ORGANIC LETTERS

2012
Vol. 14, No. 10
2462–2464

A Tandem Cross-Metathesis/Semipinacol Rearrangement Reaction

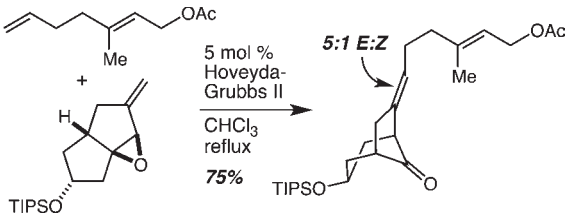
Christopher W. Plummer, Arash Soheili, and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027, United States

leighton@chem.columbia.edu

Received March 19, 2012

ABSTRACT

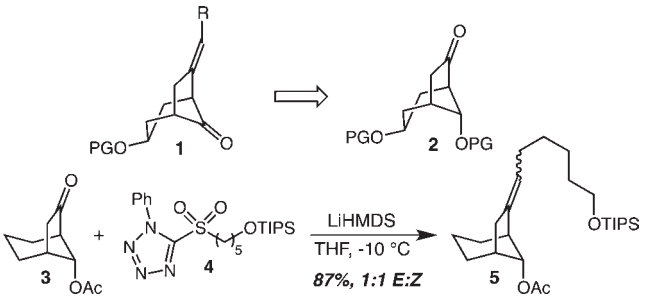


An efficient and (*E*)-selective synthesis of a 6-alkylidenebicyclo[3.2.1]octan-8-one has been developed. The key step is a tandem cross-metathesis/semipinacol rearrangement reaction, wherein the Hoveyda–Grubbs II catalyst, or more likely a derivative thereof, serves as the Lewis acid for the rearrangement. Despite the fact that both the starting alkene and the cross-metathesis product are viable rearrangement substrates, only the latter rearranges, suggesting that the Lewis acidic species is generated only after the cross-metathesis reaction is complete.

As part of an ongoing natural product synthesis effort, we required a step-economical, scalable, and highly diastereo- and enantioselective synthesis of (3*S*,*E*)-6-alkylidene-3-hydroxybicyclo[3.2.1]octan-8-ones of type **1** (Scheme 1). Among the challenges presented by this target, it quickly became apparent that a stereoselective synthesis of the trisubstituted alkene would be the most difficult, as a review of the literature revealed nothing particularly relevant. Initially, we were content to pursue a Julia–Kociensky olefination[1] strategy from ketones of type **2**, but we were aware that significant diastereoselectivity would be unlikely. Indeed, model ketone **3** was prepared and found to undergo Julia–Kociensky reactions with no selectivity (the illustrated reaction with sulfone **4** to give **5** is representative). While this route did allow us to obtain material with which to move forward (isomer separation was possible), it was always clear that we would have to devise a better solution.

The conceptual breakthrough came when we conceived that a semipinacol rearrangement[2] of an epoxide of type **6** might be expected to produce **1** directly (Scheme 2). This did not, of course, provide a solution for the stereoselective synthesis of the trisubstituted alkene, but it seemed at least possible that a diastereoselective olefination of epoxyketone **7** might be devised. This seemed worth pursuing because **7**

Scheme 1



seemed readily accessible from enone **8**, which in turn could arise from a Pauson–Khand reaction[3] with enyne **9**.

(*R*)-Epichlorohydrin (which may be obtained commercially or by employing the Jacobsen HKR reaction[4]) was ring opened with vinylmagnesium bromide, and the unpurified product was distilled from KOH to give

(1) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. For a review, see: (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

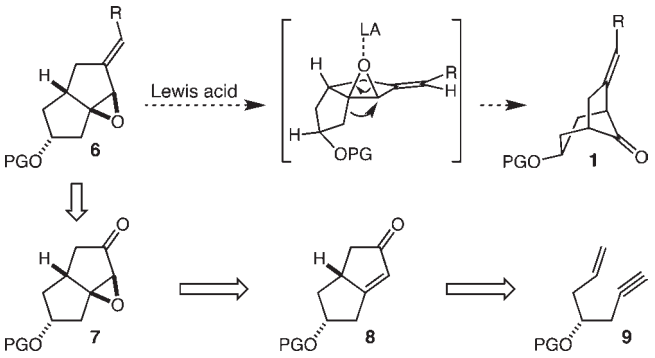
(2) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556.

