Asymmetric Synthesis Hot Paper

DOI: 10.1002/anie.201306749

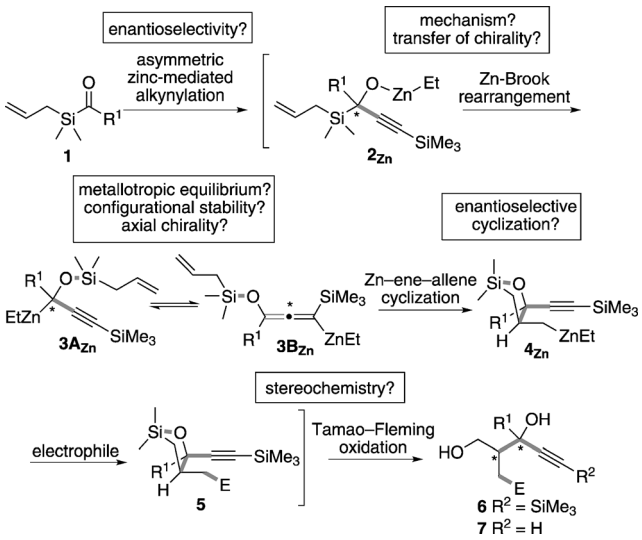
One-Pot Zinc-Promoted Asymmetric Alkynylation/Brook-Type Rearrangement/Ene–Allene Cyclization: Highly Selective Formation of Three New Bonds and Two Stereocenters in Acyclic Systems**

*Polina Smirnov, Jomon Mathew, Anne Nijs, Einat Katan, Miriam Karni, Carsten Bolm, Yitzhak Apeloig, and Ilan Marek**

In memory of Michael Bendikov

Since the pioneering reports in the 1960s,[1] asymmetric organometallic catalysis has played a crucial and dominant role in organic chemistry, and has led to the rapid development of a myriad of widely used synthetic transformations.[2] During the past five decades, great effort has been devoted to the development of catalytic reactions; however, these highly valued transformations generally combine only two components and thus result in the formation of a single carbon–carbon bond in the critical step. If one could develop asymmetric catalytic reactions in which more than one carbon–carbon bond is created in a single-pot operation, it would tremendously improve the efficiency of catalytic processes.[3] Thus, the challenging goal of step economy can be achieved through one-pot operations that combine several steps that collectively provide a high increase in complexity.[4] In this context, we[5] and others[6] have recently developed different approaches to create several carbon–carbon bonds in acyclic systems and in single-pot operations with excellent control of the configuration of all stereogenic centers, including the challenging all-carbon quaternary stereogenic centers.[7] These methodologies produce sophisticated molecular frameworks while complying with synthetic efficiency.[5,6] Nevertheless, in our previously studied cases, selectivity was controlled by chiral auxiliaries. If one could combine, in a single pot-operation, asymmetric catalysis with the creation of several new bonds in acyclic systems, it would be extremely useful in organic synthesis and would pave the way to new approaches for synthetic transformations.[8] Herein we describe the development of reactions that meet these challenges.

Our hypothesis, shown in Scheme 1, is based on an asymmetric alkynylation of acyl silanes **1**[9] in the presence of chiral zinc species derived from Et_2Zn and chiral Lewis bases to give the corresponding enantiomerically enriched zinc α-hydroxypropargyl silanes $\mathbf{2_{Zn}}$.[10] Acyl silanes are powerful substrates owing to a potential [1,2]-anion transposition, defined as the Brook rearrangement,[11] that leads to new carbanions which can undergo further synthetic transformations (anion relay chemistry).[12] Therefore, the tetrahedral intermediate $\mathbf{2_{Zn}}$ is expected to undergo a C→O silyl migration to give the stabilized carbanion $\mathbf{3A_{Zn}}$,[13] which can be in metallotropic equilibrium with its allenyl counterpart $\mathbf{3B_{Zn}}$.[14] Several important questions arise, such as: 1) Would the zinc-promoted Brook rearrangement proceed in the presence of a stoichiometric amount of a base?[15] 2) Would a complete transfer of chirality occur? 3) Would the propargyl zinc species $\mathbf{3A_{Zn}}$ be configurationally stable before its transformation into $\mathbf{3B_{Zn}}$ through metallotropic equilibration? 4) What would be the stereochemical outcome of the Zn-Brook rearrangement of $\mathbf{2_{Zn}}$ to $\mathbf{3A_{Zn}}$ and how does this rearrangement proceed? 5) Assuming that this Zn-Brook



Scheme 1. General scheme describing the proposed combined zinc-promoted alkynylation/Brook rearrangement followed by a Zn–ene–allene cyclization.

