

Harvesting the Strain Installed by a Paternò–Büchi Step in a Synthetically Useful Way: High-Yielding Photoprotolytic Oxametathesis in Polycyclic Systems

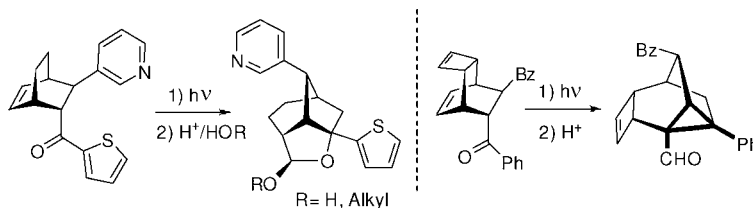
Roman A. Valiulin and Andrei G. Kutateladze*

Department of Chemistry and Biochemistry, University of Denver,
Denver, Colorado 80208

akutatel@du.edu

Received June 30, 2009

ABSTRACT



High-yielding one-pot photoinduced transformation of readily available endoaroyle and heteroaroyle Diels–Alder adducts into novel polycyclic aldehydes or their hemiacetals, decorated by carbo- and heterocyclic pendants, is described.

Photocyclization reactions hold unparalleled promise for building prohibitively strained carbo- and heterocyclic scaffolds, which offer expeditious access to difficult synthetic targets. Secondary transformations are often used to take advantage of the strain installed in the photochemical step. As an example, the Paternò–Büchi reaction in acylbornenes, studied extensively by Sauers,¹ was more recently extended by Rawal into a “general strategy for increasing molecular complexity”,² providing rapid access to di- and triquinanes via a radical fragmentation of strained polycyclic oxetanes. The significance of this is hard to overestimate; in a few key steps, one grows synthetic complexity, while small variations in simple starting materials ensure rather broad diversity of the resulting polycyclic scaffolds.

Oxetanes can be converted pyrolytically (Jones³) or via an electron transfer-induced reaction (Griesbeck⁴) to an alternative pair of an alkene and an aldehyde, which constitutes a carbonyl–olefin metathesis (the term is suggested by Jones³). Most pyrolytic cycloreversions are not suited for delicate polyfunctional compounds, although a single example of a milder TsOH-catalyzed reaction was found in the literature more than three decades ago.^{3b} Such oxametathesis has ample synthetic potential but surprisingly has been all but abandoned.

We hypothesized that if the oxetane moiety itself was a part of a strained polycycle, the cycloreversion could be effected under exceptionally mild conditions. Here we report a high-yielding two-step sequence, whereby the carbonyl–alkene metathesis is induced by a very mild acid-catalyzed

(1) Sauers, R. R.; Kelly, K. W.; Sickles, B. R. *J. Org. Chem.* **1972**, *37*, 537–543.

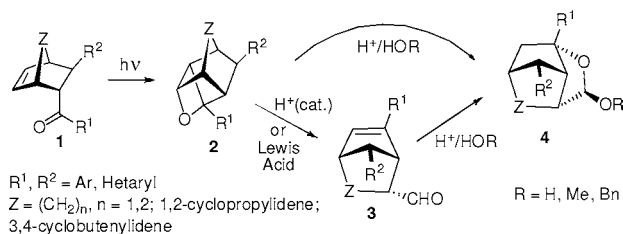
(2) (a) Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 261–2614. (b) Dvorak, C. A.; Dufour, C.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 5302–5303.

(3) (a) Jones, G.; Schwartz, S. B.; Marton, M. T. *Chem. Commun.* **1973**, *11*, 374–375. (b) Jones, G.; Acquadro, M. A.; Carmody, M. A. *Chem. Commun.* **1975**, *6*, 206–207.

(4) Perez-Ruiz, R.; Miranda, M. A.; Alle, R.; Meerholz, K.; Griesbeck, A. *Photochem. Photobiol. Sci.* **2006**, *5*, 51–55.

reaction in the strained α -aryl or α -hetaryl oxetanes, affording novel polycyclic aldehydes **3** or their (hemi)acetals **4** (Scheme 1).

