Synthetic Methods

International Edition: DOI: 10.1002/anie.201704936
German Edition: DOI: 10.1002/ange.201704936

Catalytic Reductive Pinacol-Type Rearrangement of Unactivated 1,2-Diols through a Concerted, Stereoinvertive Mechanism

*Nikolaos Drosos, Gui-Juan Cheng[+], Erhan Ozkal[+], Bastien Cacherat, Walter Thiel, and Bill Morandi**

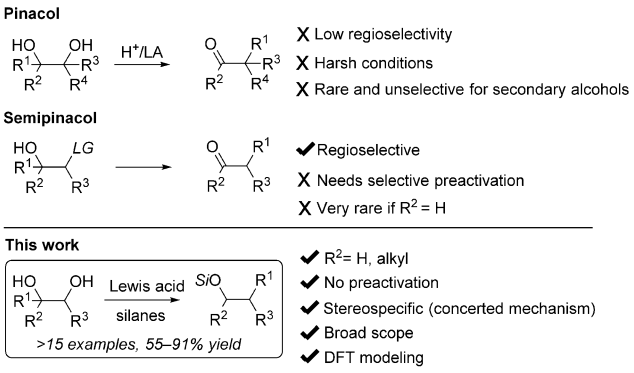
Abstract: *A catalytic pinacol-type reductive rearrangement reaction of internal 1,2-diols is reported herein. Several scaffolds not usually amenable to pinacol-type reactions, such as aliphatic secondary–secondary diols, undergo the transformation well without the need for prefunctionalization. The reaction uses a simple boron catalyst and two silanes and proceeds through a concerted, stereoinvertive mechanism that enables the preparation of highly enantiomerically enriched products. Computational studies have been used to rationalize the preference for migration over direct deoxygenation.*

The controlled, stereoselective rearrangement of carbon skeletons is an important strategy for the preparation of value-added molecules from more readily available starting materials. The pinacol rearrangement can transform diols into the corresponding rearranged ketones through the formation of a carbocation under acidic conditions.[1] However, generally harsh conditions, a limitation of the scope to tertiary or benzylic alcohols, the formation of alkene side products, and a general lack of regioselectivity have considerably limited its broader application in synthesis. In particular, and despite its synthetic potential, the pinacol rearrangement of ubiquitous vicinal aliphatic secondary diols is extremely rare because of the poor ability of these substrates to stabilize positively charged intermediates and the instability of the resulting aldehydes under strongly acidic conditions.[2] Moreover, in the few reported cases, mixtures of ketone and aldehyde products resulted from unselective migration.[2] Collectively, these limitations have prevented the application of the pinacol rearrangement in organic synthesis. The related semipinacol rearrangement of diol derivatives can address some of these limitations, such as regioselectivity, but requires the regioselective preactivation of the diol and is also challenging to perform on vicinal secondary diols.[3]

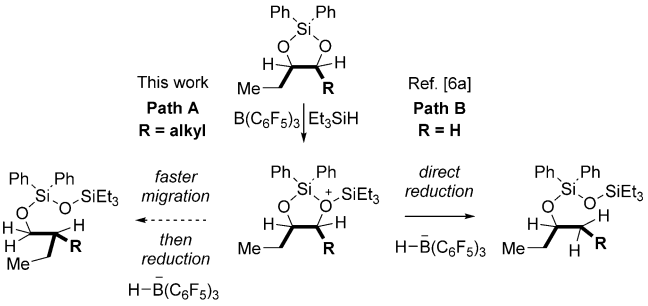
Herein, we present a distinct approach to pinacol-type rearrangements, wherein a boron catalyst mediates the reductive and stereoinvertive rearrangement of a broad range of structurally different diols, including unactivated internal 1,2-diols, to form primary and secondary alcohols (Scheme 1).

