■ Synthetic Methods

Conformational Bias by a Removable Silyl Group: Construction of Bicyclo[*n*.3.1]alkenes by Ring Closing Metathesis

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Dedicated to Professor Robert H. Grubbs on the occasion of his 75th birthday

Abstract: Herein, we report a novel strategy based on a conformationally controlled RCM by a removable silyl group, which allows the facile synthesis of various bicyclo[*n*.3.1]alkenes, especially a set of highly strained bicyclo[5.3.1]alkenes. Further derivatizations of the silyl group and the resultant double bond of bicyclo[5.3.1]undecene **2f** enabled a concise synthesis of A-B-C ring skeleton of taxol. Density functional theory (DFT) calculations suggest that the introduction of a bulky silyl group at C-5 position of the 1,3-dialkenylcyclohexanol substrates dramatically lowers the energy bias gap between diaxial conformers (to RCM) and diequatorial conformers (to cross metathesis), thereby favoring the expected RCM reaction to give the challenging bridged molecules.

Scheme 1. Selected natural products containing bicyclo[*n*.3.1] skeleton and the construction of bicyclo[5.3.1] ring systems through RCM reactions.
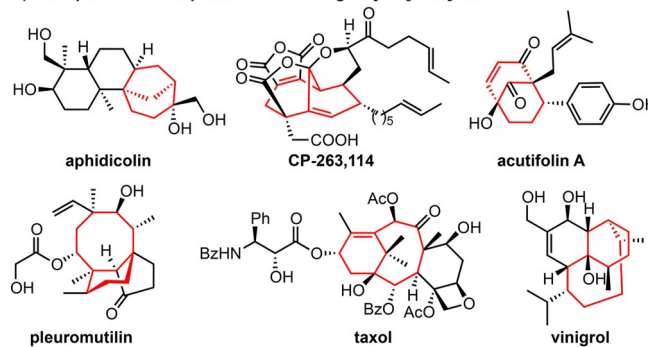
Bridged carbocycles, commonly found in terpene natural products, are arguably the most topologically complex structures. As a very important subclass, bicyclo[*n*.3.1] ring system is the privileged core skeleton of many biologically active natural products and drugs, such as aphidicolin,[1] acutifolin A,[2] CP-263,114,[3] vinigrol,[4] pleuromutilin[5] and taxol[6] (Scheme 1A). Among them, due to unfavorable entropy and transannular interactions of eight-membered ring, the construction of bicyclo[5.3.1] ring systems (also known as 6–8 bridged bicycles) is one of the most challenging topics in the syntheses of the related natural products (i.e., taxol and vinigrol). Although a few strategies have been developed,[7] construction of the bicyclo[5.3.1] ring system in a sequence of [6]→[8], that is, the direct formation of a bridged eight-membered ring in a template of six-membered ring remains a challenging problem.[8]

RCM is one of the most efficient and straightforward methods for the ring closure and has played crucial roles in the syntheses of a huge number of polycyclic natural products.[9] In 1998, Grubbs and co-workers[10] reported the construction of a series of bridged bicycloalkenes by RCM. Unfortunately, in the cases involving eight-membered ring formation, no desired bicyclo[5.*x*.1]alkenes were obtained and only oligomeric products were observed (Scheme 1B). Additionally, the ring contracted RCM reactions to form seven-membered rings through a double bond migration–RCM cascade often occurred in the reported efforts to make an eight-membered ring via diene metathesis.[11] To the best of our knowledge, despite the extensive use of RCM in organic synthesis, there are few applications to the synthesis of bicyclo[5.3.1]alkenes.[12] To address these limitations, we envisaged that a bulky yet removable silyl

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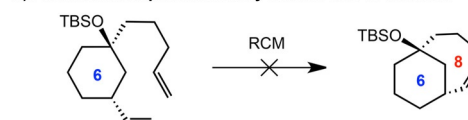E-mail: ydzhang@xmu.edu.cn

