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Cu(II)-Catalyzed Aerobic Hydroperoxidation of Meldrum's Acid Derivatives and Application in Intramolecular Oxidation: A Conceptual Blueprint for O_2/H_2 Dihydroxylation

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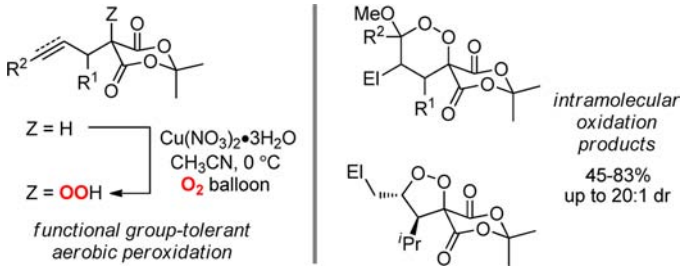
ABSTRACT



Aerobic hydroperoxidation of Meldrum's acid derivatives via a Cu(II)-catalyzed process is presented. The mild reaction conditions are tolerant to pendant unsaturation allowing the formation of endoperoxides via electrophilic activation. Cleavage of the O−O bond provides 1,*n*-diols with differentiation of the hydroxy groups.

Enolate oxidation is an important tool in organic synthesis for the preparation of various α-functionalized carbonyl compounds.[1] This reaction is often achieved through the application of oxygen-based electrophiles such as oxaziridines, dioxiranes, and diacyl peroxides (Scheme 1a); these reagents are useful for the installation of a hydroxyl group or hydroxyl surrogate but their atom economy is relatively poor.[2] In the rarer cases where hydroperoxides are generated during the course of enolate functionalization (often as ROH/RO_2H mixtures), it is common practice to reduce the mixture to the hydroxylation (ROH) product upon workup. This reductive workup in essence squanders one oxidation level conferred by the oxidant. By contrast, an enolate oxidation that preserved the elevated product oxidation state could in principle be used to functionalize remote sites (Scheme 1b), so long as the distal functionality was compatible with the oxidation conditions. Initially providing an endoperoxide (**3**), hydrogenolysis of the O−O bond would provide formal dihydroxylation products (**4**) in a redox economical manner.[3] Moreover, a catalytic enolate oxidation reaction that used O_2 would carry the inherent advantages of complete atom economy and the use of a green oxidant. At issue in translating this construct to practice is (1) the development of a mild, functional group-tolerant enolate oxidation using O_2 and (2) the development of tools for remote functionalization using the hydroperoxide products. The purpose of this communication is to report efforts to this end in the form of an efficient, operationally simple method for the catalytic aerobic hydroperoxidation of Meldrum's acid[4]

(1) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637–1656.
(2) (a) Bang-Chen, C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React. (N.Y.)* **2003**, *62*, 1–356. (b) For direct hydroxylation of active methines using $Pd(II)/O_2$, see: Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760–1762.
(3) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867.
(4) For recent reviews of Meldrum's acid in organic synthesis, see: (a) Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440–454. (b) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789–811.

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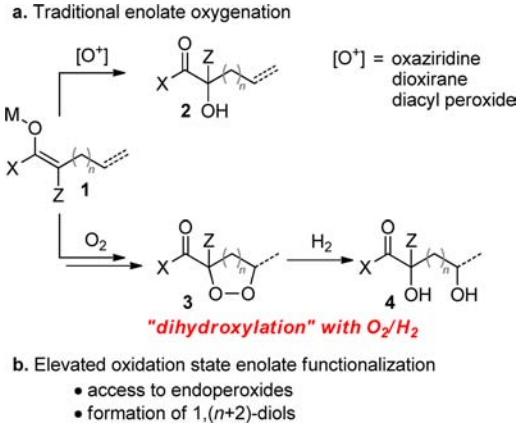
derivatives and the application of the products in intramolecular $\pi_{C\equiv C}$ and $\pi_{C=C}$ oxidation, including the first Au(I)-catalyzed hydroperoxide/alkyne cyclization.

The projected intervention of intermediates such as **3** in this strategy is significant since cyclic peroxides are prevalent in a number of natural products exhibiting antimalarial (artemisinin and its derivatives) and anticancer (plakinic acids) activity.[5−7] With this knowledge and the findings that structurally simpler cyclic peroxides can still exhibit useful biological activity,[8] the short and efficient synthesis of new cyclic peroxides has become a topic of increased effort.[9] Thus, the value of endoperoxides **3** is twofold as they are both biologically relevant and potential precursors to ubiquitous 1,*n*-diols **4**.

