ORGANIC LETTERS

2013
Vol. 15, No. 23
6066–6069

A Two-Step Synthesis of α-Keto Vinyl Carbinols from Ketones

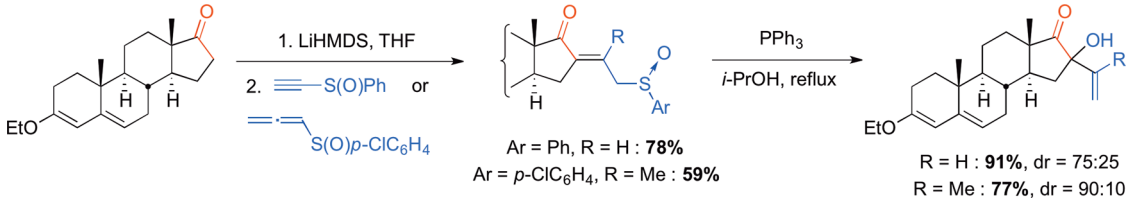
Laurent Debien and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique, 91128 Palaiseau Cedex, France

Zard@poly.polytechnique.fr

Received October 14, 2013

ABSTRACT



Conjugate addition of lithium enolates onto terminal alkynyl- and allenyl-sulfoxides furnishes the corresponding allylic sulfoxides. The latter readily undergo a Mislow–Braverman–Evans rearrangement to yield the targeted α-keto vinyl carbinols. This two-step procedure does not require purification of the intermediates and constitutes the shortest approach to α-keto vinyl carbinols.

α-Keto vinyl carbinols are polyfunctional compounds bearing three of the most essential functionalities in organic synthesis: a ketone, an alkene, and an alcohol. Not surprisingly they are important synthetic intermediates that can be further elaborated into 1,4-diketones,[1] heterocycles,[2] or α,β-unsaturated ketones.[3] They have also been exploited in total syntheses[4] and are present in some biologically active compounds.[5] Their chemistry has nevertheless remained underexplored due to the lack of general methods for their preparation. Indeed, the main routes to α-keto vinyl carbinols exploit the addition of vinylmetal reagents to symmetric or monoprotected 1,2-diones,[6] the addition of acyl anions to enones,[7] or the rearrangement of α-epoxy enones.[4d,8] These established routes generally require over three steps and are often limited by the use of elaborate building blocks, some of which are quite tedious to prepare.[9]

We recently reported that allylic sulfoxides obtained in three steps from xanthates and ethyl vinyl sulfide are readily converted into α-keto vinyl carbinols under Mislow–Braverman–Evans (MBE) conditions.[10,11] Herein, we

(1) (a) Ruedi, G.; Oberli, M. A.; Nagel, M.; Hanse, H.-J. *Org. Lett.* **2004**, *6*, 3179. (b) Hancock, K. G.; Wylie, P. L.; Lau, J. T. *J. Am. Chem. Soc.* **1977**, *99*, 1149.

(2) (a) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Overman, L. E.; Mishra, P. *J. Am. Chem. Soc.* **1991**, *113*, 5365. (b) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1980**, *45*, 2741.

(3) (a) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem.* **1990**, *55*, 4614. (b) Taub, D.; Hoffsommer, R. D.; Wendler, N. L. *J. Org. Chem.* **1964**, *29*, 3486.

(4) (a) Suzuki, H.; Aoyagi, S. *Org. Lett.* **2012**, *14*, 6374. (b) Buchanan, G. S.; Cole, K. P.; Tang, Y.; Hsung, R. P. *J. Org. Chem.* **2011**, *76*, 7027. (c) Chanu, A.; Castellote, I.; Commeureuc, A.; Safir, I.; Arseniyadis, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2565. (d) Syhora, K. *Tetrahedron Lett.* **1960**, *17*, 34.

