne **20** into tetrahydropyran **21** proceeded in 71% yield after 33 hours at 45 °C; furthermore, **22** provided **23** in 41% yield and **24** in 25% yield after 18 hours at 45 °C. The similarity of the cyclization rates for silylallylic and propargylic ethers results from alkynes being less sterically demanding, and also less adept at cation stabilization than vinylsilanes. Diastereocontrol in the cyclization of **22** was diminished in comparison to the complete stereocontrol that had been observed in all previous cyclization reactions. This result is attributed to the sterically undemanding alkyne groups which cause a mininal energetic difference between the intermediate *E*- and *Z*-oxocarbenium ions. In contrast, there is a significant energetic preference for the *E* geometry

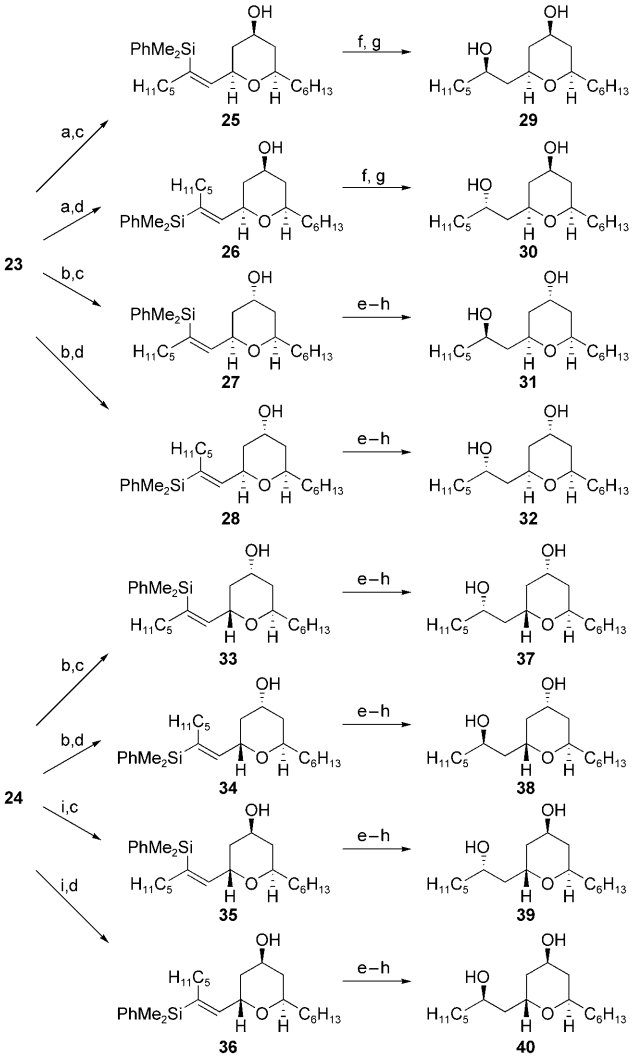


Scheme 4. Cyclization reactions of propargylic ethers. DCE = dichloroethane.

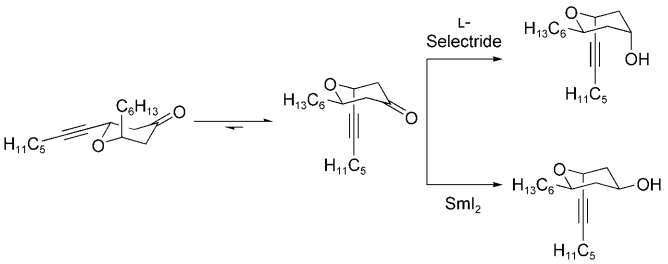
(ca. 2 kcal mol^{-1})[19] for alkyl- and alkenyl-substituted intermediates.

The wide range of biological activities which tetrahydropyran-containing molecules possess, indicates that preparing a stereochemically diverse library[20] of these structures would be an attractive goal, particularly when considering the growing interest in saturated compounds in drug discovery.[21] We have achieved this objective by exploiting the accessibility to *cis*- and *trans*-cyclization product, and numerous options for alkyne functionalization. This approach proceeds through the non-stereoselective cyclization of **22** into **23** and **24** (Scheme 5). The stereoselective reductions of **23** were achieved with either $NaBH_4$ (equatorial alcohol product) or L-Selectride (axial alcohol product). The *E* vinylsilanes were then formed by hydrosilylation using $PhMe_2SiH$ and $[Cp^*Ru(CH_3CN)_3PF_6]$,[22] and the *Z* vinylsilanes were formed by hydrosilylation using a H_2PtCl_6 catalyst. The regiocontrol of the platinum-mediated reaction was lower (ca. 3:1) than that obtained in the ruthenium-mediated reactions, but the desired products were isolated in moderate yields (62–67 %) to complete the synthesis. The resulting vinylsilanes **25**–**28** were reduced using H_2 and Crabtree's catalyst.[23] The stereocontrol in these reactions arises from the combination of coordination of the catalyst to the tetrahydropyranyl oxygen atom and conformational control of the vinylsilane, which is in accord with the models from Scheme 2. The levels of stereocontrol for **25** and **26** were excellent, whereas substrates **27** and **28** required the conversion of the free hydroxy group into a silyl ether to achieve complete stereocontrol; the axial hydroxy group can competitively deliver H_2 from the opposite face of the alkene. Oxidation of the hydrogenation products under Fleming's conditions,[24] and subsequent silyl ether cleavage (where necessary) provided tetrahydropyranols **29**–**32**.