Scheme 1



Both the Paternò–Büchi step **1** \rightarrow **2** and the cycloreversion **2** \rightarrow **3** \rightarrow **4** are remarkably clean reactions. Irradiation of ketones **1** with a UV source, conditioned to excite the aryl groups into their $n \rightarrow \pi^*$ excited state, produces oxetanes which are 97+% pure by NMR. The trace acid-catalyzed cycloreversion into aldehydes **3** or hemiacetals **4** is also nearly quantitative by NMR in most cases (see Supporting Information).⁵

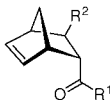
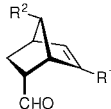
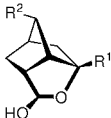
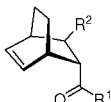
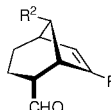
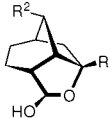
A variety of (het)aryl polycycloalkenes are available via the Diels–Alder (D–A) addition of heterocyclic chalcones^{6,7} and other benzoyl ethylenes to an assortment of dienes. In many cases, chiral catalysts have been developed to yield enantiopure adducts.^{7d,8} With such abundance of oxetane precursors, this oxametathesis sequence allows for expeditious access to structures **4** having diverse polycyclic

(5) In most cases, *endo*-aldehydes **3** are obtained from oxetanes **2** upon treatment with trace amounts of HCl/dioxane or $\text{BF}_3 \cdot \text{OEt}_2$ in dry solvents. This transformation occurs quantitatively as determined by NMR. Further purification of **3** on silica gel columns causes epimerization and, in most cases, partial or full conversion into hemiacetals **4**, which is reflected in lower isolated yields presented in Table 1.

(6) Syntheses of heterocyclic chalcones are extensively documented: (a) Özdemir, A.; Turan-Zitouni, G.; Kaplançikili, Z. A.; Revial, G.; Güven, K. *Eur. J. Med. Chem.* **2007**, *42*, 403–409. (b) Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeonh, B.-S.; Jeong, T. C.; Lee, C.-S.; Lee, E.-S. *Bioorg. Med. Chem.* **2007**, *15*, 4351–4359. (c) Ziener, U.; Lehn, J.-M.; Mourran, A.; Möller, M. *Chem.–Eur. J.* **2002**, *8*, 951–957. (d) Butkiewicz, K. *Electroanal. Chem. Interfacial Electrochem.* **1972**, *39*, 419–428. (e) Marvel, C. S.; Coleman, L. E., Jr.; Scott, G. P. *J. Org. Chem.* **1955**, *20*, 1785–1792. (f) Durinda, J.; Szücs, L.; Krasnec, L.; Heger, J.; Springer, V.; Kolena, J.; Keleti, J. *Acta Fac. Pharm. Bohemoslov.* **1966**, 89–129.

(7) Diels–Alder adducts: (a) dibenzoyl ethylene–cycloheptatriene: Saito, K.; Horie, Y.; Mukai, T.; Toda, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3118–24. (b) dibenzoyl ethylene–cyclooctatriene: Valiulin, R. A.; Dressen, D. G.; Riggs, J. R.; Habte, F. M.; Kutateladze, A. G. *J. Org. Chem.* **2009**, *74*, 3484–3490. (c) diphenyl chalcone–cyclohexadiene: Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2000**, *2*, 3517–3520. (d) diphenyl chalcone–cyclopentadiene: Reetz, M. T.; Jiao, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 2416–2419. (e) bicyclic *endo*-pyridinoyls: Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G. *J. Med. Chem.* **2000**, *43*, 4582–4593. Oltra, N. S.; Roelfes, G. *Chem. Commun.* **2008**, *45*, 6039–6041. Reetz, M. T.; Rentzsch, M.; Pletsch, A.; Maywald, M.; Maiwald, P.; Peyralans, J. J.-P.; Maichele, A.; Fu, Y.; Jiao, N.; Hollmann, F.; Mondiere, R.; Taglieber, A. *Tetrahedron* **2007**, *63*, 6404–6414. Reetz, M. T.; Jiao, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 2416–2419. Roelfes, G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3230–3232. Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238–4239. (f) bicyclic *endo*-thienyl and furanoyl: Arai, Y.; Masuda, T.; Masaki, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1078–1083. Martinelli, M. J. *J. Org. Chem.* **1990**, *55*, 5065–73. Ohta, A.; Kobayashi, T.; Kato, H. *Perkin Trans. 1* **1993**, *8*, 905–11. Sauers, R. R.; Hagedorn, A. A., III.; Van Arnum, S. D.; Gomez, R. P.; Moquin, R. V. *J. Org. Chem.* **1987**, *52*, 5501–5.

