Organic LETTERS
Letter
pubs.acs.org/OrgLett

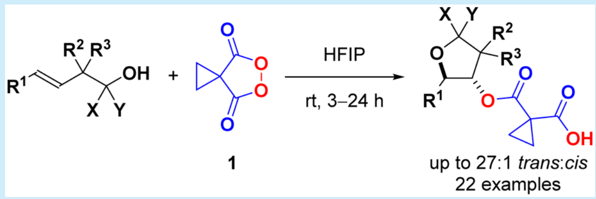
Alkene Dioxygenation with Malonoyl Peroxides: Synthesis of γ-Lactones, Isobenzofuranones, and Tetrahydrofurans

Carla Alamillo-Ferrer,[†] Marianna Karabourniotis-Sotti,[†] Alan R. Kennedy,[†] Matthew Campbell,[‡] and Nicholas C. O. Tomkinson*,[†]

[†]WestCHEM, Department of Pure and Applied Chemistry, Thomas Graham Building, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, United Kingdom
[‡]GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, United Kingdom

Supporting Information

ABSTRACT: Treatment of homoallylic alcohols or carboxylic acids with malonoyl peroxide **1** provides a stereoselective method for the preparation of tetrahydrofurans, γ-lactones, and isobenzofuranones in 44−82% yield and up to 27:1 *trans* selectivity. Application of this simple and effective heterocyclization in the synthesis of the antidepressant citalopram is also described.

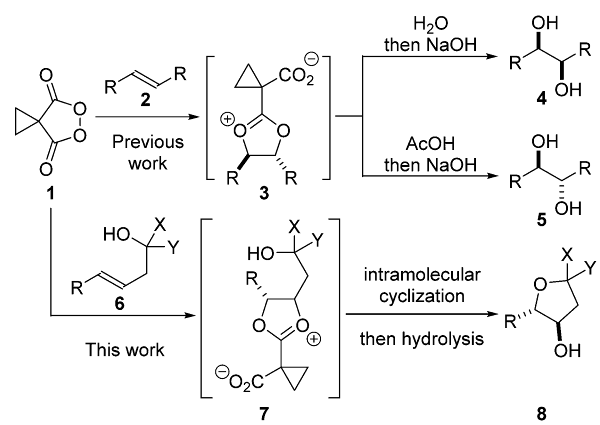


Saturated oxygen heterocycles are ubiquitous in nature and have been shown to have profound and diverse biological activities.[1,2] In addition, they have provided molecular frameworks for the development of multibillion dollar drug molecules.[3] It is therefore not surprising that methods for the preparation of this class of compound have inspired advances in synthetic chemistry.

The intramolecular cyclization of unsaturated acids and unsaturated alcohols provides a powerful and reliable family of methods for the construction of oxygen heterocycles. Cyclization can be triggered by transformation of the alkene into a strongly electrophilic intermediate which is trapped intramolecularly in a stereospecific manner by an oxygen nucleophile. The use of iodonium[4] and seleniranium[5] ions as the electrophile is well established and has been used extensively for the formation of cyclic ethers and lactones. Activation of the alkene with oxygen electrophiles is far less common. Protonated epoxides can be ring-opened stereoselectively with oxygen nucleophiles to furnish cyclic ethers.[6] This chemistry has been extended such that under strongly acidic conditions a one-pot, two-step epoxidation ring-opening sequence is possible using ammonium persulfate and trifluoromethanesulfonic acid in acetic acid at 70 °C.[7] Elaboration of the products from the Sharpless asymmetric dihydroxylation is also possible to prepare both ethers and lactones.[8]

Malonoyl peroxide **1** is an effective reagent for the metal-free *syn*- and *anti*-dioxygenation of alkenes.[9] Reaction of **1** with alkene **2** leads to the dioxonium species **3**. In the presence of water, **3** reacts to deliver the *syn*-diol **4** after basic hydrolysis,[10,11] whereas conducting the reaction in the presence of acetic acid leads to the corresponding *anti*-diol **5** (Scheme 1).[12] We were intrigued to discover if an intermediate such as **7** could be trapped intramolecularly through introduction of a nucleophile, pendant to the alkene architecture, to deliver a series of important heterocyclic structures. Within this paper, we show that oxygen nucleophiles (**6**: X = Y = H and X = Y = O) incorporated within the alkene substrate provide a simple and effective method to deliver γ-lactones, isobenzofuranones, and saturated furans stereoselectively through an oxidative cyclization.