Recent studies have demonstrated that the catalyst $B(C_6F_5)_3$,[4,5] in the presence of silanes, is exceptionally active in reductive transformations of polyols.[6] In this context, we showed the synergistic effect of two different silanes in the selective deoxygenation of terminal 1,2-diols through the formation of a key cyclic siloxane intermediate (Scheme 2, path B).[6a,b] We reasoned that if increased steric bulk (R = alkyl) of the cyclic siloxane intermediate sufficiently retarded direct hydride delivery, migration of an alkyl group (path A) could proceed faster than the usually observed deoxygenation.

This new mechanistic manifold would probably address the traditional limitations of the pinacol rearrangement because: 1) the in situ formation of an extremely reactive oxonium leaving group should help overcome the traditional low reactivity of secondary alcohols; and 2) the reaction would be reductive in nature, thus leading to the formation of



Scheme 1. Context of the study. *LG* = leaving group, *Si* = silyl group.

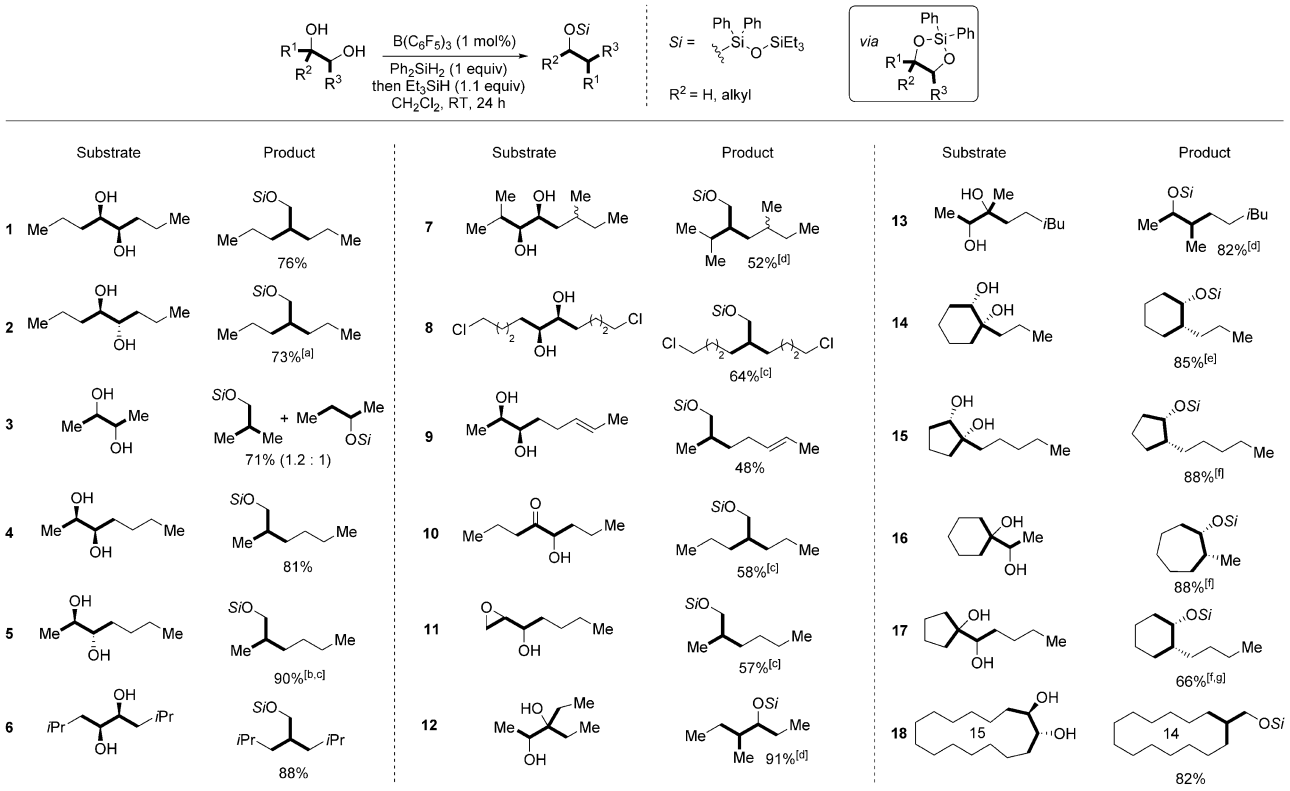


Scheme 2. Working hypothesis.