[*] P. Smirnov, Dr. J. Mathew, E. Katan, Dr. M. Karni, Prof. Dr. Y. Apeloig, Prof. Dr. I. Marek
Schulich Faculty of Chemistry and the Lise Meitner–Minerva Center for Computational Quantum Chemistry
Technion-Israel Institute of Technology
Technion City, Haifa 32000 (Israel)
E-mail: chilanm@tx.technion.ac.il
Dr. A. Nijs, Prof. Dr. C. Bolm
Institute für Organische Chemie der RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)

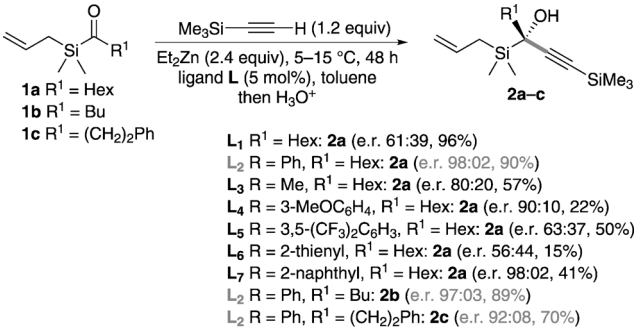
[**] This research was supported by grants from the German Israeli Foundation for Scientific Research and Development (GIF), the German–Israeli Project Cooperation (DIP), and the Minerva Foundation in Munich. J.M. thanks the Lady Davis Foundation for a fellowship.

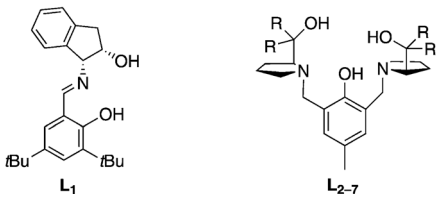
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306749.

rearrangement proceeds with preservation of the stereochemical information, would enantiomerically enriched delocalized organometallic species $\mathbf{3A_{Zn}}/\mathbf{3B_{Zn}}$ undergo an enantioselective Zn–ene–allene cyclization to the corresponding methylzinc-substituted cyclic siloxy derivative $\mathbf{4_{Zn}}$?[16]

The success of this single-pot strategy requires positive answers to *all* questions raised in Scheme 1. The addition of electrophiles to $\mathbf{4_{Zn}}$ would then produce functionalized adducts **5** that could be oxidized[17] to acyclic compounds **6** in which *three new bonds and two new stereogenic centers have been created in a one-pot operation* through an initial asymmetric catalytic reaction.

Before performing the entire one-pot transformation of **1** into **5**, we initially focused on the alkynylation of **1** through asymmetric catalysis (Scheme 2). The enantiomerically enriched α-hydroxypropargyl silane **2** was first prepared in