(3) (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283. (b) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810. (c) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037. (d) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336. (e) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, 789–811.

(4) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

10.1021/ol300691u
Published on Web 04/27/2012

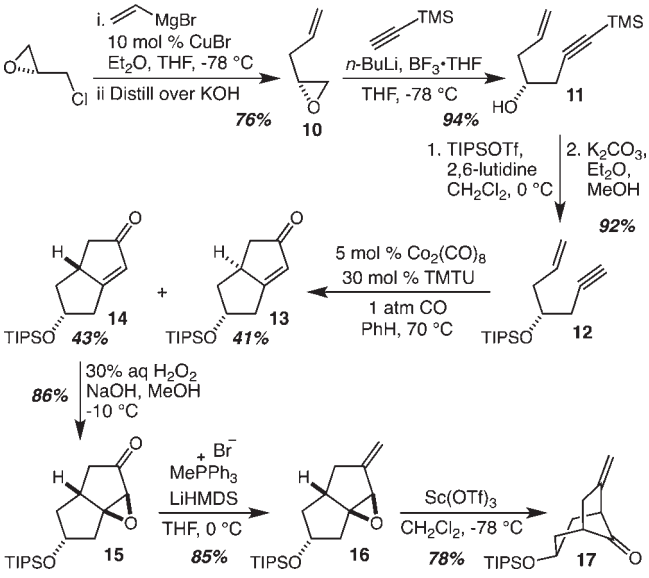
Scheme 2



epoxide **10** in 76% yield (Scheme 3). Another ring opening with trimethylsilyl (TMS) acetylene proceeded smoothly to give alcohol **11**[5] in 94% yield. Alcohol protection with triisopropylsilyl triflate (TIPSOTf) was followed without purification by removal of the TMS group with K_2CO_3 in MeOH to give enyne **12** in 92% yield. With a scalable and brief route to enyne **12** worked out, we screened a variety of Pauson–Khand conditions, most of which gave a mixture of the undesired *exo* product **13** and the desired *endo* product **14** (typically ~1:1). We found the conditions of Chen and Yang (catalytic $Co_2(CO)_8$ and tetramethylthiourea (TMTU))[6] to be particularly effective in terms of overall yield and convenience, and while we could not achieve selectivity for **14**, this procedure did allow the isolation of **14** in 43% yield (along with 41% of **13**) on multigram scales. Epoxidation with alkaline hydrogen peroxide proceeded smoothly to give **15** in 86% yield and set the stage for our efforts to devise a stereoselective ketone olefination. To establish first the validity of our semipinacol rearrangement hypothesis, however, we performed a methylene Wittig reaction that produced **16** in 85% yield. Allylic epoxide **16** was then subjected to the action of a variety of Lewis acids, with many successfully promoting the desired rearrangement to give **17**. The use of a full equivalent of $Sc(OTf)_3$ proved most effective, leading to the isolation of **17** in 78% yield.