(5) (a) Liu, L.; Song, Y.-X.; Li, S.-W.; Cheng, B.; Chen, B.; Lin, Y.-C.; Wang, J.; Li, L.; Gu, Y.-C. *Planta Medica* **2012**, *78*, 172. (b) Klaiklay, S.; Rukachasirikul, V.; Sukpondma, Y.; Phongpaichit, S.; Buatong, J.; Bussaban, B. *Arch. Pharm. Res.* **2012**, *35*, 1127. (c) Sugawara, F.; Strobel, G.; Fisher, L. E.; Van Duyne, G. D.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8291.

(6) For recent examples, see: (a) Cossy, J.; BouzBouz, S.; Laghgar, M.; Tabyaoui, B. *Tetrahedron Lett.* **2002**, *43*, 823. (b) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237. (c) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2001**, *3*, 1181.

(7) (a) Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron* **2002**, *58*, 7559. (b) Fronza, G.; Fuganti, C.; Pedrocchi-Fantoni, G.; Servi, S. *J. Org. Chem.* **1987**, *52*, 1141. (c) Souppe, J.; Mamy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 2869. (d) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(8) (a) Maignan, C.; Rouessac, F. *Bull. Soc. Chim. Fran.* **1976**, *3–4*, 550. (b) Mehrhof, W.; Irmscher, K.; Erb, R.; Pohl, L. *Chem. Ber.* **1969**, *102*, 643.

(9) For other methods, see: (a) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231. (b) Nagao, Y.; Tanaka, S.; Ueki, A.; Kumazawa, M.; Goto, S.; Ooi, S.; Sano, S.; Shiro, M. *Org. Lett.* **2004**, *6*, 2133. (c) Mauze, B.; Doucoure, A.; Miginiac, L. *J. Organomet. Chem.* **1981**, *215*, 1. (d) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem.* **1990**, *55*, 4614.

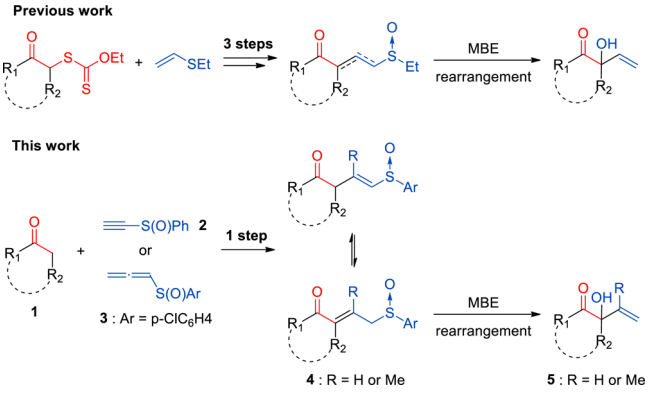
(10) Braun, M.-G.; Zard, S. Z. *Org. Lett.* **2011**, *13*, 776.

(11) For other examples exploiting the MBE rearrangement for the synthesis of α-keto vinyl carbinols, see: (a) Tuba, Z.; Bardin, C. W.; Francsics-Czinege, E.; Molnár, C.; Csörgei, J.; Falkay, G.; Koide, S. S.; Kumar, N.; Sundaram, K.; Dukát-Abrók, V.; Nalogh, G. *Steroids* **2000**, *65*, 266. (b) Boivin, J.; Chauvet, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 4913. (c) Lidert, Z.; Williams, S. F. *Tetrahedron Lett.* **1988**, *29*, 1347.

10.1021/ol4029594
Published on Web 11/11/2013

report that α-keto vinyl carbinols **5** may similarly be obtained from allylic arylsulfoxides **4**, which are obtained in a single step from terminal alkynyl-sulfoxide **2** or allenyl-sulfoxide **3** and simple ketones **1** (Scheme 1). This method relies on the use of sulfoxides **2** and **3** that are readily made on gram scale from commercially available starting materials.[12]