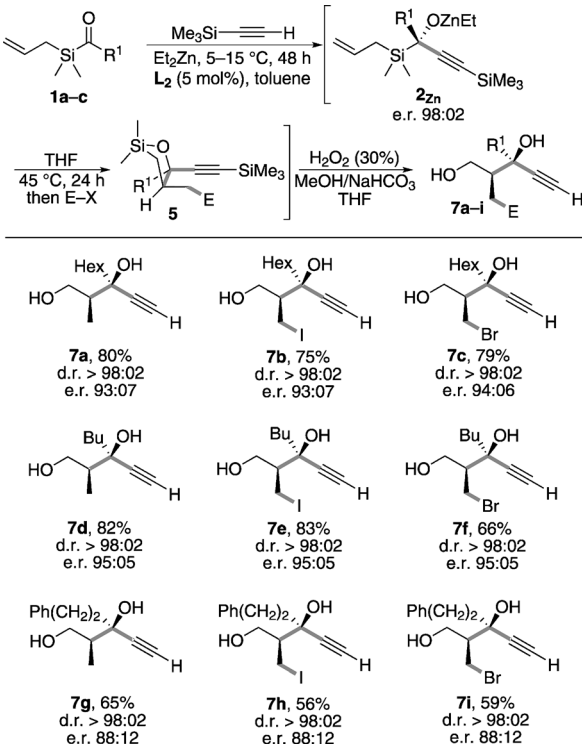




Scheme 2. Enantioselective zinc-catalyzed alkynylation of acyl silanes **1a–c**.

excellent yield but with modest enantioselectivity by the use of the tridentate Schiff base ligand $\mathbf{L_1}$.[10a] However, with the ProPhenol-type ligand $\mathbf{L_2}$,[18] products **2** were obtained with excellent enantiomeric ratios of 98:2 (Scheme 2; see the Supporting Information).[19] The absolute configuration of **2** was established by chemical correlation.[9]

Having established straightforward access to enantiomerically enriched zinc propargyl silanols $\mathbf{2_{Zn}}$, we carried out the whole sequence described in Scheme 3, namely, the preparation of highly functionalized compounds **7** from acyl silanes **1** through the unique combination of an asymmetric zinc-promoted alkynylation followed by the Brook rearrangement and ene–allene cyclization. To perform the desired rearrangement, we simply added THF to $\mathbf{2_{Zn}}$ and heated the reaction mixture at 45 °C for 24 h. We were pleased to observe that the transformation of the zinc alcoholate $\mathbf{2_{Zn}}$ under these conditions yielded $\mathbf{4_{Zn}}$, presumably through a Zn-Brook rearrangement and subsequent cyclization to $\mathbf{4_{Zn}}$ (as initially suggested in Scheme 1). The addition of electrophiles led to



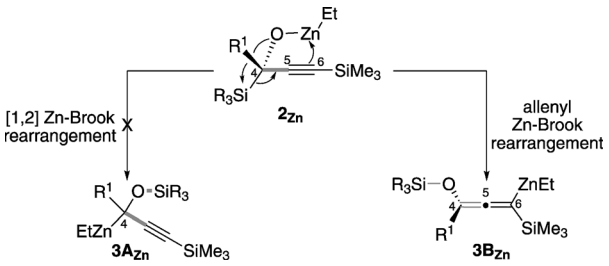
Scheme 3. Tandem enantioselective zinc-promoted alkynylation/Brook rearrangement/ene–allene cyclization and subsequent addition of an electrophile and oxidation in a single reaction vessel.

cyclic oxysilanes **5**, which were found to be relatively unstable and were directly oxidized to **6**. However, under these conditions, the trimethylsilyl group on the alkyne was partially cleaved; complete desilylation occurred upon the treatment of the crude reaction mixture with an aqueous base.

We were delighted to obtain enantiomerically enriched propargylic alcohols **7a–i** directly from **1** in high yield as single diastereomers through the creation of three new bonds and two stereogenic centers (Scheme 3). Except for the conversion of **1c** into **7g–i** ($R^1 = (CH_2)_2Ph$), the enantiomeric ratios of which were slightly lower than that of the precursor **2c** (e.r. 92:8), the enantiomeric ratios of products **7** were very similar to those of $\mathbf{2_{Zn}}$ resulting from the enantioselective alkynylation reaction (Scheme 2; **2a**: e.r. 98:2, **2b**: e.r. 97:3). The high enantiomeric ratios of compounds **7** suggest that the Zn-Brook rearrangement and the following reactions (Scheme 1) proceed with almost complete transfer of chirality. The treatment of ligand-free **2a** with Et_2Zn in THF at 45 °C led to **7a** with the same enantiomeric ratio (e.r. 93:7), which implies that the chiral ligand has no effect on the stereochemical outcome of the subsequent steps. In the Zn–ene–allene carbocyclization, the methylzinc-substituted cyclic siloxy species $\mathbf{4_{Zn}}$ was formed as a single diastereoisomer.[14,16] Further treatment with an electrophile and subsequent Tamao–Fleming oxidation[17] under basic aqueous conditions led to acyclic adducts **7a–i** in good yields. The relative configuration of **7a** was determined by X-ray crystal-structure analysis (see the Supporting Information), and the absolute configurations of **7a–i** were deduced by analogy with previous studies.[9]