[*] N. Drosos, Dr. G.-J. Cheng,[+] Dr. E. Ozkal,[+] B. Cacherat, Prof. W. Thiel, Dr. B. Morandi
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
E-mail: morandi@kofo.mpg.de

[+] These authors contributed equally.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201704936.



Scheme 3. [a] Including 23% of the deoxygenated product. [b] Including 26% of the deoxygenated product. [c] Yield determined by ^{1}H NMR spectroscopy with nitromethane as a standard. [d] Mixture of two diasteroisomers (1:1). [e] Mixture of two diastereoisomers (3:1). [f] Only one diastereoisomer was detected by ^{1}H NMR spectroscopy. [g] The reaction was carried out with 3 mol% catalyst.

a stable primary-alcohol derivative instead of a labile aldehyde.

Accordingly, we subjected a simple unactivated internal diol to a range of reaction conditions (see the Supporting Information). We obtained the desired rearrangement product in good yield when a combination of diphenylsilane and triethylsilane was employed. The undesired deoxygenation product was not detected, thus confirming that the barrier for alkyl migration was now lower than that of direct hydride delivery.

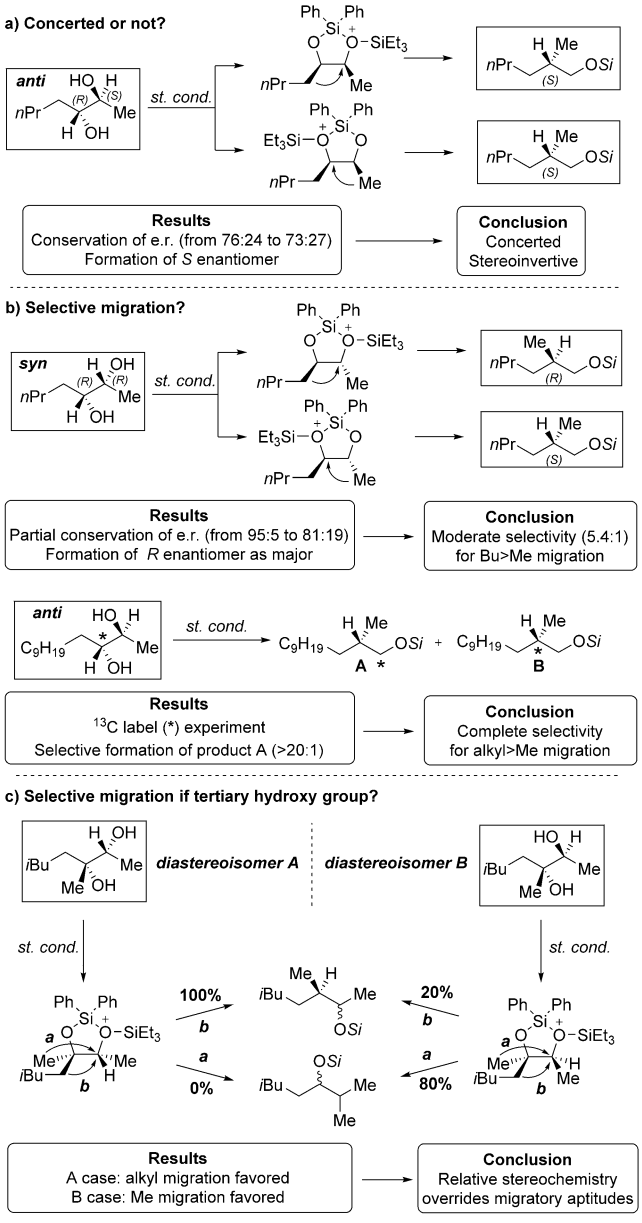
With regard to the scope of the transformation (Scheme 3), initial experiments with simple symmetrical and nonsymmetrical vicinal secondary diols, which have rarely been employed in pinacol or semipinacol rearrangements, afforded the desired product in good yields. Experiments with *syn* diols generally resulted in higher yields, with some competing deoxygenation observed in the case of *anti* diols (entries 2 and 5). Whereas the presence of one methyl substituent was tolerated, the use of butanediol (entry 3), which bears two methyl groups, as the substrate led to increased formation of the deoxygenation product. Alkene and halogen groups were well-tolerated under our reaction conditions, giving synthetically useful yields of the corresponding products. Importantly, we could also employ a hydroxyketone and even an epoxyalcohol[7] as diol surrogates (entries 10 and 11).