Scheme 1. Strategy for the Rapid Assembly of α-Keto Vinyl Carbinols



Our investigation began by examining the reaction of the enolate derived from α-tetralone **1a** with excess alkynyl-sulfoxide **2** in THF. We thus evaluated different bases for this transformation (Table 1). In our first attempt, the use of LDA gave a moderate but promising 50% isolated yield (entry 1). The compound corresponding to the direct addition of diisopropylamine onto acceptor sulfoxide **2** was identified as a byproduct and isolated in 25% yield. Such a reaction is known[13] and hinges on the relative nucleophilicity of the starting amine. We thus considered the use of a more hindered base such as LiTMP (entry 2). A very similar result was nevertheless obtained in this case, and the formation of the desired allylic sulfoxide **4a** was again accompanied by the enamine derived from the addition of tetramethylpiperidine to sulfoxide **2**. The choice of a traceless base such as NaH proved disappointing, as a quick degradation of the substrate was observed upon addition of the Michael acceptor **2** (entry 3).

To our relief, treatment of α-tetralone **1a** with LiHMDS followed by addition of sulfoxide **2** furnished the desired allylic sulfoxide **4a** in 80% isolated yield (entry 4). Substituting LiHMDS for KHMDS was found to be detrimental resulting in a diminished 35% yield (entry 5). Finally, running the reaction with excess ketone and LiHMDS or excess sulfoxide gave comparable yields (entry 6 vs 4).

With these two sets of conditions in hand, we proceeded to probe the substrate scope of the methodology. Various unsymmetrical functionalized ketones were found to be competent substrates in this transformation (**1b**, **1c**, **1d**, and **1f**, Table 2). The best results were obtained in the case

(12) See Supporting Information for more details.
(13) Yan, S.; Lam, K. T.; Wong, W. Y.; Chan, W. H.; Lee, A. W. M. *Lett. Org. Chem.* **2005**, *2*, 33.

Table 1. Optimization of the Reaction Conditions[a]

entry	base	conv **1a**[b]	conv **2**[b]	yield **4a**[c]	E/Z[d]
1	LDA	50%	80%	50%	85:15
2	LiTMP	55%	100%	50%[b]	83:17[b]
3	NaH[e]	<5%	100%	–	–
4	LiHMDS	90%	>90%	80%	85:15
5	KHMDS	38%	100%	35%[b]	≥90:10[b]
6[f]	LiHMDS	77%	≥90%	75%	90:10

[a] Reactions were carried out on a 0.5 mmol scale. [b] Estimated by analysis of the crude ^{1}H NMR. [c] Isolated yields. [d] Ratio based on ^{1}H NMR analysis of purified allylic sulfoxide. [e] 1.1 equiv of NaH were used. [f] The reaction was run using 1.3 equiv of ketone **1a** and LiHMDS and 1 equiv of sulfoxide **2**.

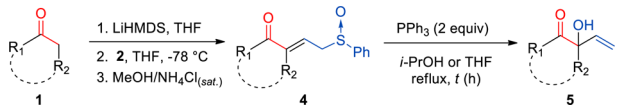
of androstanone derivatives **1b** and **1c**. Cyclohexanone derived ketones **1d**, **1e**, and **1f** also gave satisfactory results, and adducts were isolated in somewhat decreased yields compared with cyclopentenones **4b** and **4c**. Symmetrical ketones **1g**–**j** were finally evaluated, and in this situation, the reaction yield strongly depended on the structure of the starting material. Overall, the desired allylic sulfoxides **4** were obtained in fair to good yield and as mixtures of geometric isomers in favor of the *E* isomer. Furthermore, in all cases, the reaction proceeded to full conversion in sulfoxide **2**, which allowed for straightforward product isolation.

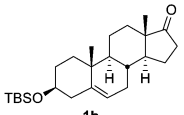
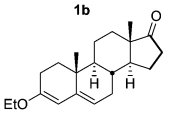
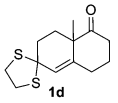
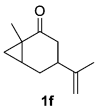
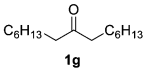
Although higher yields were generally obtained using excess sulfoxide **2** (examples **4a** and **4b**), running the reaction with excess enolate turned out to be beneficial in the case of functionalized cyclohexanone **1d**. Moreover, a larger enolate excess was required in the case of symmetric ketones **1g**–**j** with two enolizable sites in order to minimize side reactions.