Although we had achieved our synthetic objectives, we were puzzled by the apparent configurational stability at 45 °C in THF of the propargyl zinc species $\mathbf{3A_{Zn}}$ resulting from the [1,2]-Brook rearrangement. Whereas unstabilized sp^3 alkyl lithium and magnesium reagents show moderate configurational stability,[20] sp^3 alkyl zinc species are usually configurationally stable only at temperatures up to 25 °C.[21] To gain a better understanding of the mechanism of this unusual Brook rearrangement and of the following cyclization, we studied these reactions by the use of density functional theory (DFT)[22] with several functionals, which all produced similar results. The calculated free-energy profile obtained with the hybrid PBE0 functional and the 6-311G(d,p) basis set for the transformation of $\mathbf{2_{Zn}}$ into $\mathbf{4_{Zn}}$ in the solvent THF is shown in Figure 1 (full details of the calculations are given in the Supporting Information). A close model system for $\mathbf{2_{Zn}}$ with $R^1 = Et$ was used for the analysis. The overall reaction from $\mathbf{2_{Zn}}$ to the cyclic product $\mathbf{4_{Zn}}$ was calculated to be highly exothermic, by 25.9 kcal mol^{-1} (24.6 kcal mol^{-1}, gas phase), which provides the driving force for the reaction. An important result of the calculations is that the first step of the reaction is **not** the expected classical [1,2]-Brook rearrangement of $\mathbf{2_{Zn}}$ to $\mathbf{3A_{Zn}}$ (eventually transformed by a metallotropic equilibrium into $\mathbf{3B_{Zn}}$) as proposed in Scheme 1 on the basis of a previous assumption.[13,16] Instead, the calculations predict that $\mathbf{2_{Zn}}$ rearranges directly to $\mathbf{3B_{Zn}}$ through an interesting allenyl Brook rearrangement in which the new C–Zn bond is formed *anti* to the C–Si bond that is cleaved (Scheme 4).

A transition state for the classic [1,2]-Brook rearrangement in which the silyl group in $\mathbf{2_{Zn}}$ migrates to the oxygen atom and ZnEt coordinates to the central carbon atom (C4) to form $\mathbf{3A_{Zn}}$ could not be located. The calculations provide insight into the unexpected rearrangement of $\mathbf{2_{Zn}}$ to $\mathbf{3B_{Zn}}$



Scheme 4. Allenyl Zn-Brook rearrangement.

(Scheme 4), which is more exothermic by 9.2 kcal mol^{-1} than the rearrangement $\mathbf{2_{Zn}} \rightarrow \mathbf{3A_{Zn}}$ (see the Supporting Information). Species $\mathbf{2_{Zn}}$ exhibits a weak intramolecular chelation of Zn to the C≡C bond [r(Zn–C5) = 2.89 Å, r(Zn–C6) = 3.41 Å]. This weak chelation directs the reaction via transition state **TS1** through the allenyl Zn-Brook rearrangement (intermediate $\mathbf{3B_{Zn}}$) rather than the usual [1,2]-rearrangement (Figure 1). This allenyl Zn-Brook reaction is exothermic by 20.5 kcal mol^{-1} in THF ($\Delta G_{gas} = -13.7$ kcal mol^{-1}), and the free-energy barrier for the rearrangement of $\mathbf{2_{Zn}}$ to $\mathbf{3B_{Zn}}$ is 24.4 kcal mol^{-1} (Figure 1). In **TS1** (Figure 1), the C4–Si bond is stretched from 1.93 to 2.21 Å and the new silicon–oxygen bond is nearly fully made: r(O–Si) = 1.73 Å (1.68 Å in $\mathbf{3B_{Zn}}$); concurrently, the Zn atom approaches the β-propargylic carbon atom (C6) to a distance of 2.44 Å (1.94 Å in $\mathbf{3B_{Zn}}$). Thus, $\mathbf{2_{Zn}}$ undergoes a Zn-Brook rearrangement in which the zinc atom is transferred directly to the β-alkynyl carbon atom (C6) to give the allenyl zinc intermediate $\mathbf{3B_{Zn}}$, and which thus bypasses the classical [1,2]-Brook product $\mathbf{3A_{Zn}}$. Moreover, this important finding nicely rationalizes the observation that the rearrangement proceeds without racemization, as allenyl zinc species are configurationally stable.[23,24] In the