Acyclic vicinal tertiary–secondary diols afforded the corresponding rearranged products in good yields (Scheme 3, entries 12 and 13). It is likely that the regioselectivity of these reactions is controlled by silylation of the cyclic siloxane intermediate at the sterically less hindered secondary oxygen atom. A diol bearing two different substituents on the tertiary carbon atom afforded a single product through the highly selective migration of the more electron rich alkyl group (entry 13). Furthermore, two cyclic diols selectively afforded a single rearranged product, each in good yield (entries 14 and 15). In stark contrast to traditional pinacol-type rearrangements, which usually lead to ring contraction in such cases,[8] the migration of the *exo* alkyl group was strongly favored, probably because of the conformational restrictions associated with the formation of a putative bicyclic siloxane intermediate (see the Supporting Information).

Ring expansion and contraction reactions are powerful tools for the synthesis of natural products[9] and modification of bioactive compounds.[10] Under our reaction conditions, the ring expansion of both a five- and a six-membered ring proceeded with full diastereoselectivity to afford the corresponding products (entries 16 and 17). The ring contraction of a macrocylic disubstituted diol proceeded efficiently to form a 14-membered ring (entry 18). The use of a traditional pinacol-type rearrangement for such a ring contraction would arguably be challenging.

Our novel method transforms a chiral diol with, in most cases, two stereogenic centers into a product containing at least one stereogenic tertiary carbon center. It was thus interesting, from both a synthetic and a mechanistic perspective,[11] to rigorously study the stereochemical course of the transformation (Scheme 4).

To this end, (2*R*,3*R*)- and (2*S*,3*R*)-heptane-2,3-diol were synthesized by the Sharpless asymmetric dihydroxylation from alkenes.[12] In a stepwise mechanism involving carbocationic species, the stereoinformation present in the starting material would be lost through the formation of achiral, planar intermediates, thus leading to a racemic product mixture. In contrast, in a concerted mechanism, a single enantiomer of the product should form when the *anti* diol is used as the starting material, independently of the regioselectivity of the migration, because either migration pathway leads to the same enantiomer (Scheme 4a). On the basis of the conservation of enantiomeric excess, as determined experimentally, we can conclude that the reaction is stereoinvertive and probably proceeds through S_N2-type attack. In the case of the *syn* diol, two different enantiomers can be formed depending on the regioselectivity of the migration step (Scheme 4b). As we know that the mechanism is concerted, the conservation of enantiomeric excess in this case should correlate with the regioselectivity of the migratory step. Experimentally, the reaction of a starting material with e.r. 95:5 led preferentially to the formation of the *R* product with e.r. 81:19. This result indicates 5.4:1 regioselectivity in the actual migration step in favor of butyl migration. In the case of the *anti* isomer, ^{13}C-labeling experiments showed even higher selectivity (>20:1) in favor of alkyl migration. Because this selectivity is consistent both with the migratory aptitude (Bu > Me) and the steric preference in the oxonium-forming step, it is not possible to conclude which effect plays a more important role in the observed selectivity.



Scheme 4. Probing the mechanism on the basis of stereochemical considerations.

An experiment with a trisubstituted diol can be used to determine the selectivity of the migration step when two electronically different substituents are located on the tertiary hydroxy group (Scheme 4c). Assuming that only the oxonium of the less sterically encumbered secondary alcohol forms, the migration of one substituent or the other (Me or alkyl) would lead to structurally different products. Experimentally, we observed a marked divergence in selectivity depending on which diastereoisomer was employed. These results further demonstrate that the cyclic nature of the intermediate exacerbates subtle structural differences in the rearrangement process. Notably, in the case of diastereoisomer A, an enantiomerically enriched starting material conserved its *ee* value in the rearrangement process.

