ORGANIC LETTERS

2012
Vol. 14, No. 21
5510–5513

Elucidating the Mechanism of Reversible Oxiranations via Magnetization Transfer Spectroscopy

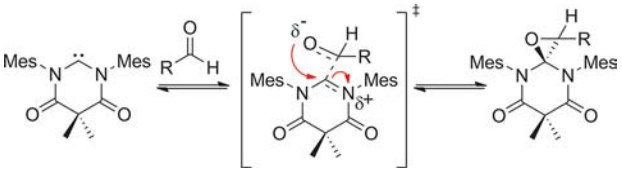
Daniel T. Chase,[†,§] Jonathan P. Moerdyk,[†,§] and Christopher W. Bielawski*[,†,‡]

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712, United States, and World Class University (WCU) Program of Chemical Convergence for Energy & Environment (C_2E_2), School of Chemical and Biological Engineering, Seoul National University, Seoul 151-742, Korea

bielawski@cm.utexas.edu

Received September 20, 2012

ABSTRACT



The reversible [2 + 1] cycloadditions between an *N,N*′-diamidocarbene (DAC) and eight aldehydes were examined using NMR spectroscopy. Variable temperature magnetization transfer experiments revealed higher exchange rates and lower activation barriers when electron-deficient aldehydes were employed. Likewise, competitive equilibrium studies indicated a thermodynamic preference for electron-deficient aryl and sterically unhindered alkyl aldehydes compared to more electron-rich or bulkier substrates. Collectively, these and other data collected were consistent with the oxiranation process proceeding in an asynchronous manner.

Due to their high ring strain, oxiranes are important precursors to a broad range of valuable small molecules and polymers.[1] Such three-membered cyclic ethers are typically synthesized via one of four routes: (1) the ring closure of an appropriately substituted alcohol, (2) the monooxidation of an olefin, (3) the Corey−Chaykovsky reaction, or (4) the [2 + 1] cycloaddition of a carbene with an aldehyde.[2] Despite its high atom economy and the availability of a wide range of aldehydes, the latter process remains largely underdeveloped, mainly because carbenes frequently react with carbonyl groups to give the corresponding ylides rather than the desired cycloadducts.[3] Moreover, most carbenes used in known oxiranation reactions (e.g., dimethoxycarbene[4]) must be generated in situ from unstable precursors.[3a,5] As such, the mechanistic details of the aldehyde/carbene cycloaddition process are relatively unrefined and derived mainly from time-resolved spectroscopic[3c] and computational studies.[6]

[†] The University of Texas at Austin.
[‡] Seoul National University.
[§] D.T.C. and J.P.M. contributed equally.

(1) (a) McMills, M. C.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry III*; Padwa, A., Ed.; Pergamon: Oxford, 2008. (b) Bergmeier, S. C.; Lapinsky, D. J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Oxford, 2009. (c) Krake, S. H.; Bergmeier, S. C. *Tetrahedron* **2010**, *66*, 7337–7360.

(2) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364. (b) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803. (c) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341–2372. (d) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933–935. (e) Träff, A.; Bogár, K.; Warner, M.; Bäckvall, J.-E. *Org. Lett.* **2008**, *10*, 4807–4810.

(3) (a) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263–309. (c) Chateauneuf, J. E.; Liu, M. T. H. *J. Am. Chem. Soc.* **1991**, *113*, 6585–6588.

(4) For excellent reviews and seminal contributions, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1971**, *10*, 529–537. (b) Moss, R. A.; Huselton, J. K. *J. Chem. Soc., Chem. Commun.* **1976**, 950–951. (c) Moss, R. A.; Włostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443–4444. (d) Warkentin, J. *Macromol. Symp.* **1998**, *134*, 167–176. (e) Warkentin, J. *Acc. Chem. Res.* **2009**, *42*, 205–212.

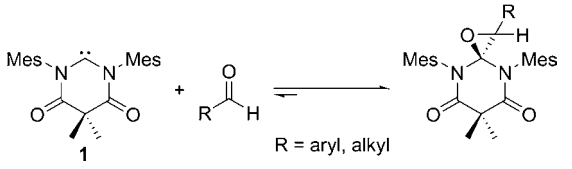
(5) (a) Scaiano, J. C.; McGimpsey, W. G.; Casal, H. L. *J. Am. Chem. Soc.* **1985**, *107*, 7204–7206. (b) Dawid, M.; Venneri, P. C.; Warkentin, J. *Can. J. Chem.* **2001**, *79*, 110–113. (c) Moss, R. A.; Wang, L.; Sauers, R. R. *Tetrahedron Lett.* **2007**, *48*, 5551–5554.