As illustrated by examples **4b**, **4c**, and **4d**, the process is tolerant of various functional groups including acid sensitive silyl or enol ether moieties. Interestingly, examples **4c** and **4d** highlight the possibility to selectively transform substrates bearing various carbonyls by preliminary mono-protection of one of these functional groups (Table 2).

The Mislow–Braverman–Evans rearrangement of allylic sulfoxides **4** was subsequently examined. Surprisingly, our previously reported conditions[10] for the rearrangement of ethyl-allylsulfoxides (PPh_3, 2 equiv in refluxing toluene) proved ineffective in the case of phenyl-allylsulfoxides **4a**, and under these conditions, a rapid degradation of the substrate was observed. We then examined THF as a more basic and lower boiling solvent, with the eventual prospect of developing a one-pot procedure. THF proved to be effective in some cases (carbinols **4a** and **4b**), but unfortunately the reaction was not general in this solvent. For instance, sulfoxide **4d** remained intact upon prolonged exposure to triphenylphosphine in refluxing THF. After a

Table 2. Scope of the Conjugate Addition onto Sulfoxide **2**



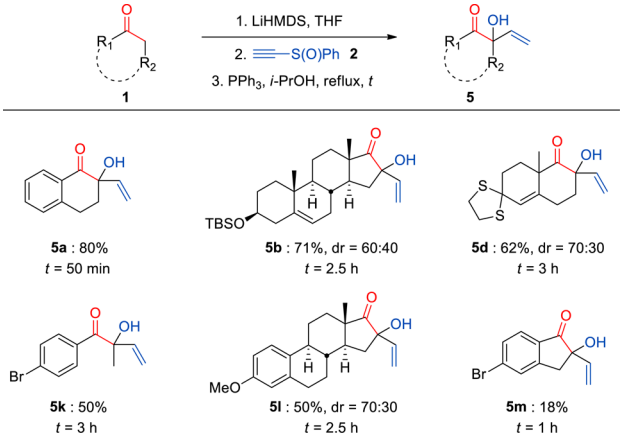
ketone **1**	sulfoxide **4**	*t* (h)	carbinol **5**
 **1a**	**4a** : 80%[a] or 75%[b] *E*/*Z* = 85:15	9	**5a** : 74%[e]
 **1b**	**4b** : 80%[a] or 77%[b] *E*/*Z* = 90:10, dr = 1:1	24	**5b** : 65%,[e] dr = 70:30
 **1c**	**4c** : 78%[a] *E*/*Z* = 90:10, dr = 1:1	2.5	**5c** : 91%, dr = 75:25
 **1d**	**4d** : 54%[a] or 77%[b] *E*/*Z* = 60:40, dr = 1:1	3	**5d** : 87%, dr = 65:35
 **1e**	**4e** : 50%,[b] *E*/*Z* = 80:20 dr = 1:1	-	**5e** : -
 **1f**	**4f** : 70%,[d] *E*/*Z* = nd	-	**5f** : -
 **1g**	**4g** : 32%,[c] *E*/*Z* = 85:15	2	**5g** : 95%
 **1h-j**	n = 1, **4h** : 46%,[c] *E*/*Z* = 75:25 n = 2, **4i** : 75%,[c] *E*/*Z* = 95:5 n = 6, **4j** : 47%,[c,e] *E*/*Z* = 85:15	2 2 3	n = 1, **5h** : 72% n = 2, **5i** : 81% n = 6, **5j** : 76%

[a] Reaction conditions: ketone **1** (1 equiv), LiHMDS (1 equiv), sulfoxide **2** (1.3 equiv). [b] Reaction conditions: ketone **1** (1.3 equiv), LiHMDS (1.3 equiv), sulfoxide **2** (1 equiv). [c] Reaction conditions: ketone **1** (2 equiv), LiHMDS (2 equiv), sulfoxide **2** (1 equiv). [d] **4f** was obtained as a mixture of allylic and vinylic sulfoxides. [e] **4j** was obtained as a 85:15 mixture of allylic and vinylic sulfoxides.

screen, we found that isopropanol was the best solvent for this transformation, as it allowed quick conversion of the starting sulfoxides and obtention of high yields (Table 2, carbinols **5c**, **5d**, and **5g**–**j**). Unfortunately, carbinols **5e** and **5f** could not be obtained using this approach. Indeed, the starting sulfoxides **4e** and **4f** proved rather unreactive or unstable in isopropanol or other higher boiling alcohols such as *n*-butanol.