Table 1. Cyclopenta- and Cyclohexadiene-Based Products of Oxametathesis

alkene 1			aldehyde 3			(hemi)acetal 4 ^c
<i>Cyclopentadiene-based</i>						
						
R ¹	R ²					
1a	Ph	benzoyl	3a (42%)	-	4b (67%)	
1b	Ph	3-pyridyl	-			
<i>Cyclohexadiene-based</i>						
						
R ¹	R ²					
1e	Ph	Ph	3e (78%) ^b	-		
1f	Ph	H	3f (68%) ^b	-		
1g	Ph	3-pyridyl	3g (72%)	-		
1h	2-furanoyl	4-pyridyl	3h (trace) ^d ^b	-	4h (^d)	
1i	2-thienyl	3-pyridyl	3i (64%) ^b	-	4i (95%)	
1j	4-methoxy-phenyl	4-pyridyl	3j (93%)	-		
1k	4-methoxy-3-pyridyl	3-pyridyl	3k (^d)	-		

^a Yield is >95%, determined by NMR. ^b Partial aldehyde epimerization is observed on the column. ^c The yields for aldehydes **3** and hemiacetals **4** are reported for individual reactions starting from oxetanes **2**. ^d Converted into hemiacetal **4h** on the column.

hemiacetal cores decorated by a variety of heterocyclic pendants.

Table 1 attests to the generality of this reaction and gives several examples where two dienes, cyclopentadiene or cyclohexadiene, and various aryl/hetaryl combinations in the dienophile moiety furnish diverse aldehydes **3** and hemiacetals **4**. The ORTEP drawing of an X-ray structure of hemiacetal **4h** bearing 2-furanyl and 4-pyridyl pendants is shown in Figure 1A.

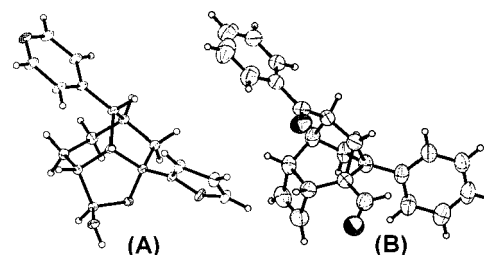


Figure 1. ORTEP drawings of (A) hemiacetal **4h** ($R = 2\text{-furanoyl}$, $R' = 4\text{-pyridyl}$, $Z = \text{CH}_2\text{--CH}_2$), and (B) aldehyde **5t** ($R = \text{phenyl}$, $R' = \text{benzoyl}$, $Z = \text{cyclobutenylidene}$). For X-ray structures of **2e** and **2r**, refer to Supporting Information.

This two-step **1** → **3** conversion can also be implemented as a *one-pot* transformation, with the cycloreversion being effected by a minute amount of HCl present in solvents such as dichloromethane. In most cases, aldehydes **3** form when the precursors **1** are irradiated in reagent grade CH₂Cl₂. With more HCl added, a secondary electrophilic addition to the newly formed styrene double bond of **3** takes place, yielding hemiacetals **4** as a result of the formyl participation.

Utilization of appropriate acids allows for full control of the outcome of the reaction. Lewis acids, such as boron trifluoride, promote oxetane transformation into aldehydes **3** but do not allow for the hemiacetal formation. Protic acids in the presence of water furnish hemiacetals in most cases.