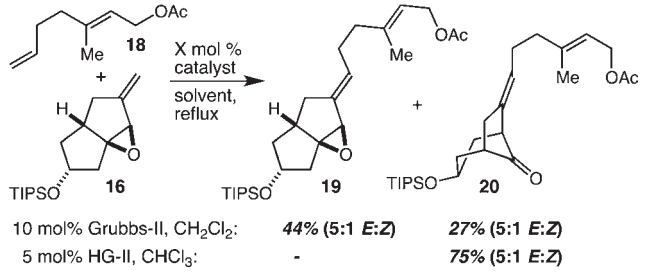
With a proof of concept in hand for the semipinacol rearrangement, both Wittig and Julia–Kociensky reactions were investigated with epoxyketone **15**. Unfortunately, however, Wittig reactions were uniformly *Z*-selective, whereas Julia–Kociensky reactions were both nonselective and inefficient. Forced to consider alternatives, we decided to investigate cross-metathesis (CM) reactions with **16**. We employed alkene **18** (derived in 3 steps (1. *m*-CPBA; 2. H_5IO_6; 3. $Ph_3P=CH_2$) from commercially available geranyl

Scheme 3



acetate in 67% overall yield)[7] in these experiments and quickly found to our delight that the second generation Grubbs catalyst (Grubbs II)[8] was effective for the desired CM reaction, allowing the isolation of **19** as a 5:1 *E*:*Z* mixture (Scheme 4). Our delight only increased, however, when the other significant product of these reactions was identified as the semipinacol rearrangement product **20** (also isolated as a 5:1 *E*:*Z* mixture). Further optimization revealed that the use of 5 mol % of the Hoveyda–Grubbs II catalyst (HG-II)[9] in refluxing chloroform led to the exclusive production of **20** (as a 5:1 *E*:*Z* mixture) in 75% yield. Thus, we had not only identified a convenient method for the stereocontrolled synthesis of the trisubstituted olefin but also found that it could be run as an efficient tandem reaction with the semipinacol rearrangement.

Scheme 4



There are several intriguing mechanistic questions raised by this remarkable tandem reaction, and we have performed control experiments in order to elucidate the

(5) This synthesis of alcohol **11** from epichlorohydrin is a slightly modified version of McDonald's procedures. See: Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495–2500.

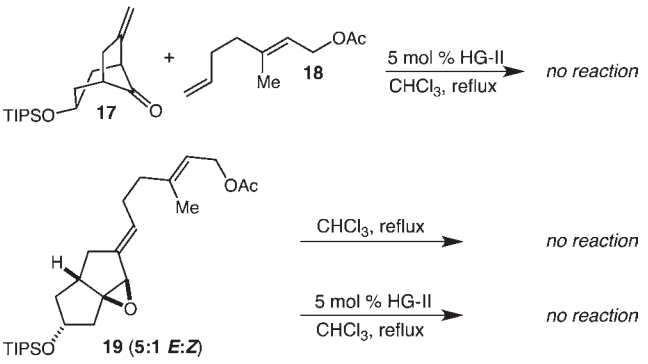
(6) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593–595.

(7) Alkene **18** is a known compound; see: (a) Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917–3948. The first two steps in its preparation were based on Yamamoto's procedures; see: (b) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649–5652. See the Supporting Information for details.

(8) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(9) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

