NHC-Catalyzed Reaction of Enals with Hydroxy Chalcones: Diastereoselective Synthesis of Functionalized Coumarins
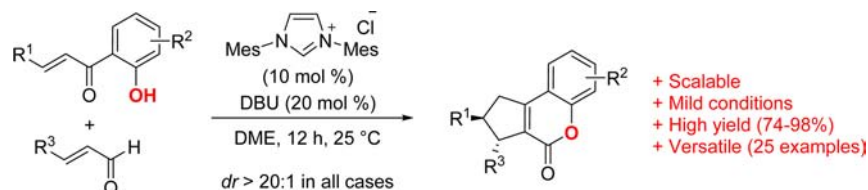
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ABSTRACT

The N-heterocyclic carbene-catalyzed annulation of enals with 2′-hydroxy chalcones afford cyclopentane-fused coumarin derivatives with an excellent level of diastereocontrol. The reaction tolerates a broad range of functional groups; 25 examples are given, and a preliminary mechanistic investigation is provided.

N-Heterocyclic carbene (NHC)-catalyzed umpolung of aldehydes represent an important class of organocatalysis and have established a broad range of applications in synthetic organic chemistry.[1] One of the important modes of action of NHCs is the generation of homoenolate equivalents from α,β-unsaturated aldehydes, which has recently received great attention.[2] The concept of NHC-catalyzed generation of homoenolates from enals was developed independently by Glorius[3] and Bode[4] in 2004, and they intercepted the homoenolate equivalents with

aldehydes leading to the formation of γ-butyrolactones. Consequently, a number of research groups have explored homoenolate chemistry for the synthesis of a variety of cyclic and acyclic compounds.[1b,2,5] In 2006, Nair and co-workers developed an unprecedented NHC-catalyzed homoenolate annulation with chalcones furnishing 1,3,4-trisubstituted cyclopentenes in high yields (Scheme 1, eq 1).[6] Subsequently, the enantioselective cyclopentene-forming reactions utilizing chiral NHCs was developed by Bode and co-workers.[7] Moreover, the enantioselective version of the Nair reaction was uncovered by Scheidt and

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(1) For selected recent reviews on NHC catalysis, see: (a) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 351. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (c) Chiang, P.-C.; Bode, J. W. In *N-Heterocyclic Carbenes*; The Royal Society of Chemistry: London, 2011; pp 399. (d) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (e) Cohen, D. T.; Scheidt, K. A. *Chem. Sci* **2012**, *3*, 53. (f) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (g) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (h) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (i) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686.

(2) (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. For a highlight on homoenolate chemistry, see: (b) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506.

(3) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418.

(4) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131.

(5) For selected recent reports, see: (a) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963. (b) Maji, B.; Ji, L.; Wang, S.; Vedachalam, S.; Ganguly, R.; Liu, X.-W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8276. (c) Zhang, B.; Feng, P.; Sun, L.-H.; Cui, Y.; Ye, S.; Jiao, N. *Chem.—Eur. J.* **2012**, *18*, 9198. (d) Fu, Z.; Sun, H.; Chen, S.; Tiwari, B.; Li, G.; Chi, Y. R. *Chem. Commun.* **2013**, *49*, 261.

(6) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. For related selected reports from the Nair group, see: (b) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E.; Viji, S. *Synthesis* **2007**, 3195. (d) Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun.* **2008**, 747. (e) Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. *Org. Lett.* **2009**, *11*, 5570. (f) Nair, V.; Paul, R. R.; Seethalakshmi, K. C.; Menon, R. S.; Jose, A.; Sinu, C. R. *Tetrahedron Lett.* **2011**, *52*, 5992.

(7) (a) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. For a related homoenolate annulation with unsaturated N-sulfonyl ketimines, see: (b) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418.

Scheme 1. NHC-Catalyzed Reaction of Enals with Chalcones and 2'-Hydroxy Chalcones
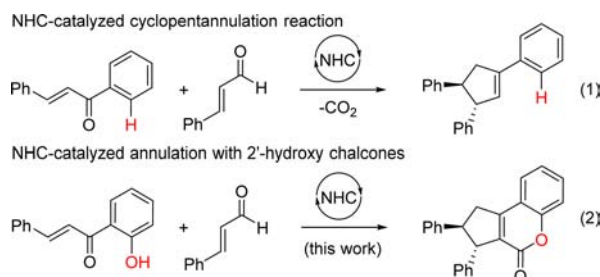

co-workers utilizing the cooperative NHC/Lewis acid strategy.[8] We envisaged that if the reaction is carried out using hydroxy chalcones, there is a possibility of δ-lactonization to furnish functionalized coumarin derivatives (Scheme 1, eq 2). The results of our studies leading to a highly diastereoselective synthesis of cyclopentane-fused coumarins are presented herein. Notably, functionalized coumarin derivatives are important synthetic targets due to their biological properties and some of them are endowed with important fluorescent properties.[9,10]