Scheme 1. Alkene Dioxygenation with Malonoyl Peroxides

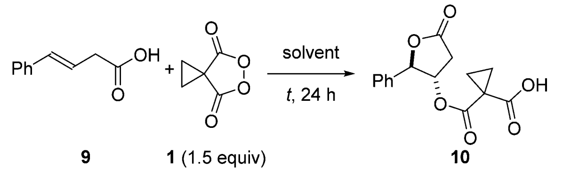


Studies began by investigating the reaction of alkene **9**, which contained a potential carboxylic acid nucleophile, with malonoyl peroxide **1**. A selection of data relevant to the development of the cyclization is collected in Table 1. Reaction of **9** with peroxide **1** (1.5 equiv) at 40 °C in dry dichloromethane gave the γ-lactone **10** with the product from *trans*-addition across the alkene predominating (entry 1; 88% conversion, *cis*/*trans* 1:6). Previous investigations with **1** had

Received: May 1, 2016

DOI: 10.1021/acs.orglett.6b01253
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of γ-Lactone Synthesis[a]



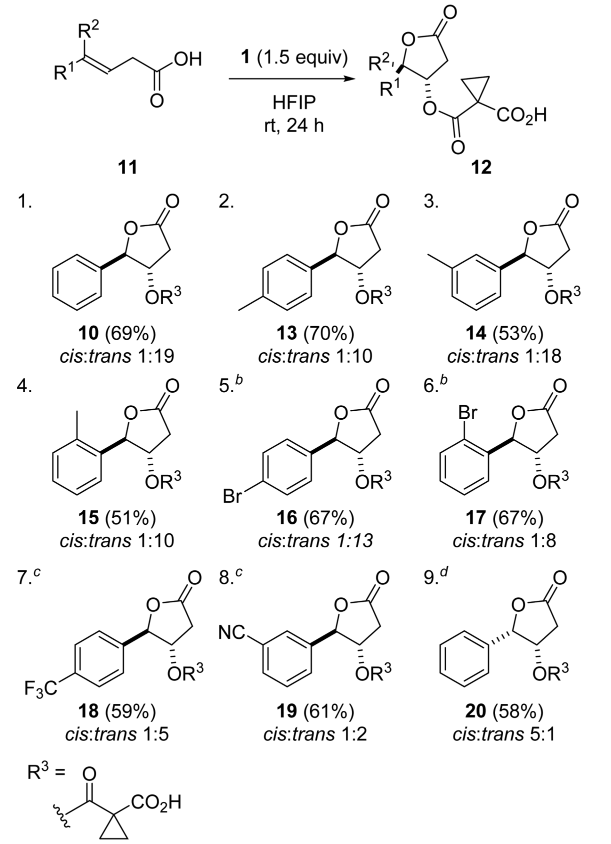
entry	solvent	additive (equiv)	temp (°C)	conv[b] (%)	*cis*/*trans*[b]
1	CH_2Cl_2		40	88	1:6
2	CH_2Cl_2	HFIP (1)	40	98	1:3
3	CH_2Cl_2	HFIP (1)	25	57	1:3
4	CH_2Cl_2	HFIP (2)	40	97	1:3
5	CH_2Cl_2	HFIP (2)	25	61	1:3
6	CH_2Cl_2	HFIP (1)	50	100	1:3
7[c]	HFIP		50	100	1:13
8	**HFIP**		**25**	**100**	**1:19**
9[d]	HFIP		25	92	1:19
10	EtOH		25		
11	^{i}PrOH		25		

[a]All reactions performed in duplicate with *trans*-styrylacetic acid (1 mmol) at 0.5 M concentration for 24 h. [b]Determined by ^{1}H NMR spectroscopy on crude reaction mixture. [c]Solvent dried over 3 Å molecular sieves for 24 h prior to use. See the Supporting Information for full details. [d]Reaction conducted for 15 h.