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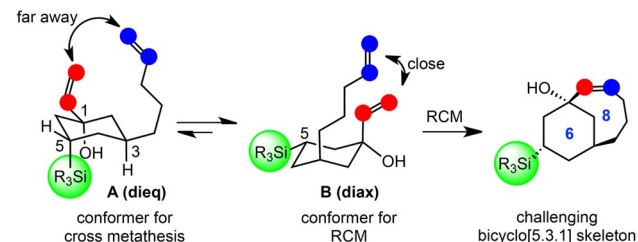
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📖 Supporting information and the ORCID identification numbers for the authors of this article can be found under https://doi.org/10.1002/chem.201705275.

group[13] might effect a conformational bias[14] which would enable the synthesis of the challenging bicyclo[5.3.1]alkenes and other bicyclo[n.3.1]alkenes by metathesis from 1,3-dialkenylcyclohexanes.

We envisioned that with the introduction of a large silyl group at C-5 position of the substituted cyclohexane, the thermodynamically more stable diaxial conformer (**B**) that is required for the RCM reaction,[12b] would dominate (or the energy difference between diequatorial conformer **A** and diaxial conformer **B** could be dramatically reduced) and thus the RCM reaction would become favored (Scheme 1C). By contrast, without this conformational control element, to avoid 1,3-diaxial interactions, the two terminal enes would occupy the equatorial positions in a stable chair conformer like **A**, making the enes far away from each other. Consequently, the substrate is prone to cross-metathesis (CM) to give oligomers or polymers. This could be an explanation for Grubbs' results shown in Scheme 1B. Furthermore, the silyl group can be easily removed or converted to a useful hydroxyl group to provide a desilylated bridged system. Here we present our successful implementation of such a conformation control strategy by a bulky silyl group to effect the RCM reaction for the syntheses of a diverse array of bicyclo[n.3.1]alkenes. A concise synthesis of A-B-C ring skeleton of taxol with current method as the key transformation was also reported.
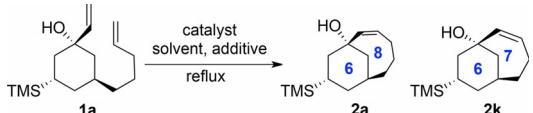
To reduce these ideas to practice, our studies commenced with diene **1a** (Table 1). A highly stereoselective synthesis of **1a** and other substrates from 5-trimethylsilylcyclohex-2-enone[15] was developed (for details, see the Supporting Information). Initial metathesis reactions were carried out with the four commonly used Ru-based metathesis catalysts (Table 1, **A–D**).

Interestingly, complete conversion of the starting materials was observed in almost all cases, whereas the distribution of products varied. We found that the exposure of diene **1a** to 10 mol% of Hoveyda–Grubbs II catalyst (**D**) in refluxing CH_2Cl_2 afforded the desired bicyclo[5.3.1]undecene **2a** and bicyclo[4.3.1]decene **2k** in a good combined NMR yield (45 and 26% respectively, Table 1, entry 4). The formation of **2k** could be attributed to the double bond isomerization catalyzed by ruthenium hydrides prior to RCM.[11] Gratifyingly, in the presence of 1.0 equivalent of $Ti(OiPr)_4$[16] under otherwise identical conditions with entry 4, **2a** was obtained in 61% yield and only a trace amount of **2k** was observed (Table 1, entry 5). We attributed this success to a synergistic conformational effect of the internal bulky silyl group and the external additive $Ti(OiPr)_4$. The catalyst loading could be lowered to 5 mol% without an adverse effect on either the yield or the selectivity (Table 1, entry 7). Moreover, despite the addition of 1,4-benzoquinone (BQ)[17] which has often been used to suppress the isomerization of the terminal alkene in RCM, a significant amount of **2k** was still formed (Table 1, entry 8). The structures of **2k** and **2a** were confirmed by single crystal X-ray diffraction.