Variations in the carbocyclic framework slightly modulate the reactivity. Diels–Alder adducts **1rs** of *cycloheptatriene*, possessing a tricyclo[3.2.2.0^{2,4}]nonane core, form oxetanes **2rs**, which are stable at room temperature in the presence of HCl. However, they are converted into aldehydes **3rs** via a BF₃-catalyzed reaction as shown in Figure 2. The starting

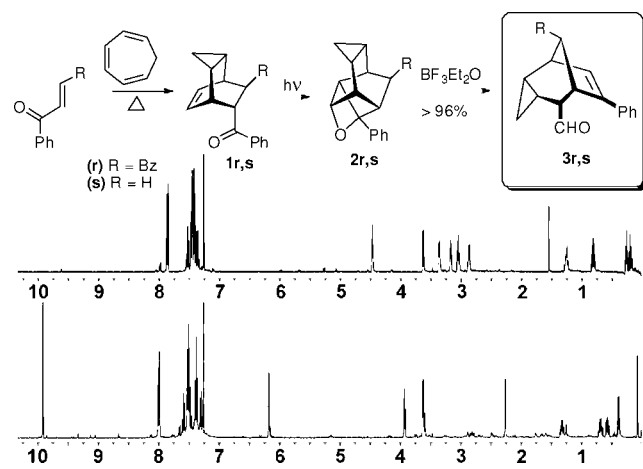
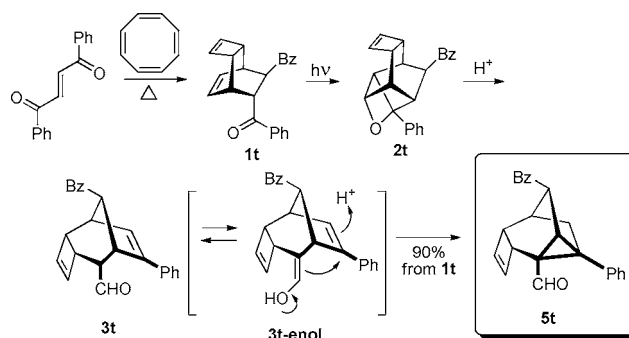


Figure 2. **2r** → **3r** transformation as followed by NMR. Top spectrum: starting oxetane **2r**. Bottom: unpurified reaction mixture containing 96+% of the rearranged aldehyde **3r**.

oxetane **2r** (top spectrum) is cleanly converted into the aldehyde **3r** upon addition of BF₃·OEt₂. The bottom spectrum is a snapshot of the reaction mixture without purification, and **3r** is formed with 96+% purity.

Oxametathesis of the oxetane **2t** derived from the 1:1 adduct of dibenzoyl ethylene and *cyclooctatetraene* (COT) **1t^{7b}** gave the expected aldehyde **3t** (Scheme 2). However, upon further acidolysis, **3t** did not cyclize into a hemiacetal but rather yielded formylcyclopropane **5t**. A plausible mechanism for the formation of **5t** involves the enol moiety in **3t-enol** acting as an internal nucleophile. The conversion of **3t** into **5t** was approximately 90% with 10% of residual **3t** remaining in the reaction mixture. The structure of **5t** is determined by X-ray (Figure 1B).

Scheme 2

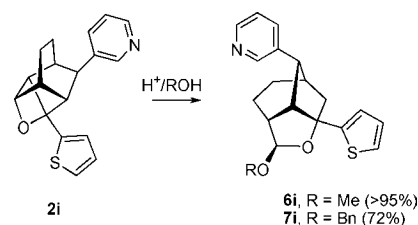


At this point, we are not entirely sure why **3t** cyclizes into **5t**, whereas **3r** does not form the second cyclopropyl ring upon reaction with HCl. Conceivably, it could be driven by simple thermodynamics: according to our Force Field (Sybyl) calculations, the **3t** → **5t** reaction is energy degenerate within 0.2 kcal/mol, while the related cyclization in **3r** would be 8.1 kcal/mol endergonic. For aldehyde **3f** in the bicyclo[2.2.2]octane series, such cyclopropanation is calculated to be 6.1 kcal/mol uphill.