The stereoselective reductions of 2,6-*trans*-dialkyltetrahydropyran-4-ones are difficult to achieve when the alkyl substituents are sterically similar because the two possible chair conformations are energetically similar.[25] However, 2-alkynyl-6-alkyltetrahydropyrans exist preferentially in the chair conformation, in which the alkynyl group is axially oriented and the alkyl group is equatorially oriented, because of the significant difference in the A values (Scheme 6). This conformational preference should allow predictable additions to the ketone. Indeed, subjecting **24** to L-Selectride resulted in reduction from an equatorial trajectory with excellent stereocontrol. Proceeding through the sequence of stereodivergent hydrosilylation, vinylsilane reduction, and Fleming oxidation provided products **37** and **38**. The reduction of **24** with $NaBH_4$ was unselective, because the alkynyl group blocks the axial approach of the hydride. In contrast, SmI_2 and *i*PrOH[26] provided the equatorial alcohol as a single isomer in 85 % yield. The selective reductions in this series illustrates that alkynyl substitution could be extremely useful for the synthesis of 2,6-*trans*-dialkyltetrahydropyran-containing natural products. Completion of the sequence allowed the formation of the final two stereoisomers **39** and **40** with high selectivity. Furthermore, the triethylsilyl ethers are sufficiently stable to allow the synthetic sequence to proceed with similar efficiencies to that employing *tert*-butyldimethyl-



Scheme 5. Synthesis of a stereochemically diverse library. a) $NaBH_4$, MeOH, −10 °C, 85 %. b) L-Selectride, THF, −90 °C, 65 % from **23**, 89 % from **24**. c) $PhMe_2SiH$, $[Cp^*Ru(NCCH_3)_3]PF_6$, acetone, 0 °C, 91 % for **25**, 92 % for **28**, 100 % for **33**, 86 % from **35**. d) $PhMe_2SiH$, $H_2PtCl_6{\cdot}6H_2O$, THF, 50 °C, 65 % for **26**, 67 % for **28**, 64 % for **34**, 62 % for **36**. e) TBSCl, imidazole, CH_2Cl_2 or DMF. f) H_2, Crabtree's catalyst, CH_2Cl_2. g) CH_3CO_3H, KBr, NaOAc, HOAc, 53 % from **25**, 67 % from **26**. h) Bu_4NF, THF, 50 % from **27**, 63 % from **28**, 67 % from **33**, 57 % from **34**, 53 % from **35**, 58 % from **36**. i) SmI_2, THF, *i*PrOH, 85 %. Cp* = pentamethylcyclopentadienyl, Crabtree's catalyst = $[(cod)(py)(Cy_3P)Ir]PF_6^-$, L-Selectride = lithium tri(*sec*-butyl)borohydride, DMF = *N*,*N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl. THF = tetrahydrofuran.



Scheme 6. Stereoselective reduction of 2,6-*trans* isomers.

silyl ethers, and they can be easily removed in the same step as the Fleming oxidation, thus eliminating one step in the sequence.[27]

We have shown that vinylsilane-substituted tetrahydropyrans provide access to a broad range of structurally and stereochemically diverse products. This versatility arises because vinylsilanes exist in predictable, rigid conformations and offer multiple options for functional group interconversion, through oxidative or cross-coupling protocols. These products can be accessed by employing oxidative cyclization reactions on silylallylic ethers or on propargylic ethers, and subsequent alkyne hydrosilylation. The cyclization of silylallylic ethers is preferable for convergent applications to natural product or other target-oriented syntheses, which is in contrast to cyclizations of propargylic ethers, which are preferable in divergent strategies for diversity-oriented synthesis. Stereocontrol in propargylic ether cyclizations is diminished owing to the similar energies of the *E*- and *Z*-alkynyl oxocarbenium ion intermediates. Access to the rare *Z*-oxocarbenium ions has potential applications, and has been exploited to prepare the eight possible diastereomers of a tetrahydropyran structure. Although, hydrogenation was selected to demonstrate the capacity for stereoselective alkene functionalization, the predictable conformations and directing effects create abundant opportunities for structural diversification. The efficiency of the oxidative C–H bond functionalization protocol, the potential medicinal significance of tetrahydropyran structures, and the growing number of protocols[28] that utilize vinylsilanes as substrates for C–C bond-forming reactions indicates that the approach outlined herein will have broad applications in natural product and library synthesis.