With the optimized conditions in hand, we next applied our conformationally controlled RCM strategy to the syntheses of a series of bicyclo[n.3.1]alkenes (Table 2). By adjusting the lengths of 1,3-alkenyl chains in substrates, it is expected that not only different [n.3.1] bicycles but also the same kind of bicycles bearing a double bond at different positions of the newly forged bridge can be synthesized, which would allow diverse postmetathesis transformations. Although formation of the bicyclo[5.3.1]undecenes in a [6]→[8] sequence is challenging, four 6-8 bridged bicycles (**2a–2d**) were successfully synthesized in moderate to good yields by our strategy. However, an attempt to construct **2e**, which bears an anti-Bredt double bond,[18] failed and only homo-dimers were identified (see Supporting Information). When we used a more easily removable dimethylphenylsilyl (DMPS) group to promote the RCM reaction, it was equally efficient (**1f**→**2f**, 61% yield). It is noteworthy that highly strained 6-9 bridged bicycle **2g** could also be prepared by this method, albeit in a low yield.
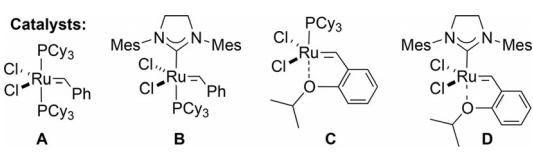
With these success, four TMS ether substrates (**oTMS-1a** to **oTMS-1d**) were also prepared and subjected to the RCM conditions (Table 2). We were wondering if oTMS group in the substrate could have a similar positive impact on RCM reaction as the $Ti(OiPr)_4$ did. By treatment with standard conditions in the absence of $Ti(OiPr)_4$, the reaction of **oTMS-1a** failed to produce any **oTMS-2a** and only homo-dimers were obtained in 50% yield (Supporting Information), presumably for reasons of high steric hindrance. However, to our delight, the other three TMS ethers (**oTMS-1b** to **oTMS-1d**) were smoothly converted to corresponding bicyclo[5.3.1]undecenes in yields of 62–82%. By contrast, in the aforementioned Grubbs' studies,[10] a similar silyl ether substrate devoid of a TMS group at C-5 position of cyclohexane backbone failed to produce any RCM product but oligomers (the RCM reaction also failed under our present optimized conditions) (Scheme 1B). By comparing the above results, we found that, although the introduction of an oTMS

Table 1. Optimization of the reaction conditions.[a]

Entry	Catalyst [mol%]	Solvent	t [h]	Additive	Yield [%][b] (2a/2k)
1	A (10)	CH_2Cl_2	12	–	22:16
2	B (10)	CH_2Cl_2	12	–	20:13
3	C (10)	CH_2Cl_2	12	–	17:trace
4	D (10)	CH_2Cl_2	4	–	45:26
5	D (10)	CH_2Cl_2	4	$Ti(OiPr)_4$	61[c]
6	D (10)	toulene	4	$Ti(OiPr)_4$	0:15
7	**D (5)**	**CH_2Cl_2**	**4**	**$Ti(OiPr)_4$**	**60[c]**
8	D (5)	CH_2Cl_2	4	BQ[d]	53:29

Catalysts:

A   B   C   D

[a] Reactions were performed with 0.375 mmol of **1a**, 5–10 mol% of catalyst, and 0 or 1.0 equiv of $Ti(OiPr)_4$ in specified solvent (0.005 M). [b] NMR yield with anthracene as an internal standard. [c] Isolated yield of **2a**. [d] 1.0 equivalent of 1,4-benzoquinone (BQ) as additive.
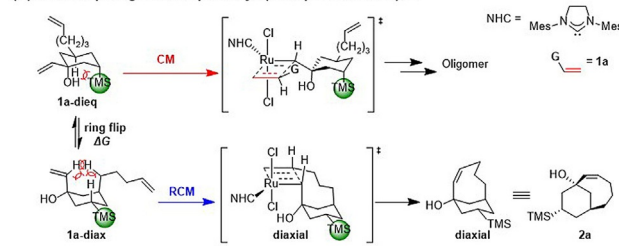
Table 2. Construction of bicyclo[*n*.3.1] ring systems.[a]

[a] Reaction conditions: **1** (1.0 equiv), catalyst **D** (5 mol%), and Ti(O*i*Pr)₄ (1.0 equiv) in refluxing CH₂Cl₂ (0.005 M) for 2–4 h. [b] Ti(O*i*Pr)₄ was not used. [c] Reaction performed with 10 mol% of catalyst **D** for 12 h.