With these results in hand, we attempted preparing the desired α-keto vinyl carbinols in a one pot manner. All our efforts to develop such a sequence with our model substrate **1a** failed and a quick degradation of allylic sulfoxide **4a** was generally observed upon heating in the presence of excess triphenylphosphine. We were, however, able to demonstrate that a simple workup of the conjugate addition reaction followed by treatment of the crude mixture with triphenylphosphine in refluxing isopropanol afforded sulfoxide **5a** in a good 80% isolated yield (Scheme 2). This sequence was repeated for the preparation of previously synthesized α-keto vinyl carbinols **5b** and **5d** as well as some others (Scheme 2). In particular, the rearrangement of sulfoxides **4a** and **4b** proved both much faster and much more efficient in isopropanol than in THF, furnishing the corresponding carbinols **5a** and **5b** in overall better yields (Table 2 vs Scheme 2). This sequence proceeds under mild reaction conditions and gives access to the desired α-keto vinyl carbinol motif in useful yields.

Scheme 2. Direct Synthesis of α-Keto Vinyl Carbinols



The results obtained with alkynyl-sulfoxide **2** encouraged us to evaluate the use of alkynyl-sulfoxide **7** and allenyl-sulfoxide **3** for the preparation of α-keto vinyl carbinols bearing a synthetically useful isopropenyl moiety. The reaction of α-tetralone **1a** with sulfoxide **7** furnished an equimolar mixture of enone **4n** and *β*,*γ*-unsaturated ketone **6n** in a combined 48% isolated yield (Table 3). The presence of 10% of allene **3** in the crude mixture indicated that the lack of efficiency of the reaction is likely due to the deprotonation of the propargylic position in **7**.

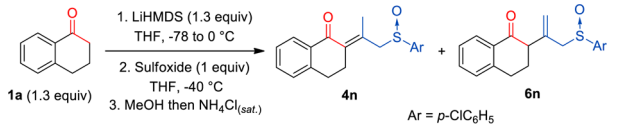
To our delight, substituting sulfoxide **7** for allene **3** provided a 78% isolated yield of Michael adduct, albeit as a 1:1 mixture of regioisomers **4n** and **6n**. Noteworthy, in this case, the mechanism of the reaction is different and compound **6n** is derived from protonation of the allylic anion generated after conjugate addition.[14]

Sulfoxide **4n** and **6n** were then separately subjected to the Mislow–Braverman–Evans rearrangement. Enone **4n** smoothly rearranged in THF to give carbinol **5n** in good yield while *β*,*γ*-unsaturated ketone **6n** proved to be surprisingly rather unreactive in either THF or isopropanol (Scheme 3).

In contradistinction, submitting androsterone derivative **1b** and **1c** to the reaction gave the corresponding α,*β*-unsaturated ketones **4o** and **4p** as the sole products.

(14) Protonation of allylic anions generally give mixtures of regioisomers; however, in our case, enone **4n** probably arises from the isomerization of the vinylic sulfoxide upon aqueous workup.

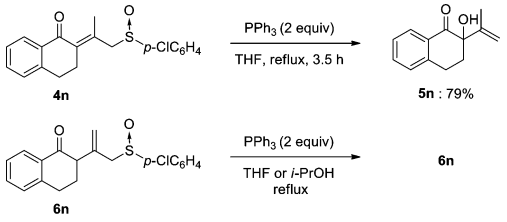
Table 3. Evaluation of Sulfoxides **7** and **3**[a]



entry	sulfoxide	conv **7** or **3**[b]	yield **4n**	*E*/*Z* (**4n**)	yield **6n**
1	S(O)*p*-ClC$_6$H$_4$ **7**	58%	26%[b]	75:25[b]	22%[b]
2	S(O)*p*-ClC$_6$H$_4$ **3**	100%	39%[c]	93:7[d]	39%[c]

[a] Reactions were carried out on a 0.5 mmol scale. [b] Estimated by analysis of the crude ^{1}H NMR. [c] Isolated yields. [d] Ratio based on ^{1}H NMR analysis of purified allylic sulfoxide.