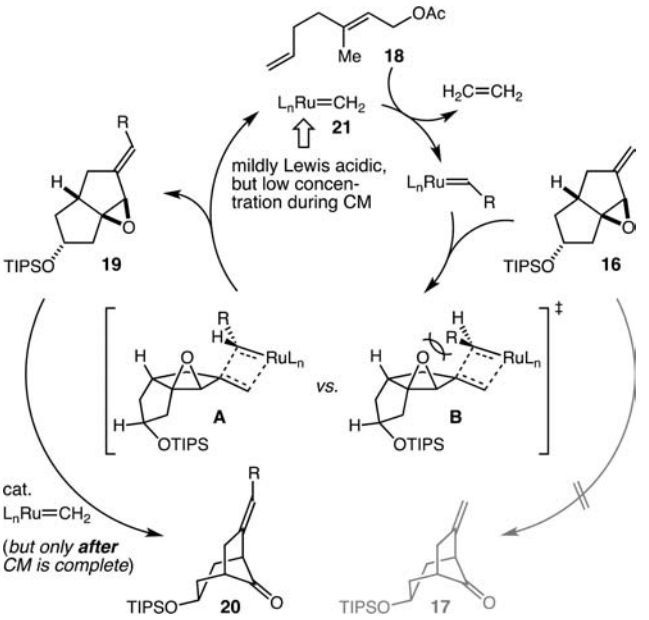
Scheme 5



details. First, an attempted cross-metathesis reaction between **17** and **18** resulted in no reaction (Scheme 5), a result that established that the cross-metathesis happens first and only then does the rearrangement occur, despite the fact that **16** is a viable rearrangement substrate. Second, the HG-II-catalyzed tandem reaction does proceed in CH_2Cl_2 (albeit slightly less efficiently), and when **19** was heated in refluxing $CHCl_3$, no rearrangement occurred. These data together established that adventitious HCl in the chloroform is not the rearrangement catalyst. A third control experiment (treatment of **19** with 5 mol % of the HG-II catalyst in refluxing $CHCl_3$ resulted in no reaction) established that the HG-II catalyst itself is not the catalyst for the rearrangement.

There have been several reports of tandem cross-metathesis/Lewis acid catalyzed reactions,[10] but in all of them unactivated olefins were transformed into α,β-unsaturated carbonyls that subsequently underwent a Lewis acid catalyzed conjugate addition process. The unique feature of the tandem reaction reported here is that both the starting olefin (**16**) and the CM product (**19**) are viable substrates for a Lewis acid catalyzed semipinacol rearrangement, yet only **19** actually undergoes the rearrangement. While it would be reasonable to expect that **19** rearranges at a somewhat faster rate than **16** (the trisubstituted olefin should provide greater stabilization of building positive charge at the allylic epoxide carbon), we think it unlikely that that is a sufficient explanation for the total selectivity observed. Instead, and as first postulated by Fustero,[10a] we believe that the actual Lewis acidic species is ruthenium methylidene **21** and that this species is present in any significant concentration only after completion of the CM reaction. Thus, **16** and **21** are never present in any significant concentration at the same time, and the implication of this is that the use of the HG-II catalyst for tandem metathesis/Lewis acid catalyzed reactions need not be restricted to the conversion of unactivated alkenes into activated ones. Effectively, the Lewis acid switch only gets turned on after the metathesis is complete. Finally, we note that transition states **A** and **B** provide a reasonable explanation for the *E*-selectivity of the key metathesis step (Scheme 6).

Scheme 6



We have devised a step-economical, scalable, and enantiocontrolled synthesis of bicyclic ketone **20** (8 steps in the longest linear sequence from (*R*)-epichlorohydrin). The key step is a novel HG-II-catalyzed tandem CM/semipinacol rearrangement reaction that delivers the desired bicyclic ketone with the challenging trisubstituted olefin installed diastereoselectively from two very readily accessible alkene substrates. While related tandem CM/Lewis acid catalyzed conjugate addition reactions have been described,[10] the present case is unique in that while both the starting alkene (**16**) and the CM product (**19**) are viable substrates for the Lewis acid catalyzed part of the tandem process (the semipinacol rearrangement), only **19** actually rearranges. This strongly suggests that the Lewis acidic species is generated only upon completion of the metathesis reaction and thereby expands the pool of substrates and reactions for this type of tandem catalysis.

Acknowledgment. We gratefully acknowledge the support of Merck Research Laboratories by way of Graduate Fellowship support for C.W.P. and A.S.

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

The authors declare no competing financial interest.

(10) (a) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701. (b) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492. (c) Fuwa, H.; Noto, K.; Saskai, M. *Org. Lett.* **2010**, *12*, 1636–1639. (d) Kwon, S.-H.; Lee, H.-J.; Cho, C.-W. *Bull. Korean Chem. Soc.* **2011**, *32*, 315–318. (e) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2011**, *17*, 2048–2051. (f) Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 3742–3745.