Our present study commenced with the treatment of 2'-hydroxy chalcone **1a** and cinnamaldehyde **2a** with 10 mol % of imidazolium salt **4** and 20 mol % of 1,8-diazabicyclo-[5.4.0] undec-7-ene (DBU) as the base in THF as the solvent. Delightfully, a facile reaction occurred leading to the formation of the cyclopentane-fused coumarin derivative **3a** in 88% yield with an excellent diastereoselectivity of > 20:1 (based on ^{1}H NMR spectroscopy, Table 1, entry 1). Interestingly, in this process, many selectivity issues arose, and the competing cyclopentene formation as well as the redox esterification was largely suppressed under the present reaction conditions.[11,12] Remarkably, in contrast to the NHC derived from **4**, other common NHCs derived from precursors **5−8** are far less effective (entries 2−6). Other bases such as NaOAc, KOt-Bu, NEt₃, and dimethylamino pyridine (DMAP) furnished the desired product in

Table 1. Optimization of the Reaction Conditions[a]

entry	variation of the standard conditions[a]	dr[b]	yield of 3a[c] (%)
1	None	>20:1	88 (86)
2	**5** instead of **4**	nd	<1
3	**6** instead of **4**	nd	<1
4	**7a** instead of **4**	nd	<1
5	**7b** instead of **4**	>20:1	67
6	**8** instead of **4**	nd	<1
7	NaOAc instead of DBU	>20:1	46
8	KO-t-Bu instead of DBU	>20:1	86
9	Et₃N instead of DBU	>20:1	10
10	DMAP instead of DBU	>20:1	6
11	1,4-dioxane instead of THF	>20:1	89
12	toluene instead of THF	>20:1	49
13	CH₂Cl₂ instead of THF	>20:1	50
14	DME instead of THF	>20:1	99 (98)[d]
15	7 mol % of **4**, 14 mol % of DBU in DME	>20:1	72

[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), NHC·HX (10 mol %), DBU (20 mol %), THF (1.0 mL), 25 °C and 24 h. [b] Determined by ^{1}H NMR analysis of crude products. [c] The yields were determined by ^{1}H NMR analysis of crude products using CH₂Br₂ as the internal standard, isolated yield in 1.0 mmol scale in parentheses. [d] The reaction was completed in 12 h.
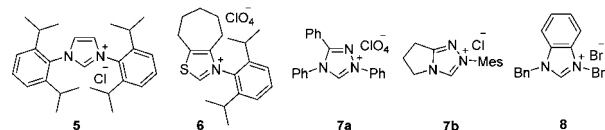
reduced yields, but maintaining the diastereoselectivity (entries 7−10). Among the various solvents screened, 1,4-dioxane resulted in comparable result (entry 11), whereas the reaction carried out in other solvents such as toluene and CH₂Cl₂ resulted in inferior yields of **3a** (entries 12 and 13). Gratifyingly, the reaction carried out in dimethoxy ethane (DME) afforded the *trans*-diastereomer **3a** in 98% yield with a selectivity of > 20:1 (entry 14).[13,14] Furthermore, lowering the amount of catalyst **4** below 10 mol % resulted in reduced yield of the product (entry 15).[15]

With the optimized reaction conditions in hand, we then examined the scope of this unique homoenolate annulation reaction (Scheme 2). The parent system worked well, and a

(8) (a) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345. See also: (b) Wadamoto, M.; Phillips, E, M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098.

(9) For selected reports, see: (a) Riveiro, M. E.; Kimpe, N. D.; Moglioni, A.; Vazquez, R.; Monczor, Shayo, C.; Davio, C. *Curr. Med. Chem.* **2010**, *17*, 1325. (b) Garazd, M. M.; Garazd, Y. L.; Shilin, S. V.; Panteleimonova, T. N.; Khilya, V. P. *Chem. Nat. Compd.* **2002**, *38*, 230. (c) Liu, X.; Cole, J. M.; Waddell, P. G.; Lin, T.-C.; Radia, J.; Zeidler, A. *J. Phys. Chem. A* **2012**, *116*, 727. (d) Jung, H. S.; Kwon, P. S.; Lee, J. W.; Kim, J. I.; Hong, C. S.; Kim, J. W.; Yan, S.; Lee, J. Y.; Lee, J. H.; Joo, T.; Kim, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 2008.