(6) (a) Illa, O.; Gornitzka, H.; Baceiredo, A.; Bertrand, G.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2003**, *68*, 7707–7710. (b) Illa, O.; Gornitzka, H.; Branchadell, V.; Baceiredo, A.; Bertrand, G.; Ortuño, R. M. *Eur. J. Org. Chem.* **2003**, 3147–3152. (c) Illa, O.; Álvarez-Larena, Á.; Baceiredo, A.; Branchadell, V.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2007**, *18*, 2617–2620.

10.1021/ol302596r
Published on Web 10/24/2012

To expand the scope of the carbene/aldehyde cycloaddition reaction and to gain additional insight into the corresponding mechanism, the use of an isolable carbene[7] as a cycloaddition partner is desirable. However, for the past 20 years, the only known isolable carbenes capable of reacting with aldehydes to give the corresponding oxiranes were Bertrand's phosphinosilyl carbenes.[6,8] Recently, we reported that diamidocarbenes (DACs; e.g., **1**),[9,10] which are also isolable and obtained from readily available precursors, undergo [2 + 1] cycloadditions with a wide range of alkyl and aryl aldehydes (Scheme 1).[11] Moreover, the corresponding reactions were found to be rapid and reversible under mild conditions (< 80 °C). We reasoned that additional insight into the [2 + 1] cycloaddition mechanism as well as the corresponding activation parameters may be obtained by probing the equilibration process.

Scheme 1. Known [2 + 1] Cycloadditions of **1** with Aldehydes



Building upon our previous results,[11] a range of aryl and alkyl substituted diamidooxiranes (**2**) were first synthesized by combining **1** with the appropriate aldehyde at 23 °C. The formation of **2a**–**g** was complete within 30 min, as determined by NMR spectroscopy, and the new oxirane products **2b**,**c** were isolated in good yield (76–83%) in a manner similar to that used for previously reported **2a**,**d**–**f**.[11,12] However, incomplete (< 85%) conversion was observed for **2h** even in the presence of excess pivaldehyde (10 equiv), presumably due to steric inhibition.[13]

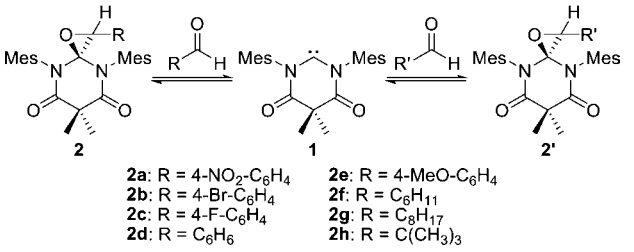


Figure 1. Competitive oxiranation equilibria. Conditions: $[\mathbf{1}]_0$ = 0.066 M, $[\text{aldehyde}]_0 = [\text{aldehyde}']_0$ = 0.07 M, C_6D_6, 60 °C, 2 h.

With **2** in hand, subsequent efforts were directed toward probing the oxiranation equilibria. Two different aldehydes (1.05 equiv each) were mixed with **1** in C_6D_6 ($[\mathbf{1}]_0$ = 0.066 M), and the product ratios were measured by ^{1}H NMR spectroscopy over time. For every combination of aldehydes studied (Figure 1), three separate experiments were performed: (1) the addition of one aldehyde followed by the other, (2) vice versa, and (3) the simultaneous addition of both aldehydes to **1**. Afterward, the mixture was allowed to stir for 20 min at rt. Following ^{1}H NMR analysis, each solution was then heated to 60 °C for 2 h, cooled to rt, and then reanalyzed. Similar product ratios were observed regardless of the order of aldehyde addition which indicated that the reactions were reaching equilibrium.

