

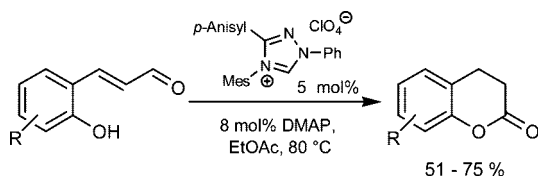
An Efficient Carbene-Catalyzed Access to 3,4-Dihydrocoumarins

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Dihydrocoumarins play an important role as flavor and fragrance compounds and can be prepared efficiently from *o*-hydroxycinnamaldehydes in a mild, atom-economic *N*-heterocyclic carbene-catalyzed redox lactonization. Corresponding coumarins are accessible via a one-pot domino oxidation lactonization procedure in the presence of oxidants.

With respect to an increasing need for efficient and new catalytic synthetic methods, organocatalysis represents a powerful field and has found widespread application over the past decade.^{1,2} The rapidly growing interest in *N*-heterocyclic carbene (NHC)-catalyzed processes might be attributed to the great versatility of these organocatalytic transformations³ but is also associated with the possibilities that arise from the NHC's characteristic inversion of the classical reactivity, i.e., umpolung.⁴

Inspired by Nature's ability to perform nucleophilic acylations within thiamine-dependent enzymes,⁵ NHC catalysis merges two important strategic advantages for efficient synthetic methods.

(1) (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim 2005. (b) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007.

(2) For some recent reviews on organocatalysis, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660. (b) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107* (12), 5413–5883. (c) Special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37* (8), 487–631. (d) Special issue on organocatalysis: *Adv. Synth. Catal.* **2004**, *346* (9/10), 1007–1249. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (f) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.

(3) For recent reviews on NHC-catalyzed reactions, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (b) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007**, *2*, 183–206. (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (d) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506–7510. (e) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541.

(4) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258.

(5) (a) Kluger, R.; Tittman, K. *Chem. Rev.* **2008**, *108*, 1797–1833. (b) Frank, R. A. W.; Leeper, F. J.; Luisi, B. F. *Cell. Mol. Life Sci.* **2007**, *64*, 892–905. (c) Müller, M.; Sprenger, G. A. In *Oxidative Stress and Diseases - Thiamine: Catalytic Mechanisms and Disease States*; Jordan, F., Patel, M. S., Eds.; Marcel Dekker: New York, 2004; pp 77–90.

First, the high chemoselectivity of nucleophilic carbenes can be utilized for protecting group-free synthesis;⁶ moreover, the potential to alter the practice of traditional retrosynthetic analysis is of particular interest.⁷

Synthetic approaches to lactone derivatives that rely on the catalytic generation of activated carboxylates or enols via *N*-heterocyclic carbene-catalyzed reactions of α -functionalized aldehydes^{3d} have witnessed impressive and rapid progress in the past few years.^{8,9} In connection with our work on NHC-mediated umpolung reactions,¹⁰ we considered application of nucleophilic carbenes for a catalytic access to coumarin derivatives. Herein, we disclose that *o*-hydroxycinnamaldehydes cyclize efficiently in the presence of triazolin-5-ylidene carbenes to form dihydrocoumarins or, under oxidative conditions, their unsaturated counterparts in moderate to high yield.

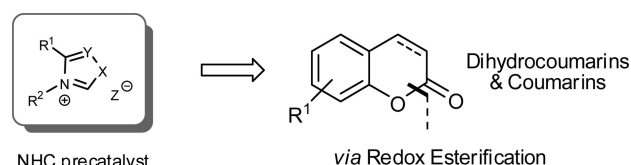


FIGURE 1. Dihydrocoumarins and coumarins by carbene-catalyzed extended umpolung lactonization.

Coumarins and dihydrocoumarins present a large class of natural products that have attracted considerable interest due to their various biological activities.¹¹ Moreover, coumarins play an important role as fluorescent materials and as dyes in laser technology.^{11c,12} Hence, several conventional methods¹³ are available to prepare coumarin derivatives, but most of these

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(7) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1995.

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(9) For a different NHC-catalyzed approach to δ -lactones via ketene-derived zwitterionic enolates, see: Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473–8476.

(10) (a) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (b) Zeitler, K.; Mager, I. *Adv. Synth. Catal.* **2007**, *349*, 1851–1857.