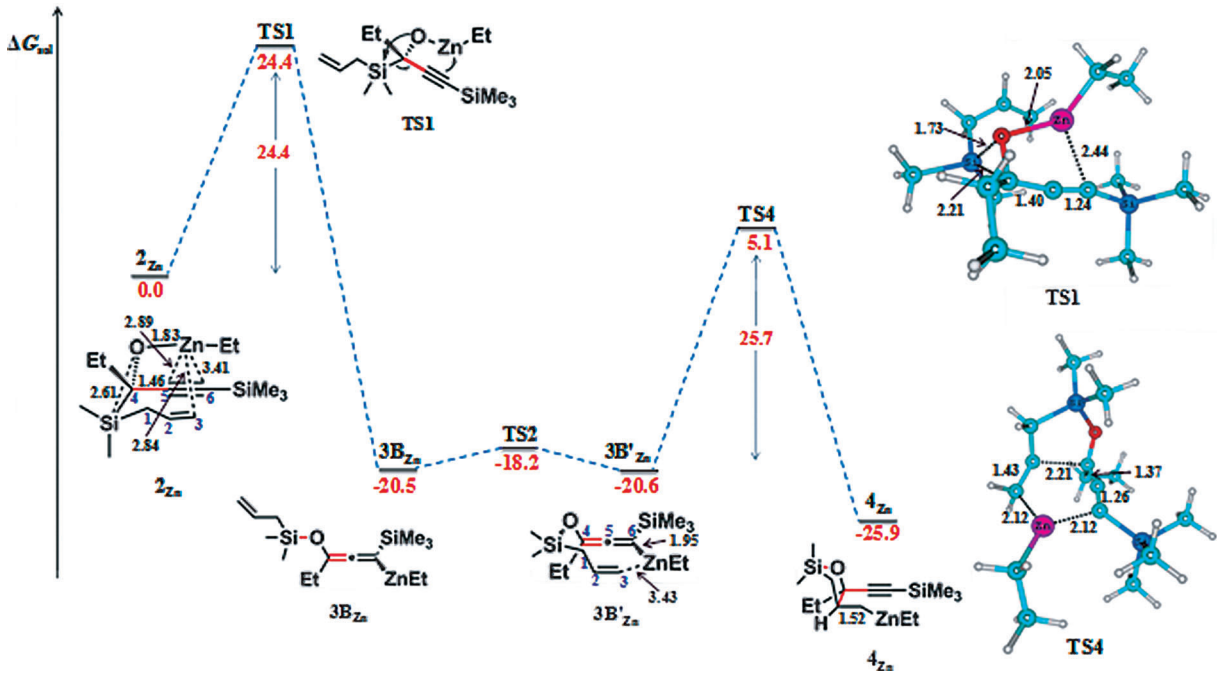


Figure 1. Free-energy profile in THF (at 298 K) and transition-state geometries calculated at the PBE0/SDD-6-311G(d,p) level (ΔG_{sol} in kcal mol^{-1} and bond lengths in Å).