(A) Two competing reaction pathways (exemplified with 1a).[a]

(B) DFT computed energy differences between the diaxial and diequatorial conformers.[b]
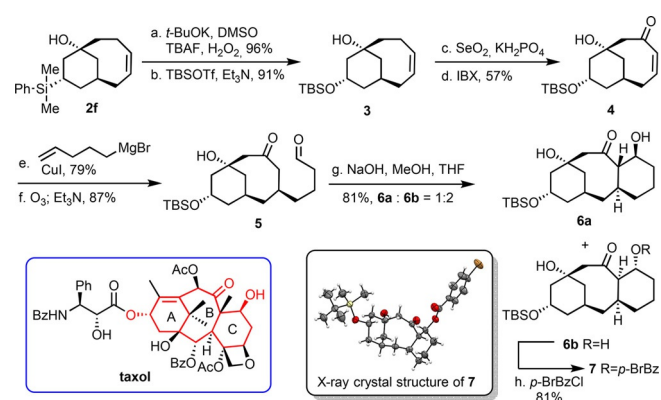

Scheme 2. Conformational analysis. [a] The depicted reaction initiation sites of the metathesis reactions are arbitrary). [b] Gibbs free energetic differences between the thermodynamically lowest diaxial and diequatorial conformers were calculated at SMD(DCM)/M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.

group markedly promoted the RCM reaction in most cases, it is the C-5 TMS group that played the pivotal role in this conformationally controlled RCM reaction.

With the successful syntheses of a set of 6–8 bridged bicycles, this strategy was smoothly extended to the syntheses of other bridged bicycles, providing bicyclo[3.2.1]octene (**2h**), bicyclo[3.3.1]nonenes (**2i** and **2j**) and bicyclo[4.3.1]decenes (**2k**, **2l** and **2m**) in good to high yields (Table 2).

To gain preliminary insights into the conformational effects of C-5 TMS group and oTMS group in RCM reactions and to support our initial proposal, we used DFT calculations[19] at the SMD(DCM)/M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level[20] to carry out a conformational analysis on a series of diene substrates (Scheme 2). First, to elucidate the crucial role of the conformers of substrates in the reaction, **1a** was chosen as an example. In general, RCM and CM are two major competing pathways in the reaction (Scheme 2A). The RCM pathway requires the diaxial conformer **1a**–**diax**, while the diequatorial

conformer **1a**–**dieq** which is usually more stable, can only lead to oligomers or polymers through CM pathway. The repulsive interactions in the two conformers are maintained in the following steps in both RCM and CM pathways, consequently the energy gap between the diaxial and diequatorial conformers would influence the final selectivity between the two pathways, which means the higher the energy of diaxial conformer is as compared to diequatorial conformer, the more inhibited the RCM pathways is.

As shown in the first column of Scheme 2B, the diaxial conformers are less favored than diequatorial conformers by 4 kcal mol⁻¹. When the TMS group was introduced in the substrates, the energy gap between diaxial conformers and diequatorial conformers was reduced to about 1 kcal mol⁻¹ (column II, Scheme 2B). These calculations suggest that, the RCM reaction should be more favored for substrates in column II than those in column I. We reasoned that the 1,3-repulsion between two alkenyl chains can be offset by the strong repulsive interactions induced by the axial bulky TMS group, thereby lowering the energy gap between the diaxial and diequatorial conformers of **1a**–**1d**. When the hydroxyl groups were further protected by TMS, the energy gap was reduced further. Even in some cases, the relative stability of the two conformers is reversed and the diaxial conformers (column III, Scheme 2B) become more stable than the diequatorial conformers. This suggests that the substrates favor RCM further. That can explain why