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traditional approaches suffer from harsh reaction conditions and are only rarely catalytic.¹⁴ Dihydrocoumarins (DHC), which play an important role as flavor and fragrance compounds in both food and cosmetics (perfumes), are traditionally prepared by transition-metal-catalyzed hydrogenations of coumarins or, more recently, by biotechnological methods.¹⁵ Interestingly, despite the need for metal-free and environmentally benign routes, only very few organocatalytic examples have been reported.¹⁶ A synthesis of 3-alkylcoumarins using a “non-innocent” imidazolium ionic liquid as (super)stoichiometric mediator was recently described by Bräse and co-workers.⁸ⁱ

We assumed that reaction of easy accessible *o*-hydroxycinnamaldehydes with NHCs would result in the formation of 3,4-dihydrocoumarins via an intramolecular redox lactonization process. For exploratory studies, 2-hydroxycinnamaldehyde **1** was selected as model substrate.¹⁷

TABLE 1. Dihydrocoumarin Synthesis with Different Heterazolium Carbene Precursors

entry ^a	catalyst	mol %	yield ^a (%)
1 ^b	3	10	no conv
2 ^c	4	10	no conv
3	5	5	no conv
4 ^c	6a	10	41
5 ^d	6b	10	42
6 ^c	7a	10	34
7	7b	5	53
8	7c	5	22
9	7d	5	61

^a Yield of isolated product after column chromatography. ^b 20 mol % of KO^tBu was used as base instead of DMAP. ^c 20 mol % of base was used. ^d NEt₃ was used instead of DMAP (reaction was significantly slower with DMAP).

We started our experimental investigations with a survey of different heterazolium precatalysts. Notably, thiazolium **3**, benzimidazolium **4**, and imidazolium **5** salts—all known as potent precatalysts for internal redox reactions¹⁸—failed to give any conversion and proved to be ineffective for the desired ring-closing transformation.¹⁹

(14) For some recent transition-metal-catalyzed reactions, see: (a) Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P. *J. Org. Chem.* **2008**, *73*, 756–759. (b) Kotani, M.; Yamamoto, K.; Oyama, J.; Fujiwara, Y.; Kitamura, T. *Synthesis* **2004**, 1466–1470. (c) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643–3646. (d) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518–4526.

(15) (a) Kuhn, W.; Funk, H.-U.; SenftG. (Haarmann & Reimer GmbH) WO2002018360, 2002. (b) Zhang, Z.; Ma, Y.; Zhao, Y. *Synlett* **2008**, 1091–1095. (c) Häser, K.; Wenk, H. H.; Schwab, W. *J. Agric. Food Chem.* **2006**, *54*, 6236–6240.

(16) (a) For an elegant phosphine-catalyzed exception, see: Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069–3072. For the preparation of furo-coumarins using an enamine approach, see: (b) Rueping, M.; Merino, E.; Sugiono, E. *Adv. Synth. Catal.* **2008**, *350*, 2127–2131. (c) For a concurrent related NHC-catalyzed access, see: Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949–4954.

(17) Substrates could be prepared in good yields via Wittig olefination of the corresponding salicylaldehydes and (formylmethylene)triphenylphosphorane: Bunce, R. A.; Schilling, C. L., III. *Tetrahedron* **1996**, *53*, 9477–9486. For a general procedure, see the Supporting Information.

(18) (a) Thiazolium: Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (b) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127. (c) Benzimidazolium: Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. Imidazolium, see ref 8c,d.

(19) Application of reaction conditions as reported by Scheidt et al. (ref 18c) for a related intermolecular reaction did not yield the desired product.

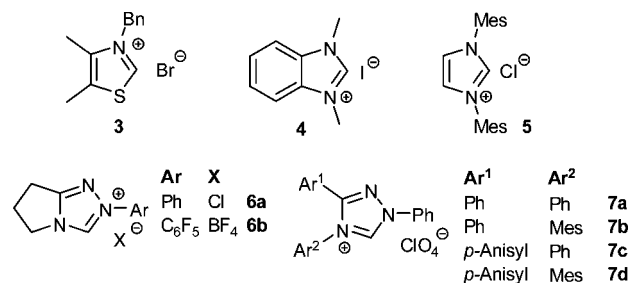


FIGURE 2. Evaluated heterazolium carbene precursors.