second step of the reaction, $\mathbf{3B}_{Zn}$ first rotates via **TS2** (with a barrier of 2.3 kcal mol^{-1}; see the Supporting Information and Figure 1) to $\mathbf{3B'}_{Zn}$, which is 0.1 kcal mol^{-1} lower in energy. Activation of the terminal double bond of $\mathbf{3B'}_{Zn}$ by the electrophilic zinc atom leads via the cyclic six-membered transition state **TS4**, held by zinc chelation (Figure 1), to the cyclic product $\mathbf{4}_{Zn}$, which is obtained as a single diastereomer. This Zn–ene–allene carbocyclization is exothermic by 5.3 kcal mol^{-1} and has an activation free energy of 25.7 kcal mol^{-1}. In **TS4** (Figure 1), the Zn atom moves towards the β-vinyl carbon atom (C3) so that it is at an equal distance between C3 and the allenic C6 atom (2.12 Å). Concurrently, the α-vinyl carbon atom (C2) approaches the π-bond of the α-allenylic carbon atom (C4) to a distance of 2.21 Å. The nature of this cyclic transition state dictates that enantiomerically enriched $\mathbf{3B'}_{Zn}$ cyclizes diastereoselectively to give enantiomerically enriched $\mathbf{4}_{Zn}$.[25] The cyclization of $\mathbf{3B}_{Zn}$ to $\mathbf{4}_{Zn}$ is an example of an enantioselective carbometalation reaction of an unactivated alkene.[26] The free-energy barriers for the two critical steps of the overall reaction, that is, $\mathbf{2}_{Zn}\rightarrow\mathbf{3B}_{Zn}$ and $\mathbf{3B'}_{Zn}\rightarrow\mathbf{4}_{Zn}$, are nearly the same (ca. 25 kcal mol^{-1}), and therefore both steps are important in determining the reaction rate.

In summary, we have presented a catalytic enantioselective alkynylation of acyl silanes **1** that leads in a one-pot operation to propargylic alcohols **7**. The impressive transformation **1**→**7** in which three new bonds and two new stereogenic centers are created with excellent diastereo- and enantioselectivity proceeds through a combined allenyl Zn-Brook rearrangement/Zn–ene–allene cyclization followed by the addition of an electrophile and an oxidation reaction. Quantum-mechanics calculations show that $\mathbf{4}_{Zn}$ is obtained from $\mathbf{2}_{Zn}$ via $\mathbf{3B}_{Zn}$, and that transformation bypasses the intermediate derived from the classic [1,2]-Brook rearrangement (i.e., $\mathbf{3A}_{Zn}$). A remarkable feature of the reaction $\mathbf{2}_{Zn}\rightarrow\mathbf{4}_{Zn}$ is the transfer of chirality in both the allenyl Zn-Brook rearrangement and the highly organized six-membered transition state of the Zn–ene–allene carbocyclization. We continue to explore the synthetic potential of this intriguing transformation.

Received: August 1, 2013
Revised: October 1, 2013
Published online: October 23, 2013

Keywords: acyl silanes · alkynylation · asymmetric synthesis · Brook rearrangement · zinc

[1] a) H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 5239; b) J. C. Sheehan, R. E. Chandler, *J. Am. Chem. Soc.* **1961**, *83*, 4795.

[2] a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2004**; c) *Fundamentals of Asymmetric Catalysis* (Eds.: P. J. Walsh, M. C. Kozlowski), University Science Books, **2009**; d) *Classics in Stereoselective Synthesis* (Eds.: E. M. Carreira, L. Kvaerno), Wiley-VCH, Weinheim, **2009**.

[3] a) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010; b) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; e) B. M. Trost, *Science* **1991**, *254*, 1471.