shown that fluorinated alcohols could accelerate reactions with alkenes.[13,14] This proved to be the case with hexafluoro-2-propanol (HFIP, 1−2 equiv), the reaction proceeding effectively in the presence of this additive (entries 2−6) albeit with lower levels of selectivity (*cis*/*trans* 1:3). Conducting the transformation using dry HFIP as the reaction solvent improved the stereoselectivity of the reaction significantly, with the product from *trans*-addition to the alkene being preferred (entry 7; 100% conversion, *cis*/*trans* 1:13). Lowering the reaction temperature to 25 °C improved this selectivity further (entry 8; 100% conversion, *cis*/*trans* 1:19). Conveniently, it was also established that the HFIP did not require drying prior to use in order to maintain these high levels of selectivity (entries 8 and 9). Use of the non-fluorinated alcohols ethanol (entry 10) and 2-propanol (entry 11) resulted in complex mixtures of products, potentially due to reaction of alcohol and peroxide, suggesting that use of the less nucleophilic fluorinated alcohols was important within this transformation.[15] Based upon this screening, we adopted a standard set of conditions for the reaction of alkenes containing a pendant carboxylic acid functionality of 1.5 equiv of peroxide at room temperature for 24 h in HFIP as the reaction solvent (entry 8).

Having optimized the process we went on to explore some of the substrate scope of this simple oxidative cyclization (Scheme 2). The product from the optimization procedure **10** was prepared in an excellent *cis*/*trans* selectivity of 1:19 and isolated as a single isomer in 69% yield. Substitution of electron-donating substituents at the 2-, 3-, and 4-positions of the aromatic ring was tolerated (entries 2−4; 51−70%), where 2- and 4-substitution led to a decrease in the selectivities observed (*cis*/*trans* 1:10). Electron-withdrawing substituents led to lower reactivity of the alkene. However, simply warming the reaction to 50 °C provided the products with acceptable yields and selectivities (entries 5−8). Altering the stereochemistry of the starting alkene provided access to the diastereomeric product, with the reaction of (*Z*)-4-phenylbut-3-enoic acid leading to **20** (entry 9; 58%, *cis*/*trans* 5:1). Confirmation of the relative stereochemistry of the γ-lactone products came through single-crystal X-ray analysis of compound **16** where the two newly formed C−O bonds bore a *trans* relationship (Figure 1).

Scheme 2. Substrate Scope for γ-Lactone Synthesis[a]



[a]Yields quoted are isolated yields of major isomer. All reactions run in duplicate. Stereoselectivities were determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [b]Reaction conducted at 50 °C for 24 h. [c]Reaction conducted at 50 °C for 72 h. [d](Z)-4-Phenylbut-3-enoic acid used as substrate.

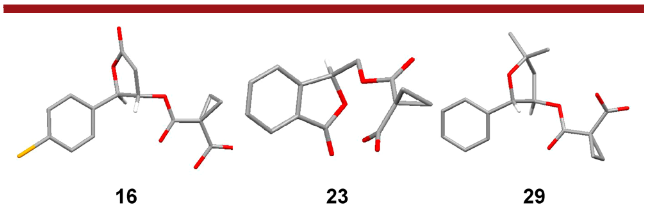
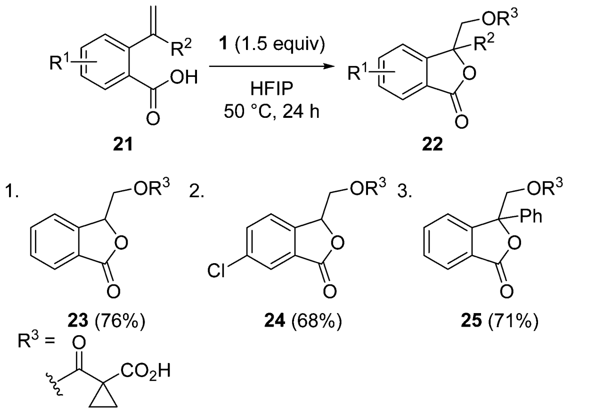


Figure 1. Single-crystal X-ray structures of **16**, **23**, and **29**.