Systematic evaluation of a variety of triazolium salts revealed that both the sterically demanding mesityl *N*-substituent (entry 7, catalyst **7b**) and an electron-rich backbone *p*-methoxyphenyl substituent (entry 8, catalyst **7c**) were important to achieve useful reaction rates and yields (entry 9, catalyst **7d**). Moreover, the catalyst loading could be reduced to 5 mol %. The importance of the *N*-aryl substituents of triazolium salts was highlighted by Rovis²⁰ only recently, and Bode et al. reported on the striking differences in reactivity between triazolium and imidazolium precursors for a number of different NHC-catalyzed processes.²¹

TABLE 2. Optimization of Reaction Conditions: Influence of Bases and Solvents

entry ^a	base/cocatalyst (mol %)	solvent	yield ^b (%)
1	K ₃ PO ₄	EtOAc	51
2 ^c	DMAP	EtOAc	61
3 ^c	NEt ₃	EtOAc	63/88 ^d
4 ^c	Pyridine	EtOAc	no conv
5 ^c	Imidazole	EtOAc	15
6 ^c	PPY	EtOAc	56
7	DIPEA	THF	54
8	HOBt/DIPEA	THF	54
9	DMAP	CH ₃ CN	44
10	DMAP	<i>t</i> BuOH	50
11	DMAP	EtOAc _{degassed}	61

^a Reaction conditions: 10 mol % of **7d** at 80 °C unless stated otherwise. ^b Yield of isolated product after column chromatography. ^c 5 mol % of catalyst **7d** was used. ^d Determined by ¹H NMR analysis of crude reaction mixture relative to an internal quantitative standard (octamethylcyclotetrasiloxane). PPY = 4-pyrrolidinopyridine, HOBt = hydroxybenzotriazole, DIPEA = diisopropylethylamine.

With the identification of **7d** as a suitable catalyst, the reaction conditions were further optimized. A variety of inorganic and organic bases were examined (Table 2) and showed comparable promising results for DMAP (entry 2) and triethylamine (entry 3). A screen of possible acylation cocatalysts (entries 4, 5, 6, 8), as described concurrently by Rovis and Bode in the context of relay catalysis for amide bond formation,²² did not show a beneficial effect on further promoting the cyclization reaction.

Remarkably, the reaction can be carried out in various apolar and polar (Table 2, entries 7 and 9) and even protic solvents (entry 10) with comparable yields. The use of dry solvents is

(20) Rovis, T. *Chem. Lett.* **2008**, 37, 2–7.

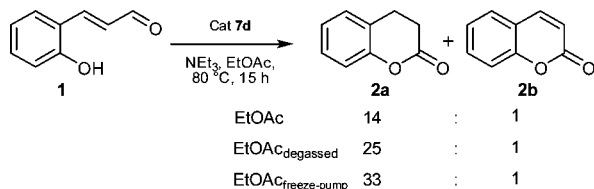
(21) Struble, J. R.; Kaebamrungs, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960.

(22) (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797.

(b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.

not mandatory; hence, single-distilled technical-grade solvents can be used. Interestingly, we noticed the formation of small amounts of the corresponding oxidized coumarin byproduct **2b** (ratio 14:1; Table 2, entry 2), but simple degassing of the solvents by purging the solvent with argon or via a freeze–pump–thaw procedure significantly reduced these oxidized side products (ratio 25:1; Table 2, entry 11, and Scheme 1).

SCHEME 1. Formation of Minor Amounts of Oxidized Coumarin Byproduct (Ratio Determined by ^1H NMR)



A rationale for this oxidative pathway of the reaction is provided by mechanistic considerations (Scheme 2): upon initial nucleophilic attack of the nucleophilic carbene **I** to the aldehyde function, oxidation of the tetrahedral intermediate **II** is facilitated by this generation of a transient “benzylic” alcohol. Rapid oxidation of similar intermediates was observed by Scheidt and co-workers in the presence of oxidizing reagents.^{23,24}

NMR studies of the reaction progress revealed the straightforward, clean transformation of both *E*- and *Z*-isomers of the unsaturated starting material to yield 3,4-dihydrocoumarin **2a** in combination with only minor amounts of the oxidized coumarin product **2b** (ratio >97:3). The yield of the model reaction was determined to be greater than 88% by quantitative NMR analysis of the crude reaction mixture relative to OMS (octamethylcyclotetrasiloxane) as a quantitative internal standard (entry 3).²⁵ Both NMR experiments underline the efficiency of this intramolecular redox lactonization. Due to the high volatility of these fragrance compounds, some product might be sacrificed during the workup and purification procedures resulting in lower isolated yields. Consequently, we turned our attention to the improvement of the procedure for the product isolation, and we were pleased to find an even simplified “column-free” purification method that allows for significantly higher isolated yields (75% vs 63%).