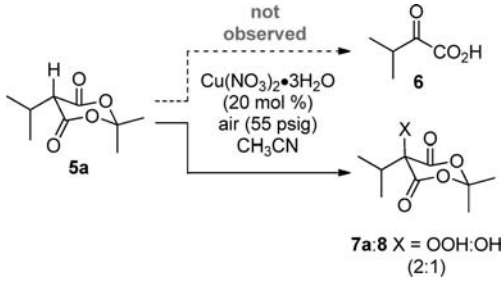
Scheme 1. Methods of Enolate Oxidation



A common strategy for the synthesis of endoperoxides is the cyclization of hydroperoxides onto pendant alkenes. This cyclization has been accomplished by peroxy radical cyclization,[10] attack onto in situ formed halonium or mercuronium ions,[11] conjugate addition into electron-deficient alkenes,[12] or olefin activation by electrophilic transition metal catalysis.[13] Endoperoxides provide access to 1,*n*-diols via O−O bond cleavage by thiourea/MeOH[14] or metal-catalyzed hydrogenolysis.[15] The latter case is especially attractive from a green chemistry perspective[16] since the overall sequence could in principle provide formal dihydroxylation with O_2 as the oxidant and H_2 as the reductant.

Our point of departure for this study was to examine oxygenation of β-dicarbonyls with the expectation that the appreciable C−H acidity could translate to relatively mild activation conditions. Extant methods for hydroperoxidation of β-dicarbonyls are scant and often suffer from harsh conditions and/or mixtures of hydroperoxide and alcohol. The use of photosensitized $^1O_2$ allows the formal addition of O_2 into an active methine,[17] and endoperoxidic hemiketals were formed in modest yield in the Ce(III)-catalyzed peroxidation/cyclization of β-dicarbonyls with styrenes.[18] The foremost methods for hydroperoxidation of active C−H bonds utilize aerobic oxidation of dimedone derivatives[19] or employ Mn(III)/O_2 to peroxidize 1,2-diphenylpyrazolidine-3,5-diones and barbituric acid derivatives.[20] The aerobic oxidation conditions are quite specific to dimedone derivatives,[21] and Mn(III) is well-known to give electrophilic radical intermediates with β-dicarbonyls, rendering this method incompatible with pendant unsaturation due to competitive cyclization.[22] A method compatible with unsaturation is highly desirable as the heightened oxidation state gained by hydroperoxidation