Overall, these experiments not only support a concerted, stereoinvertive mechanism, but also lay down the groundwork for the use of this new methodology in the enantioselective preparation of challenging oxygen-containing products from readily synthesized chiral diols.

The experimental results show that the barrier for rearrangement is now, in the case of internal diols, lower than the barrier for direct deoxygenation through direct hydride delivery. This reactivity stands in stark contrast to our earlier observations, in which terminal diols were efficiently deoxygenated under similar reaction conditions.[6a] To provide a rationale for these divergent experimental findings, we performed density functional theory (DFT) calculations[13] to compare the transition-state energies of the deoxygenation and migration steps in two model compounds representing a terminal diol (**I**) and an internal diol (**II**) with an additional ethyl substituent (see the Supporting Information for details). The computational results demonstrate that for the terminal diol the deoxygenation pathway (**I-TSA**) is kinetically more favorable than the migration pathway (**I-TSB**) by 7.1 kcal mol^{-1}, whereas for the internal diol the migration reaction is kinetically more favorable by 3.3 kcal mol^{-1} (**II-TSB** vs. **II-TSA**), which is consistent with the experimental observations.

Figure 1 shows the molecular structures of the four relevant transition states (TSs) and their relative energies.

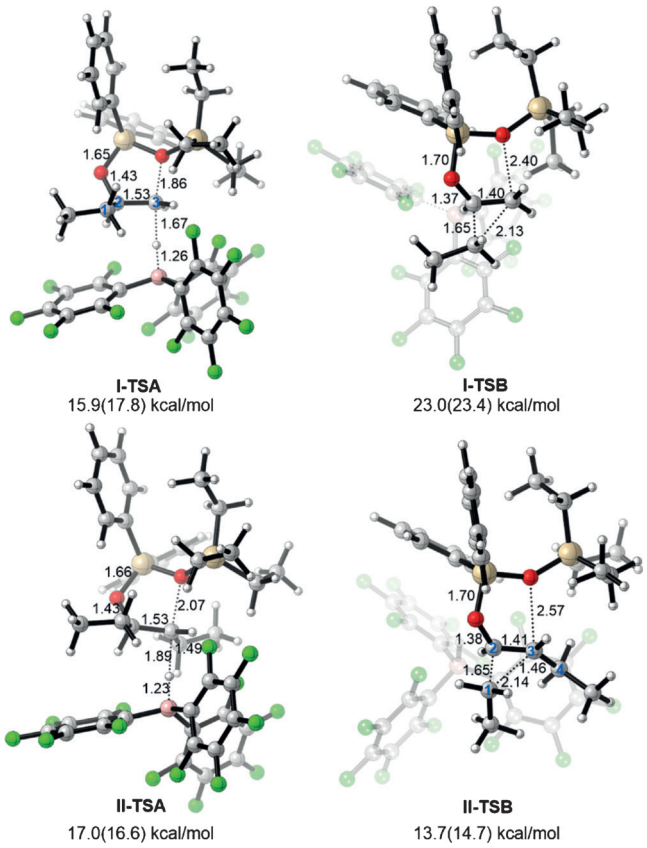


Figure 1. Transition states for migration and deoxygenation for R = H versus R = Et. Free energies (electronic energies) relative to the cyclic siloxane intermediate; distances in Å.

The TSs for deoxygenation (**TSA**) and migration (**TSB**) have quite different geometrical features and properties. **I-TSA** is an intermolecular S_N2 TS, which is stabilized by electrostatic interactions of the C3 atom with the approaching nucleophile $HB(C_6F_5)_3^-$ and the leaving group. **I-TSB** is an intramolecular TS with a three-membered ring and features weaker electrostatic interactions.[14] It benefits from electron delocalization,[15] as indicated by short C2–C3 and C2–O bonds (1.40 and 1.37 Å in I-**TSB** versus 1.53 and 1.43 Å in I-**TSA** and in the cyclic siloxane intermediate, respectively) and by natural bond orbital (NBO) analysis (see the Supporting Information).