Given the success of the formally 5-*endo-trig* oxidative cyclization triggered by malonoyl peroxide **1**, we briefly examined a formal 5-*exo-trig* cyclization (Scheme 3).[16] Under the standard reaction conditions developed (HFIP, 50 °C, 24 h) reaction of 2-vinylbenzoic acids **21** gave the corresponding isobenzofuranones **23**−**25** in 68−76% isolated yield after purification by column chromatography, with the structure of **23** confirmed through single-crystal X-ray crystallography (Figure 1). Although the scope of this transformation was less well explored, the numerous methods for the preparation of 2-vinylbenzoic acids suggest that this should be an exceedingly

DOI: 10.1021/acs.orglett.6b01253
Org. Lett. XXXX, XXX, XXX−XXX

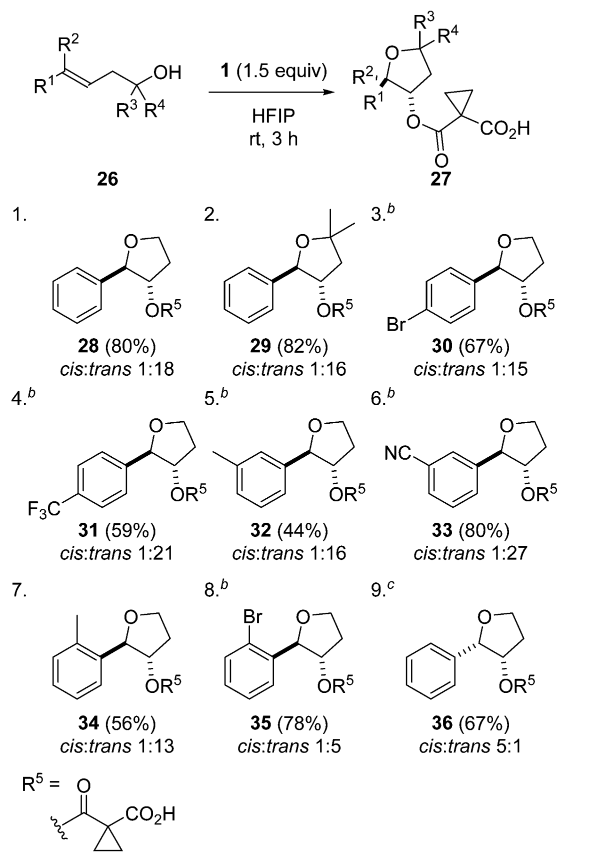
Scheme 3. Isobenzofuranone Synthesis



useful process for the preparation of this important class of biologically relevant scaffold.[17]

Having established that carboxylic acids were suitable nucleophiles for the preparation of γ-lactones and isobenzofuranones, we were intrigued to discover if the method could also be applied to the synthesis of 3-oxygenated tetrahydrofuran rings using homoallylic alcohol substrates. Optimized conditions for this transformation involved reaction of an alkene **26** with 1.5 equiv of peroxide **1** at room temperature in HFIP (Scheme 4).[18] Reaction of (*E*)-4-phenylbut-3-en-1-ol and **1** under the optimized reaction conditions gave **28** in an excellent 80% isolated yield (Scheme 4, entry 1). Introduction of substitution adjacent to the alcohol nucleophile enhanced reactivity through the Thorpe−Ingold[19] effect, providing the product **29** in 82% isolated yield (entry 2; *cis*/*trans* 1:16), the structure of which was confirmed by crystallography (Figure 1). Introduction of substitution on the aromatic ring in the 4- (entries 3 and 4), 3- (entries 5 and 6), and 2-position (entries 7 and 8) was well tolerated, with the product being isolated in good yield and with high levels of stereoselectivity. It is noteworthy that in each case selectivities for the reaction were higher than those obtained when using carboxylic acid nucleophiles (Scheme 2) which is thought to be a reflection on the rates of cyclization of the two classes of substrate. Pleasingly, use of a *Z*-alkene substrate led to the product with the opposite relative stereochemistry in good yield and selectivity (entry 9; 67%, *cis*/*trans* 5:1).

Scheme 4. Cyclic Ether Formation[a]



[a]Yields quoted are isolated yields. All reactions run in duplicate. Stereoselectivities were determined by ^{1}H NMR spectroscopy on crude reaction mixture. [b]Reaction conducted at 50 °C for 20 h. [c](*Z*)-4-Phenylbut-3-en-1-ol used as substrate.