Scheme 3. Rearrangement of Sulfoxides **4n** and **6n**



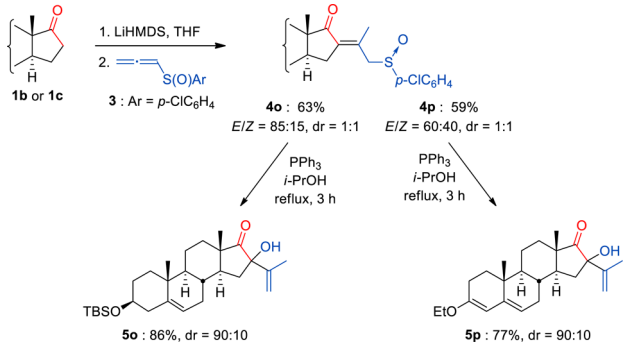
These, in turn, provided the desired α-keto vinyl carbinols **5o** and **5p** in good yields and good diastereoselectivities upon treatment with triphenylphosphine in refluxing isopropanol (Scheme 4).

We next studied symmetrical ketones possessing two enolizable centers. Reacting 8-pentadecanone **1g** with sulfoxide **3** gave rise to the desired adduct in good yield (Scheme 5). This product was however obtained as a 65:35 mixture of inseparable β,γ-unsaturated ketone **6q** and enone **4q**. Unexpectedly, subjecting this mixture to the Mislow−Braverman−Evans rearrangement furnished allylic alcohol **8** as a major product (Scheme 5). The formation of such a product is synthetically interesting but narrows somewhat the scope of our method.

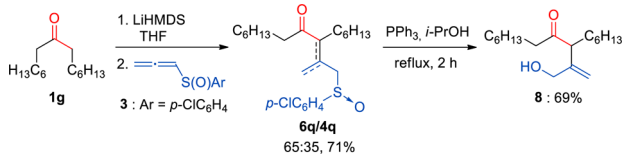
In summary, we have developed a new, operationally simple method for the rapid construction of α-keto vinyl carbinols from simple starting materials by combining the conjugate addition of enolates to alkynyl- and allenylsulfoxide acceptors with the well-known Mislow−Braverman−Evans rearrangement. Extension of the process to stabilized anions other than enolates are currently under study and will be reported in due course. It is finally interesting to note that an asymmetric version of this transformation is in principle possible, since the chiral sulfoxide reagents **2** and **3** can be easily obtained,[15] and the stereospecific rearrangement of chiral allylic sulfoxides has been documented.[16]

(15) The preparation of chiral sulfoxide **2** is known; see: (a) Paley, R. S.; de Dios, A.; Estroff, L. A.; Lafontaine, J. A.; Montero, C.; McCulley, D. J.; Rubio, M. B.; Paz Ventura, M.; Weers, H. L. *J. Org. Chem.* **1997**, *62*, 6326. The preparation of chiral sulfoxide **3** could be achieved by enantioselective oxidation; see: (b) Brunel, J. M.; Diter, P.; Deutsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086.

Scheme 4. Preparation of α-Keto Vinyl Carbinols from Steroids



Scheme 5. Case of Symmetric Ketones



Acknowledgment. We thank the ANR for financial support. This manuscript is dedicated with respect and admiration to Professor Johann Mulzer (University of Vienna).

Supporting Information Available. Experimental procedures and characterization spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) See, for example: (a) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453. (b) Kano, S.; Tanaka, K.; Hibino, S.; Shibuya, S. *J. Org. Chem.* **1979**, *44*, 1582. For a review, see: (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

The authors declare no competing financial interest.