Scheme 2. Cu(II)-Catalyzed Aerobic Oxidation of a Substituted Meldrum's Acid



(5) Keiser, J.; Utzinger, J. *Curr. Opin. Infect. Dis.* **2007**, *20*, 605–612.
(6) Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722–6724.
(7) Jefford, C. W. *Drug Disc. Today* **2007**, *12*, 487–495.
(8) (a) Dembitsky, V. M. *Eur. J. Med. Chem.* **2008**, *43*, 223–251. (b) Hencken, C. P.; Kalinda, A. S.; D'Angelo, J. G. *Annu. Rep. Med. Chem.* **2009**, *44*, 359–378.
(9) (a) Ghorai, P.; Dussault, P. H.; Hu, C. *Org. Lett.* **2008**, *10*, 2401–2404. (b) Gemma, S.; Martí, F.; Gabellieri, E.; Campiani, G.; Novellino, E.; Butini, S. *Tetrahedron Lett.* **2009**, *50*, 5719–5722. (c) Parrish, J. D.; Ischay, M. A.; Lu, Z.; Guo, S.; Peters, N. R.; Yoon, T. P. *Org. Lett.* **2012**, *14*, 1640–1643.
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(11) Bloodworth, A. J.; Curtis, R. J. *J. Chem. Soc., Chem. Commun.* **1989**, 173–175.
(12) (a) O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065–6068. (b) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M *Tetrahedron Lett.* **2001**, *42*, 7281–7285.
(13) Harris, J. R.; Waetzig, S. R.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 3290–3293.
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(15) Bloodworth, A. J.; Eggelte, H. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3272–3278.
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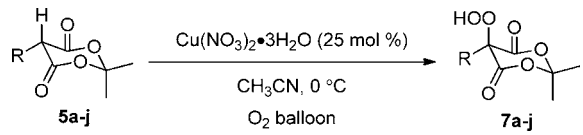
(17) Yoshioka, M.; Nishioka, T.; Hasegawa, T. *J. Org. Chem.* **1993**, *58*, 278–281.
(18) Christoffers, J.; Werner, T.; Frey, W.; Baro, A. *Eur. J. Org. Chem.* **2003**, 4879–4886.
(19) (a) Wang, G.-W.; Lu, Q.-Q.; Xia, J.-J. *Eur. J. Org. Chem.* **2011**, 4429–4438. For autoxidation of dienols, see: (b) Fuson, R. C.; Hatchard, W. R.; Kottke, R. H.; Fedrich, J. L. *J. Am. Chem. Soc.* **1960**, *82*, 4330–4333. (c) Triquiqneaux, M.; Charles, L.; André-Barrès, C.; Tuccio, B. *Org. Biomol. Chem.* **2010**, *8*, 1361–1367.
(20) (a) Rahman, T.; Nishino, H. *Org. Lett.* **2003**, *5*, 2887–2890. (b) Rahman, T.; Haque, A.; Igarashi, H.; Nishino, H. *Molecules* **2011**, *16*, 9562–9581. (c) Haque, A.; Nishino, H. *Synth. Commun.* **2012**, *42*, 608–619.
(21) In our hands, hydroperoxidation of Meldrum's acid derivatives was not observed under the reported conditions.
(22) (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–364. (b) Snider, B. B. Manganese(III)-Based Oxidative Free-Radical Cyclizations. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 481−490.

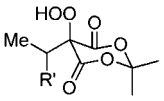
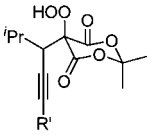
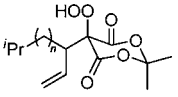
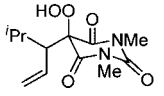
can be effectively utilized. The use of substituted Meldrum's acids as flexible starting materials for C–H hydroperoxidation was attractive since asymmetric syntheses of these compounds have been developed to a high level of sophistication, simplicity, and scalability.[23,24]

Reports on Cu(II)-catalyzed aerobic activation of β-dicarbonyls prompted us to examine these reaction conditions.[25] Isopropyl Meldrum's acid **5a** was exposed to Cu(II)/air (55 psig; standard Fisher-Porter bottle) in acetonitrile at ambient temperature. The oxidative cleavage product **6** might nominally be expected based on precedent, but the reduced electrophilicity of the ester carbonyl led instead to a mixture of hydroperoxide **7a** and alcohol **8** (Scheme 2). Reducing the temperature to 0 °C minimized or eliminated reduction to alcohol **8** while still providing good conversion to the hydroperoxide. Operational simplicity was further achieved without detriment to yield by using a balloon of O_2, eliminating the need for a pressure vessel.[26]

With optimized conditions realized,[27] a variety of Meldrum's acids **5a–j** were subjected to the hydroperoxidation (Table 1). The mild reaction conditions proved tolerant to a variety of potentially vulnerable functional groups including alkenes, terminal and internal alkynes, arenes, tertiary benzylic C–H bonds, and esters. In most cases, the hydroperoxide products **7a–h** were obtained in >90% purity after a simple aqueous workup. Alkene substrates provided modest to good yields of the desired hydroperoxides **7i–j** following purification.[28] In addition to providing hydroperoxy Meldrum's acid derivatives in good yield, this methodology also provided the barbituric acid derivative **9** with pendant unsaturation in modest yield, a product presumably unattainable in Mn(III)-catalyzed hydroperoxidations.

Table 1. Hydroperoxidation of Meldrum's Acid Derivatives



product			t (h)	yield (%)[a]
	R' = CH_3	**7a**	6	>95
	H	**7b**	6	92
	Ph	**7c**	2	>95
	R' = H	**7d**	2	80
	CH_3	**7e**	2	78
	C_5H_{11}	**7f**	2	80
	CO_2Et	**7g**	3	>95
	Ph	**7h**	2	>95
	n = 0	**7i**	4	59[b,c]
	1	**7j**	4.5	86[b,d]
		**9**	8	49[b]

[a] Isolated yield without need for purification (except **7i**, **7j**, and **9**). [b] Yield following purification on SiO_2. [c] 10:1 with alcohol. [d] 17:1 with alcohol.