Table 1. Selected Product and Equilibrium Constant Ratios Compared to **2d**[a]

entry	**2**	**2′**	**2**:**2′**	K_{eq}/K'_{eq}[b]
1	**2a**	**2d**	76:24	8.9×10^0
2	**2b**	**2d**	55:45	1.4×10^0
3	**2c**	**2d**	55:45	1.4×10^0
4	**2e**	**2d**	29:71	1.9×10^{-1}
5	**2f**	**2d**	71:29	5.6×10^0
6	**2g**	**2d**	68:32	4.3×10^0
7	**2h**	**2d**	<1:>99	$<6.7 \times 10^{-4}$

[a] The product ratios and equilibrium constants shown were calculated from an average of three separate experiments. Conditions: $[\mathbf{1}]_0$ = 0.066 M, $[\text{aldehyde}]_0 = [\text{aldehyde}']_0$ = 0.07 M, C_6D_6, 60 °C, 2 h. [b] K_{eq}/K'_{eq} = ([**2**][aldehyde′])/([**2′**][aldehyde]). Representative aldehyde combinations shown; see the SI for the results obtained from all other possible combinations.

Inspection of the results obtained from the aforementioned experiments (see Table 1 and the Supporting Information (SI)) revealed the following trend in stability: **2f** ≈ **2a** > **2g** ≈ **2b** ≈ **2c** > **2d** > **2e** ≫ **2h**. While the DAC **1** appeared to favor electron-deficient aryl aldehydes, the formation of **2f** (from **1** and cyclohexanecarboxaldehyde) was similarly favored[14] as **2a** which we believe stemmed

(7) For excellent reviews on stable carbenes, see: (a) Vignolle, J.; Cattoën, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333–3384. (b) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940–6952. (c) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8810–8849. (d) Martin, D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2011**, *2*, 389–399.

(8) (a) Igau, A.; Baceiredo, A.; Trinquier, G.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 621–622. (b) Martin, D.; Illa, O.; Baceiredo, A.; Bertrand, G.; Ortuño, R. M.; Branchadell, V. *J. Org. Chem.* **2005**, *70*, 5671–5677.

(9) (a) Hudnall, T. W.; Bielawski, C. W. *J. Am. Chem. Soc.* **2009**, *131*, 16039–16041. (b) Hudnall, T. W.; Moerdyk, J. P.; Bielawski, C. W. *Chem. Commun.* **2010**, *46*, 4288–4290.

(10) For other seminal papers that detail the development of diamidocarbenes, see: (a) César, V.; Lugan, N.; Lavigne, G. *Eur. J. Inorg. Chem.* **2010**, 361–365. (b) Hobbs, M. G.; Forster, T. D.; Borau-Garcia, J.; Knapp, C. J.; Tuononen, H. M.; Roesler, R. *New J. Chem.* **2010**, *34*, 1295–1308. (c) Braun, M.; Frank, W.; Reiss, G. J.; Ganter, C. *Organometallics* **2010**, *29*, 4418–4420.

(11) Moerdyk, J. P.; Bielawski, C. W. *Nat. Chem* **2012**, *4*, 275–280.

(12) Unfortunately, recrystallization or concentration of **2g**,**h** followed by washing with pentane returned **1** and precluded isolation.

(13) Analysis of the equilibrium between **2h** and pivaldehyde/**1** between 0 and 60 °C using VT ^{1}H NMR spectroscopy revealed ΔH and ΔS values of -11.2 kcal·mol^{-1} and -33.4 cal·mol^{-1}·K^{-1}, respectively (see the SI).

(14) Likewise, a 48:52 mixture of **2a:2f** was obtained by combining 4-nitrobenzaldehyde and cyclohexanecarboxaldehyde (1.05 equiv each) with a C_6D_6 solution of **1** ($[\mathbf{1}]_0$ = 0.066 M) followed by heating to 60 °C for 2 h; see the SI for additional details.

from a slow dissociation process (see below). In addition to electronics, sterics also prominently influenced the stability of the diamidooxiranes (cf., entries 5 or 6 to 7).

Unfortunately, due to the rapid rate of cycloaddition, all attempts to expand upon the aforementioned equilibrium studies and obtain the corresponding pseudo-first-order rate constants (k_{obs}) by variable temperature ^{1}H NMR spectroscopy were unsuccessful. For example, treating a C_7D_8 solution of **1** ($[\mathbf{1}]_0$ = 0.066 M) with 10 equiv of benzaldehyde was found to quantitatively form **2b** within 60 s at −80 °C ($k_{obs} > 1.9 \times 10^{-1}$ $M^{-1}\cdot s^{-1}$ at 99.9% conversion).