In the internal diol, **II-TSB** is stabilized by the hyperconjugative effect of the ethyl substituent,[14] which shortens the C3–C4 bond (1.46 vs. 1.52 Å in the cyclic siloxane intermediate); NBO analysis indicates that the hyperconjugative stabilization is larger in **II-TSB** than in **II-TSA** by 3.9 kcal mol^{-1} (see the Supporting Information). Furthermore, the presence of the ethyl substituent increases the distance between C3 and the nucleophile as well as the leaving group in **II-TSA**, which weakens the electrostatic interactions. Therefore, it is a combination of the hyperconjugative and steric effects of the ethyl substituent that leads to a preference for alkyl migration over deoxygenation in the internal diol.

In conclusion, we have described the reductive pinacol-type rearrangement of a wide range of diols in the presence of a $B(C_6F_5)_3$/silane system. The computational results for terminal and internal diols are in line with the experimental findings and indicate that the observed preference for rearrangement over deoxygenation in internal diols is due to hyperconjugative and steric effects of the additional alkyl substituent.

Acknowledgements

Generous funding from the Max Planck Society, the Max-Planck-Institut für Kohlenforschung, and the Fonds der Chemischen Industrie are acknowledged. We thank Prof. Dr. Benjamin List for sharing analytical equipment, and our NMR, HPLC, GC, and MS departments for technical assistance.

Conflict of interest

The authors declare no conflict of interest.

Keywords: boron · diols · pinacol rearrangement · silanes · stereoselectivity

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 13377–13381
Angew. Chem. **2017**, *129*, 13562–13566

[1] a) R. Fittig, *Justus Liebigs Ann. Chem.* **1860**, *114*, 54–63; b) "The Pinacol Rearrangement": B. Rickborn in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 721–732.

[2] a) L. A. Tapondjou, F. N. Ngounou, D. Lontsi, B. L. Sondengam, J. D. Connolly, *Tetrahedron* **1998**, *54*, 2099–2106; b) C. Pavlik, M. D. Morton, M. B. Smith, *Synlett* **2011**, 2191–2194; c) J. P. Barnier, J. Champion, J. M. Conia, *Org. Synth.* **1981**, *60*, 25–27; d) E. Feghali, T. Cantat, *Chem. Commun.* **2014**, *50*, 862–865.

[3] "The Semipinacol and Other Rearrangements": D. J. Coveney in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 777.

[4] a) M. Oestreich, J. Hermeke, J. Mohr, *Chem. Soc. Rev.* **2015**, *44*, 2202–2220.

[5] a) Y. Kim, S. Chang, *Angew. Chem. Int. Ed.* **2016**, *55*, 218–222; *Angew. Chem.* **2016**, *128*, 226–230; b) A. Simmonneau, M. Oestreich, *Nat. Chem.* **2015**, *7*, 816–822; c) A. Simonneau, M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 11905–11907; *Angew. Chem.* **2013**, *125*, 12121–12124; d) L. Süsse, J. Hermeke, M. Oestreich, *J. Am. Chem. Soc.* **2016**, *138*, 6940–6943; e) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46–76; *Angew. Chem.* **2010**, *122*, 50–81; f) I. Chatterjee, Z.-W. Qu, S. Grimme, M. Oestreich, *Angew. Chem. Int. Ed.* **2015**, *54*, 12158–12162; *Angew. Chem.* **2015**, *127*, 12326–12330; g) A. F. G. Maier, S. Tussing, T. Schneider, U. Flörke, Z.-W. Qu, S. Grimme, J. Paradies, *Angew. Chem. Int. Ed.* **2016**, *55*, 12219–12223; *Angew. Chem.* **2016**, *128*, 12407–12411.