We next assayed the utility of unsaturated hydroperoxide products in intramolecular oxidation via endoperoxide formation. Au(I)-catalyzed cycloetherifications have been reported with a variety of gold catalysts,[29] but to the best of our knowledge, the corresponding endoperoxidation is unknown. Alkyl-substituted alkynyl hydroperoxides **7e,f** undergo 6-*endo* cyclization catalyzed by triphenylphosphinegold(I) triflimide[30] in MeOH to give mixed ketal endoperoxides in good yield (Scheme 3).[31] Subsequent reductive cleavage of the O–O bond of **10a** followed by hemiketalization of the transient ketone provided **11** in excellent yield with 3:1 dr. Ionic hydrogenation[32] of **11** affords tetrahydrofuran **12** in a highly diastereoconvergent process.[33]

By reversing the order of operations, entirely different products can be accessed from the same mixed ketal endoperoxide. Ionic hydrogenation of **10a** provides endoperoxide **13** in modest yield with good diastereoselectivity as

(23) (a) Reference 4a. (b) Allen, J. C.; Kociok-Köhn, G.; Frost, C. G. *Org. Biomol. Chem.* **2012**, *10*, 32–35. (c) Cui, S.; Walker, S. D.; Woo, J. C. S.; Borths, C. J.; Mukherjee, H.; Chen, M. J.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 436–437. (d) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964–4967. (e) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635–1657. (f) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682–9683. (g) Knöpfel, T. F.; Boyall, D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2281–2283. (h) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054–6055.

(24) (a) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121–125. (b) Hong, B.-C.; Dange, N. S.; Ding, C.-F.; Liao, J.-H. *Org. Lett.* **2012**, *14*, 448–451. (c) Trost, B. M.; Osipov, M.; Kaib, P. S. J.; Sorum, M. T. *Org. Lett.* **2011**, *13*, 3222–3225.

(25) (a) Steward, K. M.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 2426–2429. (b) Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089–6092. (c) Vallejos, J.-C.; Capelle, N.; Arzoumanian, H. U.S. Patent 6,057,474, 2000.

(26) For representative thermogravimetric analyses of the peroxide products, see the Supporting Information. While we encountered no hazardous decomposition during the course of this work, anyone working with peroxides should be aware that spontaneous and exothermic decomposition is possible. For some references on peroxide properties and safety, see: (a) Zabicky, J. In *The Chemistry of the Peroxide Group*; Rappoport, Z., Ed.; John Wiley and Sons: Chichester, 2006; Part 2, Vol. 2, pp 597–773. (b) Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, p 341.

(27) (a) The Supporting Information describes additional optimization studies. (b) Simple esters and branched malonates are not suitable substrates for the Cu-catalyzed aerobic oxidation.[25a]

(28) Alcohol formation in variable amounts was observed upon purification on SiO_2. The necessity for purification of alkene substrates may be attributable to epoxidation of the alkene which was observed in the oxidative deacylation.[25a]

(29) (a) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657–1712. (b) Muzart, J. *Tetrahedron* **2008**, *64*, 5815–5849.

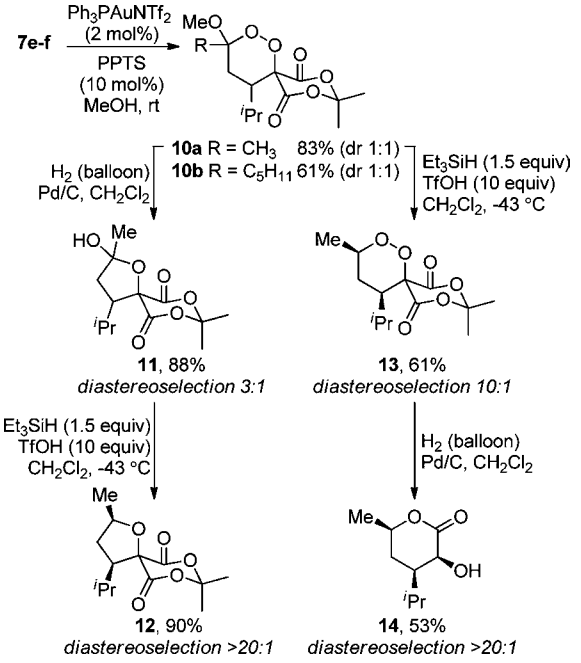
(30) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