Overall, the rapid synthesis of **5t** from dibenzoyl ethylene and COT demonstrates a rather expeditious growth of complexity in this synthetic sequence. Aldehyde **5t** has seven stereogenic centers, two of which are quaternary.

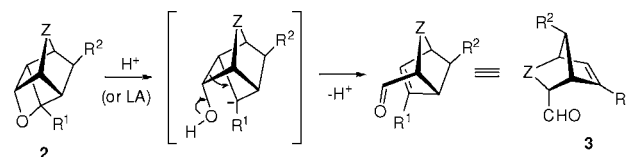
When the cycloreversion is carried out in alcohols, acetals of type **6** and **7** are formed in high yields (Scheme 3).

Scheme 3



A plausible mechanism of the **2** → **3** step (Scheme 4) involves a Grob-like fragmentation of the initial ring-opened carbocationic species and therefore imposes only one con-

Scheme 4

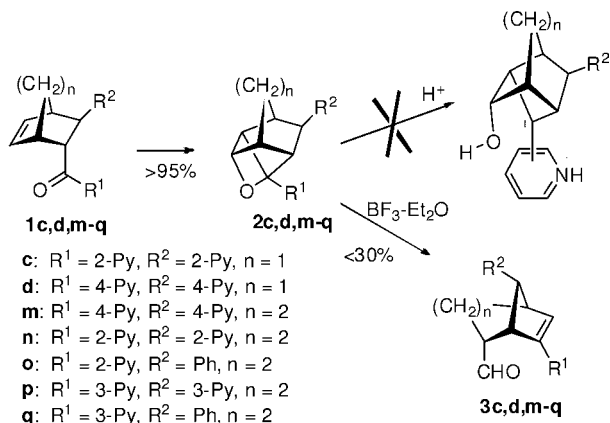


straint: the aryl substituent (R¹) in the oxetane must stabilize the cation.

(8) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117. (b) Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Org. Lett.* **2007**, *9*, 3647–3650. (c) Barroso, S.; Blay, G.; Pedro, J. R. *Org. Lett.* **2007**, *9*, 1983–1986.

That is why the *pyridyl* oxetanes **2c,d,m-q** ($R^1 = 2\text{-}, 3\text{-},$ or 4-pyridyl ; Scheme 5) rearrange into aldehydes **3** only with

Scheme 5

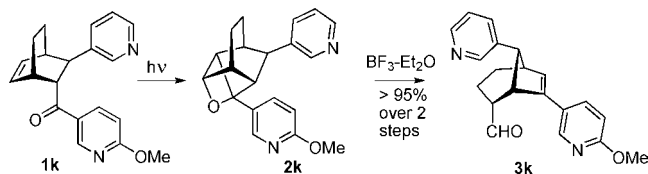


modest yields (<30%) when activated with $\text{BF}_3\cdot\text{OEt}_2$. Protic acids (HCl , TsOH , TfOH), even upon heating, do not effect the transformation in this series, presumably due to protonation of the pyridine moiety and further destabilization of the carbocation.

However, the introduction of an electron-donating methoxy group in the *para*-position, as in **1k**, supersedes the destabilizing effect of the pyridyl and restores the reactivity: **2k** undergoes BF_3 -catalyzed cycloreversion yielding aldehyde **3k** (95% yield over two steps, Scheme 6).

To summarize, we have developed a new, experimentally simple, high-yielding photoinduced transformation of readily

Scheme 6



available diverse starting materials into polycyclic aldehydes and their (hemi) acetals decorated by carbo- and heterocyclic pendants, which are rigidly held in a spatially unique configuration by the core polycyclic framework.

This methodology offers expeditious increase of molecular complexity and diversity of the target scaffolds and also is fully compatible with combinatorial methods where high-yielding transformations are highly desirable. The fact that it is the *photochemical* high-yielding transformation is even more significant, as the integration of photochemical procedures into the main stream organic synthesis and combinatorial chemistry has been spotty at best.

Acknowledgment. Support of this research by NSF (CHE-640838) is gratefully acknowledged.

Supporting Information Available: Synthetic details, ^1H , ^{13}C , COSY NMR spectra, and X-ray structural data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL901456M