[6] a) N. Drosos, B. Morandi, *Angew. Chem. Int. Ed.* **2015**, *54*, 8814–8818; *Angew. Chem.* **2015**, *127*, 8938–8942; b) N. Drosos, E. Ozkal, B. Morandi, *Synlett* **2016**, *27*, 1760–1764; for other examples of deoxygenation with this system, see: c) J. M. Blackwell, K. L. Foster, V. H. Beck, W. E. Piers, *J. Org. Chem.* **1999**, *64*, 4887–4892; d) V. Gevorgyan, J.-X. Liu, M. Rubin, S.

Benson, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 8919 – 8922; e) V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 6179 – 6186; f) V. Gevorgyan, M. Rubin, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.* **2001**, *66*, 1672 – 1675; g) R. D. Nimmagadda, C. McRae, *Tetrahedron Lett.* **2006**, *47*, 5755 – 5758; h) L. L. Adduci, M. P. McLaughlin, T. A. Bender, J. J. Becker, M. R. Gagné, *Angew. Chem. Int. Ed.* **2014**, *53*, 1646 – 1649; *Angew. Chem.* **2014**, *126*, 1672 – 1675; i) L. L. Adduci, T. A. Bender, J. A. Dabrowski, M. R. Gagné, *Nat. Chem.* **2015**, *7*, 576 – 581; j) T. A. Bender, J. A. Dabrowski, H. Zhong, M. R. Gagné, *Org. Lett.* **2016**, *18*, 4120 – 4123; k) T. A. Bender, J. A. Dabrowski, M. R. Gagné, *ACS Catal.* **2016**, *6*, 8399 – 8403; l) I. Chatterjee, D. Porwal, M. Oestreich, *Angew. Chem. Int. Ed.* **2017**, *56*, 3389 – 3391; *Angew. Chem.* **2017**, *129*, 3438 – 3441.

[7] a) M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1993**, *115*, 12208; b) T. J. Snape, *Chem. Soc. Rev.* **2007**, *36*, 1823.

[8] D. P. G. Hamon, K. L. Tuck, *Tetrahedron* **2000**, *56*, 4829 – 4835.

[9] E. J. Corey, M. Ohno, R. B. Mitra, P. A. Vatakencherry, *J. Am. Chem. Soc.* **1964**, *86*, 478 – 485.

[10] a) J. Wölfling, *ARKIVOC (Gainesville, FL, United States)* **2007**, 210 – 230; b) "D-Homo Rearrangement": Z. Wang, *Comprehensive Organic Name Reactions and Reagents*, Wiley, Hoboken, **2010**.

[11] a) A. Y. Houghton, J. Hurmalainen, A. Mansikkamäki, W. E. Piers, H. M. Tuononen, *Nat. Chem.* **2014**, *6*, 983 – 988; b) D. J. Parks, J. M. Blackwell, W. E. Piers, *J. Org. Chem.* **2000**, *65*, 3090 – 3098; c) W. E. Piers, A. J. V. Marwitz, L. G. Mercier, *Inorg. Chem.* **2011**, *50*, 12252 – 12262.

[12] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483 – 2547.

[13] a) All DFT calculations were performed at the SMD-M06L/6-311G++(d,p)// M06L/6-311G(d,p) level of theory by using the Gaussian 09 software (see the Supporting Information for details); b) K. Sakata, H. Fujimoto, *J. Org. Chem.* **2013**, *78*, 12505 – 12512; c) Y.-F. Yang, G.-J. Cheng, J. Zhu, X. Zhang, S. Inoue, Y.-D. Wu, *Chem. Eur. J.* **2012**, *18*, 7516 – 7524.

[14] R. Robiette, T. Trieu-Van, V. K. Aggarwal, J. N. Harvey, *J. Am. Chem. Soc.* **2016**, *138*, 734 – 737.

[15] K. Nakamura, Y. Osamura, *J. Am. Chem. Soc.* **1993**, *115*, 9112 – 9120.

Manuscript received: May 13, 2017
Accepted manuscript online: July 26, 2017
Version of record online: September 18, 2017