these substrates usually gave higher yields of RCM products. Based on a generally accepted role of the additive Ti(O*i*Pr)$_4$ in RCM reactions as a temporary protecting group[16] (for the hydroxyl group in current cases), a similar conformational effect with that of the oTMS group could be realized. Therefore, the C-5 TMS group together with Ti(O*i*Pr)$_4$ or the oTMS group renders the reactive diaxial conformer as the preferred conformer, thus experimentally enhanced the RCM reaction.

In order to demonstrate the value of our strategy for the synthesis of bridged bicycles, the A-B-C ring skeleton of taxol (6-8-6 tricycle) was synthesized (Scheme 3). Specifically, bicy-

Scheme 3. Synthesis of A-B-C ring skeleton of taxol.

clo[5.3.1] undecene **2f** was converted to compound **3** in a high yield via Fleming–Tamao oxidation[21] followed by TBS protection. Allylic oxidation and further oxidation furnished enone **4** in 57% overall yield. Ozonolytic cleavage of the terminal olefin that was derived from enone **4** through conjugate addition yielded keto-aldehyde **5**. Treatment of **5** with NaOH in MeOH smoothly delivered 6-8-6 tricycles as a pair of diastereomers (81%, **6a/6b** = 1:2). The relative stereochemistry of **6a** and **6b** were, respectively confirmed by NMR spectroscopic studies and single crystal X-ray diffraction of a derivative **7**. Overall, starting from bicyclo[5.3.1]undecene **2f**, through a series of subsequent transformations to derivatize the silyl group and the double bond, a concise construction of the A-B-C ring skeleton of taxol bearing six stereocenters has been achieved.

In summary, we have developed a conformationally controlled RCM approach by using a removable bulky silyl group for the synthesis of a diverse array of bicyclo[*n*.3.1]alkenes, especially highly strained bicyclo[5.3.1]alkenes. DFT calculations suggest that the introduction of a bulky silyl group at C-5 position of the 1,3-dialkenylcyclohexanol substrates dramatically promotes the population of diaxial conformers (the reactive conformer for RCM), as compared to the diequatorial conformers (the reactive conformer for cross metathesis), thus favoring the RCM. Furthermore, the subsequent functionalization over the silyl group and newly formed olefin enables a concise synthesis of the functionalized A-B-C ring skeleton of taxol. It is worth noting, based on Corey's protocol[15b] or Jørgensen's method[15c] for the preparation of optically pure 5-trialkylsilylcy-

clohex-2-enones, enantioselective syntheses of bicyclo[*n*.3.1]alkenes through the current strategy could be expected. Efforts to apply this strategy to the synthesis of bridged polycyclic natural products are currently underway.

Conflict of interest

The authors declare no conflict of interest.

[1] K. M. Brundret, W. Dalziel, B. Hesp, J. A. J. Jarvis, S. Neidle, *J. Chem. Soc. Chem. Commun.* **1972**, 1027.

[2] J. Takashima, A. Ohsaki, *J. Nat. Prod.* **2001**, *64*, 1493.

[3] T. T. Dabrah, T. Kaneko, W. Massefski, E. B. Whipple, *J. Am. Chem. Soc.* **1997**, *119*, 1594.

[4] I. Uchida, T. Ando, N. Fukami, K. Yoshida, M. Hashimoto, T. Tada, S. Koda, Y. Morimoto, *J. Org. Chem.* **1987**, *52*, 5292.

[5] F. Kavanagh, A. Hervey, W. J. Robbins, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 570.

[6] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325.