Received: January 4, 2010
Revised: February 3, 2010
Published online: March 22, 2010

Keywords: combinatorial synthesis · diastereoselectivity · hydrosilylation · molecular diversity · oxidation

[1] a) I. Larrosa, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 2683; b) P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045; c) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314; d) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285.
[2] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40.
[3] B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.
[4] a) W. Tu, L. Liu, P. E. Floreancig, *Angew. Chem.* **2008**, *120*, 4252; *Angew. Chem. Int. Ed.* **2008**, *47*, 4184; b) L. Liu, P. E. Floreancig, *Org. Lett.* **2009**, *11*, 3152; c) H. H. Jung, P. E. Floreancig, *Tetrahedron* **2009**, *65*, 10830.
[5] For recent reviews, see: a) C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron* **2010**, *66*, 413; b) I. M. Pastor, M. Yus, *Curr. Org. Chem.* **2007**, *11*, 925.
[6] W. Tu, P. E. Floreancig, *Angew. Chem.* **2009**, *121*, 4637; *Angew. Chem. Int. Ed.* **2009**, *48*, 4567.
[7] a) M. E. Green, J. C. Rech, P. E. Floreancig, *Angew. Chem.* **2008**, *120*, 7427; *Angew. Chem. Int. Ed.* **2008**, *47*, 7317; b) S. Wan, H. Gunaydin, K. N. Houk, P. E. Floreancig, *J. Am. Chem. Soc.* **2007**, *129*, 7915.
[8] M. J. Curtis-Long, Y. Aye, *Chem. Eur. J.* **2009**, *15*, 5402.
[9] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063.
[10] Please see the Supporting Information for details on substrate preparation.
[11] a) J. I. Yoshida, T. Murata, S. Isoe, *Tetrahedron Lett.* **1986**, *27*, 3373; b) K. P. Dockery, J. P. Dinnocenzo, S. Farid, J. L. Goodman, I. R. Gould, W. P. Todd, *J. Am. Chem. Soc.* **1997**, *119*, 1876.
[12] S. M. Hubig, R. Rathore, J. K. Kochi, *J. Am. Chem. Soc.* **1999**, *121*, 617.
[13] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.
[14] For examples of using vinylsilanes as conformational control elements, see: a) I. Hasan, Y. Kishi, *Tetrahedron Lett.* **1980**, *21*, 4229; b) Y. Yamamoto, H. Yatagai, K. Maruyama, *J. Am. Chem. Soc.* **1981**, *103*, 3229; c) R. K. Boeckman, Jr., T. E. Barta, *J. Org. Chem.* **1985**, *50*, 3421; d) M. Lautens, C. H. Zhang, C. M. Crudden, *Angew. Chem.* **1992**, *104*, 237; *Angew. Chem. Int. Ed.* **1992**, *31*, 232; e) B. M. Trost, J. D. Sieber, W. Qian, R. Dhawan, Z. T. Ball, *Angew. Chem.* **2009**, *121*, 5586; *Angew. Chem. Int. Ed.* **2009**, *48*, 5478.
[15] a) T. Hiyama in *Metal Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, chap. 10; b) S. E. Denmark, *J. Org. Chem.* **2009**, *74*, 2915.
[16] K. Hosoi, K. Nozaki, T. Hiyama, *Chem. Lett.* **2002**, *31*, 138.
[17] S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835.
[18] S. E. Denmark, W. Pan, *Org. Lett.* **2001**, *3*, 61.
[19] J. L. Broeker, R. W. Hoffmann, K. N. Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5006.
[20] M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48; *Angew. Chem. Int. Ed.* **2004**, *43*, 46.
[21] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752.
[22] B. M. Trost, Z. T. Ball, T. Jöge, *J. Am. Chem. Soc.* **2002**, *124*, 7922.
[23] R. H. Crabtree, M. W. Davis, *J. Org. Chem.* **1986**, *51*, 2655.
[24] I. Fleming, R. Henning, D. C. Parker, H. E. Plaut, P. E. J. Sanderson, *J. Chem. Soc. Perkin Trans. 1* **1995**, 317.
[25] A. Bhattacharjee, J. K. De Brabander, *Tetrahedron Lett.* **2000**, *41*, 8069.
[26] J. Treu, H. M. R. Hoffmann, *J. Org. Chem.* **1997**, *62*, 4650.
[27] Please see the Supporting Information for details on this scheme and for a crystallographic validation of the hypotheses regarding the stereochemical outcomes of these reactions. X-ray crystallographic structure is an analogue of compound **39**.
[28] a) D. Tomita, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4138; b) D. A. Evans, Y. Aye, *J. Am. Chem. Soc.* **2006**, *128*, 11034; c) J. R. Herron, Z. T. Ball, *J. Am. Chem. Soc.* **2008**, *130*, 16486; d) K. Aikawa, Y. Hioki, K. Mikami, *J. Am. Chem. Soc.* **2009**, *131*, 13922.