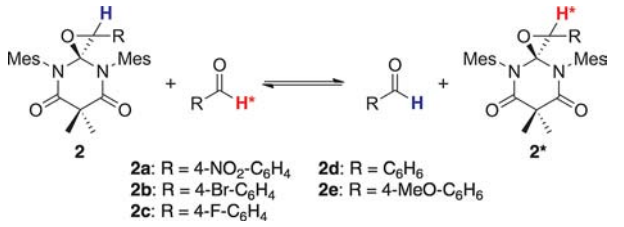


Figure 2. Substrates used in the magnetization transfer spectroscopy experiments. Conditions: $[\mathbf{1}]_0$ = 0.066 M, [aldehyde]$_0$ = 0.199 M, C_7D_8. The asterisk denotes the ^{1}H NMR resonances monitored during the magnetization transfer process. The rate-determining step is the cycloreversion of the oxirane.

To circumvent this limitation and to measure the rates of the exchange processes at equilibrium, we considered magnetization transfer spectroscopy.[15] This one-dimensional NMR technique involves the monitoring of a nucleus undergoing chemical exchange as it relaxes from a selective 180° pulse. While magnetization transfer has been previously utilized in biological,[16] organometallic,[17] and other physical chemistry[18] studies, it has not been employed to study C−C bond forming reactions to the best of our knowledge.

To test the viability of the magnetization transfer technique as a means to measure the exchange rates of the reactions summarized in Figure 2, a C_7D_8 solution of **1** ($[\mathbf{1}]_0$ = 0.066 M) and 3 equiv of an aldehyde were heated to a predetermined temperature in the NMR probe. Next, a selective 180° pulse was applied to the equilibrated sample at the ^{1}H NMR resonance frequency assigned to the aldehyde (9.4−9.6 ppm), and the corresponding nucleus was allowed to relax over time (see Figure 3 for an illustrative example). The areas of the signals assigned to the pulsed aldehyde starting material as well as the oxirane product were monitored at various relaxation delays that ranged between 0.001 and 30 s. Using the software program CIFIT,[19] the areas of the oxirane and aldehyde signals were fitted to a nonlinear, least-squares equation and an exchange rate, k_{ald}, was calculated for each aldehyde studied.

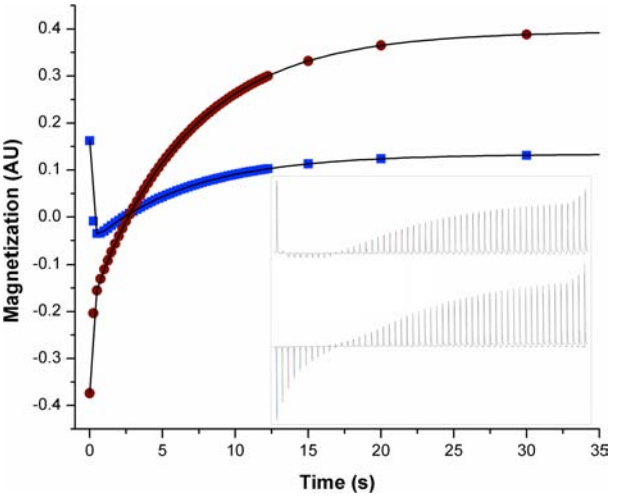


Figure 3. Plot of the measured magnetization signal versus time for **2a** (monitored at 3.9 ppm, blue squares) and 4-nitrobenzaldehyde (monitored at 9.45 ppm, red circles) and their magnetization values calculated from the best-fit parameters (black lines). Inset: Representative NMR spectra for (top) **2a** (monitored at 3.9 ppm) and (bottom) 4-nitrobenzaldehyde (monitored at 9.45 ppm) over time. Conditions: $[\mathbf{1}]_0$ = 0.066 M, [4-nitrobenzaldehyde]$_0$ = 0.199 M, C_7D_8, 100 °C.