Using these optimized conditions, we examined the scope of the new carbene-catalyzed dihydrocoumarin synthesis. A variety of different substituted *o*-hydroxycinnamaldehydes are suitable substrates for the redox lactonization. The reaction is tolerant to both electron-rich (Table 3, entries 2, 3, 6, 7, and 8) and electron-poor aldehyde derivatives (entries 4 and 5).

Notably, the electron-rich substrates appeared to be more prone to the formation of oxidized coumarin side products. Comparison of the three regioisomeric methoxy-substituted substrates (Table 3, entries 6–8) with respect to the ratio of coumarin generation nicely displays its dependency on electronic

TABLE 3. Scope of the Reaction

entry ^a	product	yield (%) ^b	ratio A/B
1	2a	78	96 : 4
2	9a	60	93 : 7
3	10a	70	91 : 9
4	11a	61	93 : 7
5	12a	62	96 : 4
6	13a	54	97 : 3
7 ^{c, d}	14a	55	88 : 12
8	15a	58	93 : 7
9 ^c	16a	19	>96 : 4

^a Reaction conditions: 5 mol % of **7d** with 8 mol % of DMAP in EtOAc at 80 °C. ^b Yield of isolated product (mixture of A and B) after optimized aqueous workup procedure. ^c 8 mol % of NEt₃ was used. ^d THF was used as solvent.

effects where the *para*-derivative (entry 7) proves to be most easily oxidized. Only the strongly electron-deficient nitro derivative failed to undergo the cyclization with useful yield (entry 9), which might be due to the diminished nucleophilicity of the electron-poor phenolate.

In addition to its robustness with regard to suitable solvents and reaction conditions, one of the strengths of our catalytic protocol is also the atom-economic²⁶ preparation of the desired dihydrocoumarins.

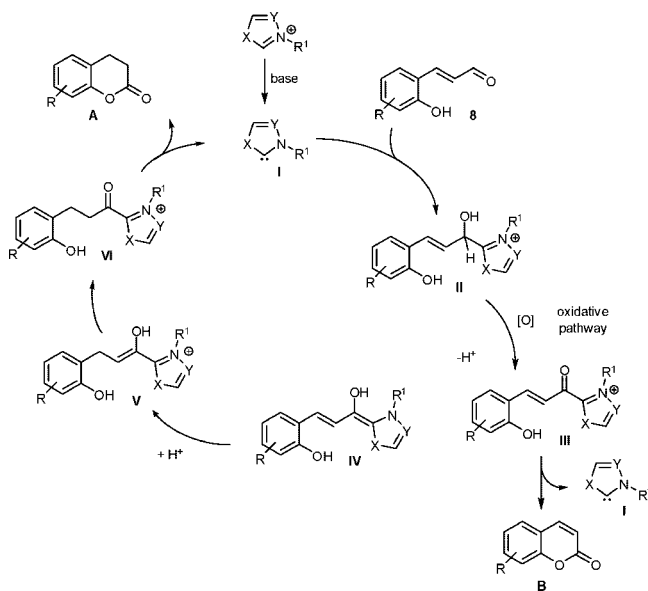
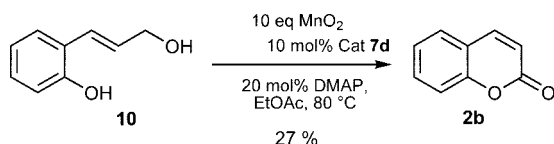
The catalytic cycle is postulated to initiate upon generation of the carbene **I**, which undergoes nucleophilic addition to the *o*-hydroxycinnamaldehyde **8** (scheme 2) forming the tetrahedral intermediate **II**. Deprotonation to furnish homoenolate equivalent **IV** and subsequent generation of the activated acyl azolium intermediate **VI** by tautomerization of the protonated species **V** allows for catalyst turnover by intramolecular acylation to yield the dihydrocoumarin **A**. Under oxidizing conditions, the reaction can proceed via an alternative, oxidative pathway (vide supra and vide infra). Here, the crucial (unsaturated) acyl

(23) (a) For a detailed study of this benzylic activation of aldehyde precursors, refer to: Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331–4334. For a MnO₂ tandem oxidation approach, see: (b) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371–374. (c) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727–8730.