Mechanistically, we believe that the reaction is proceeding as outlined in Figure 2. Nucleophilic attack of the alkene on the weak peroxide bond leads to the zwitterion **38**, which cyclizes to give the dioxonium species **39** as defined for the dihydroxylation pathway.[11] Intramolecular cyclization of the carboxylic acid forms the γ-lactone ring resulting in the *trans* relationship of the two newly formed C−O bonds in the product **41**. This mechanistic pathway is consistent with previous investigations into the reactivity of malonoyl peroxide **1** and also accounts for the important observation that the relative stereochemistry of the product can be altered by changing the geometry of the starting alkene.

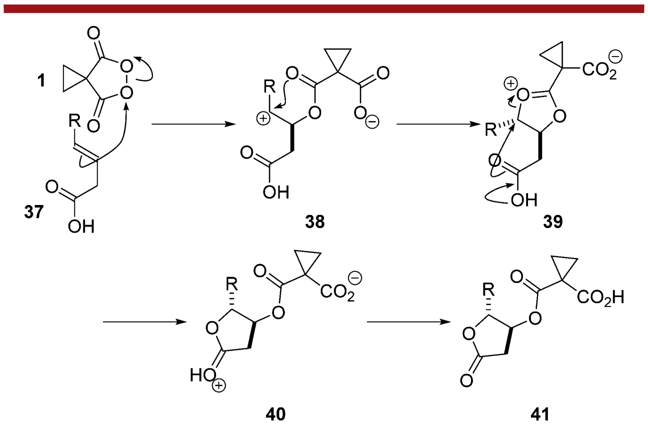
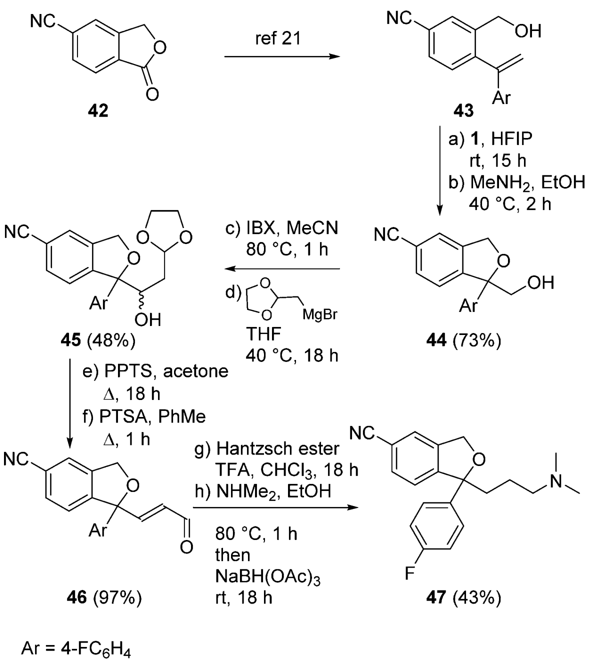


Figure 2. Proposed mechanistic pathway for the oxidative cyclization.

Application of this simple and effective heterocyclization procedure in the synthesis of the antidepressant citalopram **47** is outlined in Scheme 5.[20] The substrate for the key cyclization **43** was prepared according to the excellent method of France,[21] which proved simple, effective, and scalable allowing access to gram quantities of material. Oxidative cyclization of **43** under our standard conditions followed by hydrolysis of the resulting ester with methylamine provided **44** (73%, two steps). Functionalization of **44** proved challenging due to the hindered nature of the primary alcohol. However, oxidation followed by a Grignard addition and a hydrolysis/elimination sequence provided the α,β-unsaturated aldehyde **46** (47%). Organocatalytic conjugate reduction using a Hantzsch ester followed by reductive amination provided **47** (43%, two steps), which was identical to an authentic sample.

DOI: 10.1021/acs.orglett.6b01253
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Synthesis of Citalopram



In summary, we have developed a simple and effective stereoselective oxidative cyclization method for the preparation of γ-lactones, isobenzofuranones, and tetrahydrofurans. The reactions proceed under very mild conditions, forming two new carbon—oxygen σ bonds and further extend the applications of malonoyl peroxides in synthesis.[22] The stereochemical outcome of the reaction can be changed simply by altering the stereochemistry of the starting alkene to deliver either the *trans*- or *cis*-products. Application of this method within a transition-metal-free preparation of citalopram **47** shows the applicability of the transformation to the preparation of important active pharmaceutical agents. Use of this generic process to prepare alternative heterocyclic architectures is ongoing, and we will report on our findings in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01253.