The aforementioned experiments were then repeated with the exception that the ^{1}H NMR resonance assigned to the oxirane (2.61−3.9 ppm) was selectively inverted instead of the aldehyde. Likewise, monitoring the signal areas over time provided the corresponding exchange rate, k_{ox}. The overall exchange rate, k_{exc}, was taken as the numerical average of k_{ald} and k_{ox}. As shown in Figure 4 and summarized in Table 2 (as well as the SI), the exchange rates for **2a**−**e** were measured at 5 °C intervals from 85 to 100 °C; the exchange rates for **2f**−**h** were not measured due to premature decomposition observed at elevated temperatures.

Using the VT NMR data, Eyring plots were constructed to determine the activation energies for the cycloreversion reactions of **2a**−**e**. The corresponding $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were calculated to be large and positive (Table 2), and the exchange rate was found to be independent of the aldehyde concentration (see the SI). These data indicated that the dissociative cycloreversion was the rate-limiting step of the equilibration process. Additionally, the more

(15) Morris, G. A.; Freeman, R. *J. Magn. Reson.* **1978**, *29*, 433–462.
(16) (a) London, R. E.; Gabel, S. A. *Biophys. J.* **1995**, *69*, 1814–1818. (b) Kruiskamp, M. J.; van Vliet, G.; Nicolay, K. *Magn. Reson. Med.* **2000**, *43*, 657–664.
(17) (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750. (b) Hascall, T.; Murphy, V. J.; Parkin, G. *Organometallics* **1996**, *15*, 3910–3912. (c) Muhandiram, D. R.; Kiel, G.-Y.; Aarts, G. H. M.; Saez, I. M.; Reuvers, J. G. A.; Heinekey, D. M.; Graham, W. A. G.; Takats, J.; McClung, R. E. D. *Organometallics* **2002**, *21*, 2687–2704.
(18) (a) Brown, A. B.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 3640–3651. (b) Perrin, C. L.; Thoburn, J. D.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 8800–8807. (c) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261–4270. (d) Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038–2046.
(19) Bain, A. D.; Cramer, J. A. *J. Magn. Reson.* **1996**, *118*, 21–27.

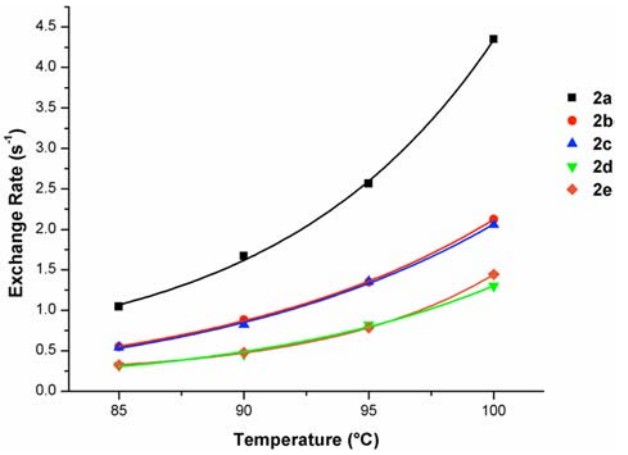


Figure 4. Measured exchange rates versus temperature. Conditions: $[\mathbf{1}]_0 = 0.066$ M, $[\text{aldehyde}]_0 = 0.199$ M, C_7D_8.

electron-deficient **2a** exchanged at nearly triple the rate as those measured for **2d** and **2e** at 100 °C. The higher exchange rates and slightly lower $\Delta G^{\ddagger}$ for the more electron-deficient derivatives reflected a partial buildup of negative charge in the transition state stabilized by the proximal electron-withdrawing aryl substituents (Scheme 2). Based on these results, the mechanism of the oxiranation was consistent with a process wherein the aldehyde underwent attack by the nucleophilic carbene in an asynchronous manner.

In summary, the dynamic equilibria of **1** with various aryl and alkyl aldehydes was investigated and the corresponding thermodynamic parameters were measured. Competitive equilibrium studies revealed a thermodynamic preference for electron-deficient aryl aldehydes **2a**, **b** and sterically unhindered alkyl aldehydes **2f**,**g** while the formation of sterically hindered oxiranes was strongly

(20) For comparison, NHCs often afford zwitterions that rearrange to the corresponding Breslow intermediates when treated with aldehydes (see: Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522). In contrast, the low-lying LUMO of the DAC may facilitate ring closure (see: Hudnall, T. W.; Moorhead, E. J.; Gusev, D. G.; Bielawski, C. W. *J. Org. Chem.* **2010**, *75*, 2763–2766).