[7] For selected examples, see: a) B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem. Int. Ed.* **2001**, *40*, 820; *Angew. Chem.* **2001**, *113*, 864; b) S. F. Martin, J. B. White, R. Wagner, *J. Org. Chem.* **1982**, *47*, 3190; c) B. M. Trost, H. Hiemstra, *J. Am. Chem. Soc.* **1982**, *104*, 886; d) J. D. Winkler, J. P. Hey, P. G. Williard, *J. Am. Chem. Soc.* **1986**, *108*, 6425; e) F. Barabe, G. Betournay, G. Bellavance, L. Barriault, *Org. Lett.* **2009**, *11*, 4236; f) A. Mendoza, Y. Ishihara, P. S. Baran, *Nat. Chem.* **2012**, *4*, 21; g) S. Zhu, Q. Zhang, K. Chen, H. Jiang, *Angew. Chem. Int. Ed.* **2015**, *54*, 9414; *Angew. Chem.* **2015**, *127*, 9546.

[8] G. Tessier, L. Barriault, *Org. Prep. Proced. Int.* **2007**, *39*, 311.

[9] For selected reviews, see: a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; *Angew. Chem.* **2005**, *117*, 4564; b) A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, A. R. Zhugralin, *Angew. Chem. Int. Ed.* **2010**, *49*, 34; *Angew. Chem.* **2010**, *122*, 38.

[10] A. Morehead, Jr., R. Grubbs, *Chem. Commun.* **1998**, 275.

[11] a) M. Michalak, J. Wicha, *Synlett* **2005**, 2277; b) G. De Bo, I. E. Markó, *Eur. J. Org. Chem.* **2011**, 1859; c) G. Liu, D. Romo, *Angew. Chem. Int. Ed.* **2011**, *50*, 7537; *Angew. Chem.* **2011**, *123*, 7679.

[12] a) M. Wenz, D. Grossbach, M. Beitzel, S. Blechert, *Synthesis* **1999**, 607; b) J. Liu, S. D. Lotesta, E. J. Sorensen, *Chem. Commun.* **2011**, *47*, 1500; c) T. Kobayashi, H. Shiroi, H. Abe, H. Ito, *Chem. Lett.* **2013**, *42*, 975.

[13] For a review, see: I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063.

[14] For selected examples, see: a) R. J. Linderman, J. Siedlecki, S. A. O'neill, H. Sun, *J. Am. Chem. Soc.* **1997**, *119*, 6919; b) E. B. Pentzer, T. Gadzikwa, S. T. Nguyen, *Org. Lett.* **2008**, *10*, 5613; c) K. Mori, K. Ohmori, K. Suzuki, *Angew. Chem. Int. Ed.* **2009**, *48*, 5638; *Angew. Chem.* **2009**, *121*, 5748; d) P. Bolduc, A. Jacques, S. K. Collins, *J. Am. Chem. Soc.* **2010**, *132*,

12790; e) M. J. Kim, T.-i. Sohn, D. Kim, R. S. Paton, *J. Am. Chem. Soc.* **2012**, *134*, 20178.

[15] a) M. Asaoka, K. Shima, H. Takei, *Tetrahedron Lett.* **1987**, *28*, 5669; b) G. Sarakinos, E. J. Corey, *Org. Lett.* **1999**, *1*, 811; c) P. Bolze, G. Dickmeiss, K. A. Jørgensen, *Org. Lett.* **2008**, *10*, 3753.

[16] A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130.

[17] S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160.

[18] a) J. Y. W. Mak, R. H. Pouwer, C. M. Williams, *Angew. Chem. Int. Ed.* **2014**, *53*, 13664; *Angew. Chem.* **2014**, *126*, 13882; b) E. H. Krenske, C. M. Williams, *Angew. Chem. Int. Ed.* **2015**, *54*, 10608; *Angew. Chem.* **2015**, *127*, 10754.

[19] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2013**.

[20] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; c) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[21] J. Wu, Y. Pu, J. S. Panek, *J. Am. Chem. Soc.* **2012**, *134*, 18440.