(31) (a) Liu, B; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907–4910. (b) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (c) In the absence of PPh_3AuNTf_2 no reaction is observed and when PPh_3AuNTf_2 is used in the absence of PPTS no desired product is observed. Several Bronsted or Lewis acid catalysts also gave no reaction (TfOH, $Cu(OTf)_2$, Ag(OTf), $PtCl_2$, AuCl, $AuCl_3$, PPh_3AuCl, and $AuCl/AgPF_6$).

(32) (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651. (b) Bullock, R. M. *Chem.—Eur. J.* **2004**, *10*, 2366–2374.

(33) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209.

Scheme 3. Gold(I)-Catalyzed Endoperoxidation of Hydroperoxides and Endoperoxide Reactions



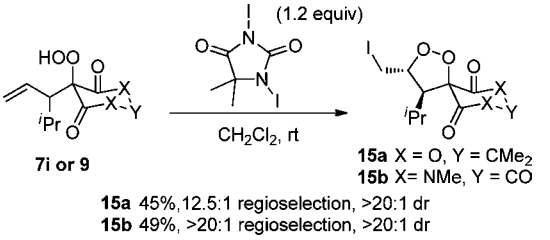
predicted by standard half-chair analysis of the intermediate oxocarbenium ion. Reductive cleavage of the O−O bond with concomitant Meldrum's acid opening and decarboxylation gives the desired 1,4-diol functionality as lactone **14** in good yield as a single diastereomer, implying that the decarboxylation/protonation is completely stereoselective.

The complementary 5-*exo* cyclization mode was realized through the remote oxidation of alkenyl hydroperoxy Meldrum's acid derivatives (Scheme 4). Homoallylhydroperoxy **7i** cyclized via electrophilic activation of the alkene with 1,3-diiodo-5,5-dimethylhydantoin (DIH).[34] This process was highly regio- and stereoselective providing the 1,2-dioxolane **15a** with pendant iodide in modest yield. The *N,N*-dimethylbarbituric acid derivative **9** reacted analogously giving the endoperoxide **15b** in 49% yield.

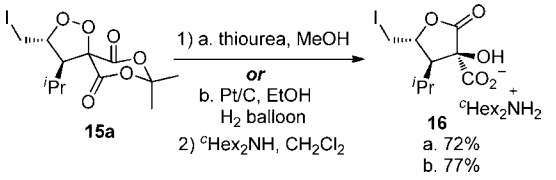
Metal-catalyzed hydrogenolysis or thiourea/MeOH provided smooth O−O bond cleavage of **15a** (Scheme 5). Concomitant cyclization/ring-opening occurred on the Meldrum's acid with complete diastereotopic group discrimination to provide the differentiated 1,3-diol functionality in the form of lactone **16**, conveniently isolated as the dicyclohexylamine salt in good yield as a single diastereomer. The relative configuration of **16** was determined by single-crystal X-ray diffraction.

(34) (a) Reference 11. (b) Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101–1104.

Scheme 4. Iodoendoperoxidation of Homoallylhydroperoxy-Meldrum's Acid and Barbituric Acid Derivatives



Scheme 5. Endoperoxide Cleavage in 1,2-Dioxolane System



In summary, we have developed a simple, mild and efficient catalytic method for the hydroperoxidation of Meldrum's acid derivatives including those with unsaturation. The hydroperoxide products can be used for intramolecular oxidation via electrophilic activation of the pendant $\pi_{C\equiv C}$ and $\pi_{C=C}$ functionality. Au(I)-catalyzed endoperoxidations of hydroperoxyalkynes have been reported for the first time. Reductive cleavage of the O−O bond yields 1,*n*-diol functionality with convenient differentiation of the alcohols via lactonization, thereby providing the conceptual blueprint for the development of atom-efficient O_2/H_2 dihydroxylations. Current efforts in our laboratory are focused on expanding this methodology to a wider range of Meldrum's acid derivatives to provide diverse endoperoxides and 1,*n*-diols.

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Supporting Information Available. Experimental procedures, compound characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.