(21) (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (b) Lehn, J.-M. *Chem. Soc. Rev.* **2007**, *36*, 151–160.

(22) (a) Zhang, C.; Wang, Q.; Long, H.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 20995–21001. (b) Jin, Y.; Voss, B. A.; Jin, A.; Long, H.; Noble, R. D.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 6650–6658.

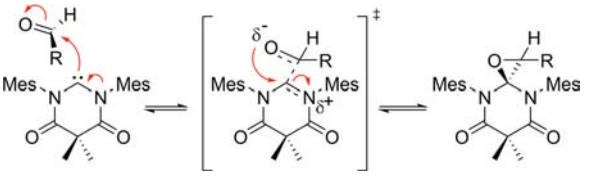
(23) (a) You, L.; Berman, J. S.; Anslyn, E. V. *Nat. Chem.* **2011**, *3*, 943–948. (b) Carroll, C. N.; Coombs, B. A.; McClintock, S. P.; Johnson, C. A., II; Berryman, O. B.; Johnson, D. W.; Haley, M. M. *Chem. Commun.* **2011**, *47*, 5539–5541. (c) Engle, J. M.; Carroll, C. N.; Johnson, D. W.; Haley, M. M. *Chem. Sci.* **2012**, *3*, 1105–1110.

(24) (a) Nitschke, J. R.; Schultz, D. J.; Bernardinelli, G.; Gérard, D. *J. Am. Chem. Soc.* **2004**, *126*, 16538–16543. (b) Aricó, F.; Chang, T.; Cantrill, S. J.; Khan, S. I.; Stoddart, J. F. *Chem.—Eur. J.* **2005**, *11*, 4655–4666. (c) Chichak, K. S.; Cantrill, S. J.; Stoddart, J. F. *Chem. Commun.* **2005**, 3391–3393.

Table 2. Summary of the Activation Parameters

oxirane	k_{exc} (s^{-1}) (100 °C)	$\Delta H^{\ddagger}$ (kcal·mol^{-1})	$\Delta S^{\ddagger}$ (cal·mol^{-1}·K^{-1})	$\Delta G^{\ddagger}$ (298 K) (kcal·mol^{-1})
2a	4.4	23.9 ± 1.9	8 ± 5	22 ± 2
2b	2.13	23.0 ± 1.4	4 ± 4	21.7 ± 1.8
2c	2.06	23.1 ± 0.9	4 ± 2	21.8 ± 1.1
2d	1.3	26.2 ± 1.4	12 ± 4	22.6 ± 1.9
2e	1.45	23.8 ± 1.9	5 ± 5	22 ± 2

Scheme 2. Proposed Mechanism for the Reversible Oxiranation



disfavored. Similarly, magnetization transfer experiments showed that the electron-deficient oxiranes underwent faster exchange than their electron-rich analogues. Collectively, the exchange rates and activation energies were consistent with an asynchronous mechanism that involved the buildup of partial negative charge at the aldehyde oxygen (and, by extension, buildup of partial positive charge within the N-heterocycle) in the transition state.[20] With knowledge of the exchange rates and thermodynamic equilibria in hand, we believe the DAC/aldehyde cycloaddition reaction is poised for use in dynamic covalent[21] applications (e.g., sensing[22,23]) wherein the rapid, reversible oxiranation process may be advantageous.[24] Beyond elucidating the mechanism of the aforementioned [2 + 1] cycloaddition reaction, magnetization transfer spectroscopy was applied for the first time to a dynamic covalent organic reaction.

Acknowledgment. We acknowledge the NSF (CHE-0645563), the Welch Foundation (F-1621), and the WCU program through the NRF of Korea (R31-10013) for their support. J.P.M. is grateful to the UT-Austin for a Powers Fellowship. We also thank Steve Sorey (UT-Austin) for assistance with the magnetization experiments.

Supporting Information Available. Synthetic and characterization details for **2c**,**d**,**g**,**h**, additional equilibrium data, VT NMR and magnetization transfer data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.