[4] a) L. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 8642; *Angew. Chem. Int. Ed.* **2011**, *50*, 8492; b) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197; c) I. Marek, *Chem. Eur. J.* **2008**, *14*, 7460; d) M. Pasco, N. Gilboa, T. Mejuch, I. Marek, *Organometallics* **2013**, *32*, 942; e) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

[5] a) Y. Minko, M. Pasco, L. Lukas, I. Marek, *Nat. Protoc.* **2013**, *4*, 749; b) Y. Minko, M. Pasco, L. Lukas, M. Botoshansky, I. Marek, *Nature* **2012**, *490*, 522; c) T. Mejuch, B. Dutta, M. Botoshansky, I. Marek, *Org. Biomol. Chem.* **2012**, *10*, 5803; d) T. Mejuch, M. Botoshansky, I. Marek, *Org. Lett.* **2011**, *13*, 3604; e) N. Gilboa, H. Wang, K. N. Houk, I. Marek, *Chem. Eur. J.* **2011**, *17*, 8000; f) B. Dutta, N. Gilboa, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 4066; g) S. Simaan, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 4066; h) S. Simaan, A. F. Goldberg, S. Rosset, I. Marek, *Chem. Eur. J.* **2010**, *16*, 774; i) A. Masarwa, A. Fürstner, I. Marek, *Chem. Commun.* **2009**, 5760; j) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; k) G. Kolodney, G. Sklute, S. Perrone, P. Knochel, I. Marek, *Angew. Chem.* **2007**, *119*, 9451; *Angew. Chem. Int. Ed.* **2007**, *46*, 9291; l) G. Sklute, I. Marek, *J. Am. Chem. Soc.* **2006**, *128*, 4642.

[6] For representative examples, see: a) G. R. Boyce, S. N. Greszler, J. S. Johnson, Z. Linghu, J. T. Malonowski, D. A. Nicewiz, A. D. Satterfield, D. C. Schmitt, K. M. Steward, *J. Org. Chem.* **2012**, *77*, 4503; b) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nat. Chem.* **2012**, *4*, 733; c) R. Larouche-Gauthier, C. J. Fletcher, I. Couto, V. K. Aggarwal, *Chem. Commun.* **2011**, *47*, 12592; d) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem.* **2007**, *119*, 7635; *Angew. Chem. Int. Ed.* **2007**, *46*, 7491; e) G. Dutheuil, M. P. Webster, P. A. Worthington, V. K. Aggarwal, *Angew. Chem.* **2009**, *121*, 6435; *Angew. Chem. Int. Ed.* **2009**, *48*, 6317; f) M. H. Kerrigan, S.-J. Jeon, Y. K. Chen, L. Salvi, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 8434.

[7] a) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593; b) G. Sklute, I. Marek, *Chem. Commun.* **2007**, 1683; c) H. K. Scott, V. K. Aggarwal, *Chem. Eur. J.* **2011**, *17*, 13124; d) R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott, V. K. Aggarwal, *Angew. Chem.* **2011**, *123*, 3844; *Angew. Chem. Int. Ed.* **2011**, *50*, 3760.

[8] a) P.-O. Delaye, D. Dorian, I. Marek, *Angew. Chem.* **2013**, *125*, 5441; *Angew. Chem. Int. Ed.* **2013**, *52*, 5333; b) F. Meng, H. Jang, B. Jung, A. H. Hoveyda, *Angew. Chem.* **2013**, *125*, 5150; *Angew. Chem. Int. Ed.* **2013**, *52*, 5046; c) H. Y. Kim, P. J. Walsh, *Acc. Chem. Res.* **2012**, *45*, 1533.

[9] a) H.-J. Zhang, D. L. Priebbenow, C. Bolm, *Chem. Soc. Rev.* **2013**, *42*, 8540; b) R. Unger, F. Weisser, N. Chinkov, A. Stanger, T. Cohen, I. Marek, *Org. Lett.* **2009**, *11*, 1853; c) R. Unger, T. Cohen, I. Marek, *Tetrahedron* **2010**, *66*, 4874.

[10] a) T. E. Reynolds, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 15382; b) D. A. Nicewicz, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 6170; c) F.-Q. Li, S. Zhong, G. Lu, A. S. C. Chan, *Adv. Synth. Catal.* **2009**, *351*, 2541.

[11] A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77.

[12] A. B. Smith III, W. M. Wuest, *Chem. Commun.* **2008**, 5883.