(24) The residual amount of oxidized byproduct (3%) could be assigned to an alternative hydride-transfer mechanism. As described by Scheidt et al. in the context of stereoselective protonation attempts of homoenolates, alternatively, intermediate **III** could be formed in a Cannizzaro-type fashion via intermolecular hydride transfer, but at the cost of the reduction of an equimolar amount of the starting material. Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, 1306–1315.

(25) For details, see the Supporting Information.

(26) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

SCHEME 2. Postulated Mechanism for the Carbene-Catalyzed Synthesis of Dihydrocoumarins and Coumarins

SCHEME 3. Domino Reaction for the Preparation of Coumarins


azolium species **III** that performs the intramolecular acyl transfer to produce coumarin derivatives **B** is generated upon an oxidation event.²⁴

Taking advantage of the functional group tolerance and the distinct chemoselectivity of both an allylic oxidation and the subsequent redox lactonization, coumarins can be accessed in a simple “one-pot” domino reaction²⁷ starting from *o*-hydroxycinnamyl alcohols.

In the presence of an oxidizing agent, such as excess MnO_2 ,^{23b,28,29} the coumarin derivatives can be generated directly from allyl alcohol precursors.³⁰

(27) For excellent reviews on domino reactions, see: (a) Enders, D.; Grondal, C.; Hüttel, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

In summary, we have developed a mild, carbene-catalyzed, atom-economical access to 3,4-dihydrocoumarins that is virtually insensitive to solvent effects. Additionally, performance of the reaction in the presence of oxidizing reagents allows for the formation of coumarin derivatives in a one-pot domino oxidation–lactonization sequence starting from simple *o*-hydroxycinnamyl alcohols.

Experimental Section

General Procedure for the Preparation of Dihydrocoumarins from 2-Hydroxycinnamaldehydes. An oven-dried screw-capped test tube equipped with a magnetic stirring bar was charged with the corresponding 2-hydroxycinnamaldehyde **8** (0.40 mmol, 1 equiv) and was then dissolved in ethyl acetate. After the addition of triazolium salt **7d** (0.02 mmol, 5 mol %), the vial was set under a positive pressure of argon. Finally, the indicated appropriate base (0.032 mmol, 8 mol %) was added, and the reaction mixture was stirred at 80 °C for 15 h (TLC control).

Workup Procedure A. The reaction mixture was concentrated under reduced pressure and purified by column chromatography to yield pure chroman-2-one **A**.³¹

Dihydrocoumarin 2a (Table 2, Entry 3). Purification by flash chromatography (hexanes/EtOAc 7:1) afforded compound **2a** as yellow oil (37 mg, 63%): ^1H NMR (300 MHz, CDCl_3) δ 7.26–7.10 (m, 2H), 7.10–6.95 (m, 2H), 3.01–2.89 (m, 2H), 2.78–2.69 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 168.6, 152.0, 128.3, 128.0, 124.4, 122.6, 117.0, 29.3, 23.7.

Acknowledgment. We gratefully acknowledge generous support by the Fonds der Chemischen Industrie (Liebig fellowship for K. Zeitler) and by the Deutsche Forschungsgemeinschaft (DFG) as part of the priority program Organocatalysis (SPP 1179).

Supporting Information Available: Experimental and characterization data for compounds **2** and **9a** to **16a** and catalyst **7d**, including NMR spectra (^1H and ^{13}C). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(28) (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617. (b) Foot, J. D.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055–1064.

(29) For a recent application of azobenzene as organic oxidizer, see: Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003–4006.

(30) In the presence of bases like DMAP, coumarins can also be formed via an alternative hemiacetal pathway,^{27b} while solely MnO_2 showed only incomplete conversion suggesting a possible promotion of double-bond isomerization and consequent acetalization by nucleophilic catalysts.

(31) For detailed information on the alternative column-free workup procedure B, see the Supporting Information.