Analytical data, experimental procedures, and NMR spectra for all compounds reported (PDF)

X-ray crystallogrphic data for **16**, **23**, and **29** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nicholas.tomkinson@strath.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank EPSRC, GlaxoSmithKline, and CNPq for financial support and the EPSRC Mass Spectrometry Service, Swansea, for high-resolution spectra.

■ REFERENCES

(1) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567.

(2) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.

(3) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.

(4) Selected reviews: (a) Laya, M. S.; Banerjee, A. K.; Cabrera, E. V. *Curr. Org. Chem.* **2009**, *13*, 720. (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273. (c) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354.

(5) Selected reviews: Tiecco, M.; Testaferri, L.; Bagnoli, L.; Marini, F.; Santi, C.; Temperini, A.; Scarponi, C.; Sternativo, S.; Terlizzi, R.; Tomassini, C. *ARKIVOC* **2006**, *vii*, 186. (b) Petragnani, N.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411. (c) Tiecco, M. In *Topics in Current Chemistry: Organoselenium Chemistry*; Wirth, T., Ed.; Springer: Heidelberg, 2000; pp 7−54.

(6) For example: Dhokte, U. P.; Rao, A. S. *Org. Prep. Proced. Int.* **1992**, *24*, 13.

(7) Tiecco, M.; Testaferri, L.; Tingoli, M. *Tetrahedron* **1993**, *49*, 5351.

(8) For example: (a) Zhang, Y.; Ye, Q.; Wang, X.; She, B.-Q.; Thorson, J. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 11219. (b) Zheng, T.; Narayan, R. S.; Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2005**, *127*, 6946.

(9) Rawling, M. J.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2013**, *11*, 1434.

(10) (a) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem. Soc.* **2010**, *132*, 14409. (b) Jones, K. M.; Tomkinson, N. C. O. *J. Org. Chem.* **2012**, *77*, 921.

(11) Rawling, M. J.; Rowley, J. H.; Campbell, M.; Kennedy, A. R.; Parkinson, J. A.; Tomkinson, N. C. O. *Chem. Sci.* **2014**, *5*, 1777.

(12) Alamillo-Ferrer, C.; Davidson, S. C.; Rawling, M. J.; Theodoulou, N. H.; Campbell, M.; Humphreys, P. G.; Kennedy, A. R.; Tomkinson, N. C. O. *Org. Lett.* **2015**, *17*, 5132.

(13) Picon, S.; Rawling, M.; Campbell, M.; Tomkinson, N. C. O. *Org. Lett.* **2012**, *14*, 6250.

(14) For reviews on the use of fluorinated alcohols in organic synthesis see: (a) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925. (b) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18.

(15) Adam, W.; Rucktäschel, R. *J. Org. Chem.* **1972**, *37*, 4128.

(16) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Alabugin, I. V.; Gilmore, K. *Chem. Commun.* **2013**, *49*, 11246.

(17) Lin, G.; Chan, S. S. K.; Chung, H. S.; Li, S. L. Chemistry and Biological Action of Natural Occurring Phthalides. In *Studies in Natural Products Chemistry* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2005; Vol. *32*; pp 611−669.

(18) See the Supporting Information for details of this optimization.

(19) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080.

(20) Roberts, P. J.; Castaner, J.; Serradell, M. N.; Blancafort, P. *Drugs Future* **1979**, *4*, 407.

(21) Hewitt, J. F. M.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. *Chem. Sci.* **2013**, *4*, 3538.

(22) For recent examples of the use of malonoyl peroxides see: (a) Terent'ev, A. O.; Vil, V. A.; Gorlov, E. S.; Nikishin, G. I.; Pivnitsky, K. K.; Adam, W. *J. Org. Chem.* **2016**, *81*, 810. (b) Dragan, A.; Kubczyk, T. M.; Rowley, J. H.; Sproules, S.; Tomkinson, N. C. O. *Org. Lett.* **2015**, *17*, 2618. (c) Terent'ev, A. O.; Vil, V. A.; Mulina, O. M.; Pivnitsky, K. K.; Nikishin, G. I. *Mendeleev Commun.* **2014**, *24*, 345.

DOI: 10.1021/acs.orglett.6b01253
Org. Lett. XXXX, XXX, XXX−XXX