[13] a) I. Kuwajima, M. Kato, *Tetrahedron Lett.* **1980**, *21*, 623; b) H. J. Reich, E. K. Eisenhart, R. E. Olson, M. J. Kelly, *J. Am. Chem. Soc.* **1986**, *108*, 7791.

[14] C. Meyer, I. Marek, G. Courtemanche, J.-F. Normant, *J. Org. Chem.* **1995**, *60*, 863.

[15] R. West, R. Lowe, H. F. Stewart, A. Wright, *J. Am. Chem. Soc.* **1971**, *93*, 282.

[16] a) E. Lorthiois, I. Marek, C. Meyer, J.-F. Normant, *Tetrahedron Lett.* **1995**, *36*, 1263; b) C. Meyer, I. Marek, J.-F. Normant, *Tetrahedron Lett.* **1996**, *37*, 857; c) R. Unger, T. Cohen, I. Marek, *Org. Lett.* **2005**, *7*, 5313; d) R. Unger, T. Cohen, I. Marek, *Eur. J. Org. Chem.* **2009**, 1749.

[17] For a review, see: G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599.

[18] a) B. M. Trost, M. J. Bartlett, A. H. Weiss, A. Jacobi von Wangelin, V. S. Chan, *Chem. Eur. J.* **2012**, *18*, 16498; b) B. M. Trost, A. H. Weiss, A. Jacobi von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8, and references therein.

[19] For reviews concerning the enantioselective addition of alkynes to (hetero)carbonyl groups, see: a) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373; b) L. Pu, *Tetrahedron* **2003**, *59*, 9873; c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095; d) G. Lu, Y.-M. Li, X.-S. Li, A. S. C. Chan, *Coord. Chem. Rev.* **2005**, *249*, 1736; e) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963; f) P. G. Cozzi, *Angew. Chem.* **2003**, *115*, 3001; *Angew. Chem. Int. Ed.* **2003**, *42*, 2895; g) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4623.

[20] a) G. M. Whitesides, M. Witanowski, J. D. Roberts, *J. Am. Chem. Soc.* **1965**, *87*, 2854; b) R. W. Hoffmann, B. Holzer, O. Knopff, K. Harms, *Angew. Chem.* **2000**, *112*, 3206; *Angew. Chem. Int. Ed.* **2000**, *39*, 3072; c) A. Boudier, E. Hupe, P. Knochel, *Angew. Chem.* **2000**, *112*, 2396; *Angew. Chem. Int. Ed.* **2000**, *39*, 2294.

[21] a) S. Klein, I. Marek, J.-F. Normant, *J. Org. Chem.* **1994**, *59*, 2925; b) S. Matsubara, N. Toda, M. Kobata, K. Utimoto, *Synlett* **2000**, 987; c) A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich, P. Knochel, *Chem. Eur. J.* **2000**, *6*, 2748; d) S. Norsikian, I. Marek, S. Klein, J.-F. Poisson, J.-F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055.

[22] a) R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, **1989**; b) W. Koch, M. C. Holthausen, *A Chemist's Guide to Density Functional Theory*, Wiley-VCH, Weinheim, **2000**.

[23] a) H. J. Reich, *J. Org. Chem.* **2012**, *77*, 5471; b) J.-F. Poisson, J.-F. Normant, *J. Am. Chem. Soc.* **2001**, *123*, 4639.

[24] Assuming that the hydrolysis of $\mathbf{3B_{Zn}}$ proceeds at its α-position,[23a] the formation of the hydrolyzed adduct of $\mathbf{3B_{Zn}}$ supports the presence of $\mathbf{3B_{Zn}}$, in agreement with the calculations, which place $\mathbf{3B_{Zn}}$ in a deep potential well (see the Supporting Information).

[25] A reaction path for the formation of $\mathbf{4_{Zn}}$ directly from $\mathbf{3A_{Zn}}$ could not be located, and all search attempts to locate a transition state for the $\mathbf{3A_{Zn}}\rightarrow\mathbf{4_{Zn}}$ conversion ended up at **TS4**.

[26] For a review, see: I. Marek, *J. Chem. Soc. Perkin Trans. 1* **1999**, 535.