(10) For selected reports on NHC-catalyzed methods for synthesis of coumarins, see: (a) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Andrew, W. O.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105. (b) Nair, V.; Sinu, C. R.; Rejithamol, R.; Seethalakshmi, K. C.; Suresh, E. *Org. Biomol. Chem.* **2011**, *9*, 5511. (c) Ding, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949. (d) Sinu, C. R.; Padmaja, D. V. M; Ranjini, U. P.; Seetha Lakshmi, K. C.; Suresh, E.; Nair, V. *Org. Lett.* **2013**, *15*, 68.

(11) CCDC-918307 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) Chan, A.; Scheidt, K. A. *Org. Lett.* **2004**, *7*, 905.

(13) To get insight into the reversibility of the reaction and to test the stability of the product **3a** under the reaction conditions, **3a** was treated with **4** and DBU. The reaction returned **3a** quantitatively, demonstrating that the product is stable under the reaction conditions and that the reaction is irreversible.

(14) It is noteworthy that the same yield was obtained from a 10.0 mmol scale reaction.

(15) See the Supporting Information for details.

variety of electron-donating and -withdrawing groups at the 4-position of the aromatic ring at β-position of **1** are well tolerated leading to the formation of cyclopentane-fused coumarin derivatives in 89−98% yields and excellent diastereoselectivity of > 20:1 in all cases (**3a−3e**). Moreover, substitution at 3-position and 2-position of β-aromatic ring resulted in a smooth conversion to the product (**3f−3h**). Additionally, disubstitution and the naphthyl moiety at β-position of **1** afforded the desired product in excellent yield (**3i,j**).

Scheme 2. Substrate Scope for the Synthesis of Functionalized Coumarins. Variation of the 2′-Hydroxy Chalcones Moiety
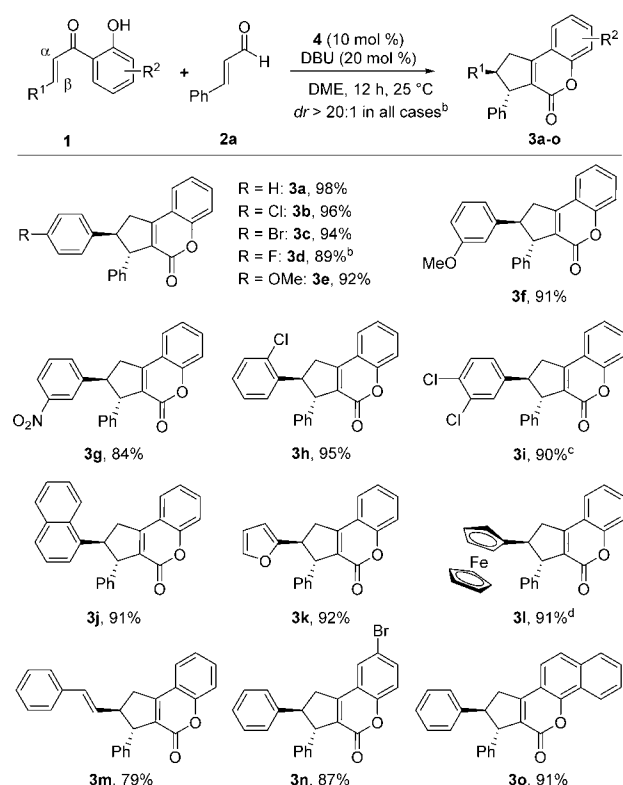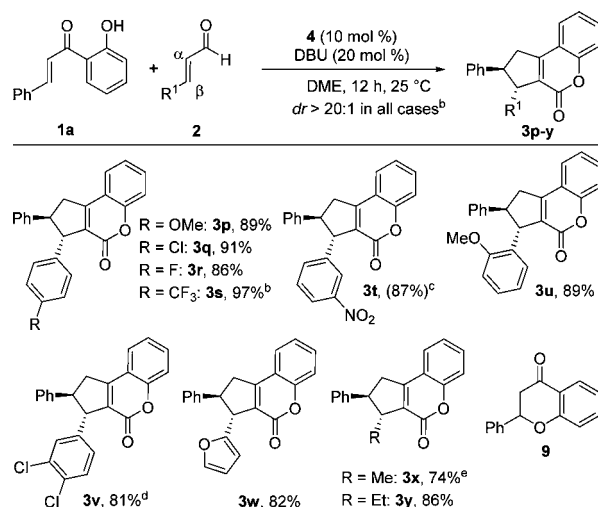

[a] General reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **4** (10.0 mol %), DBU (20.0 mol %) in DME (4.0 mL) at 25 °C for 12 h. [b] Determined by ^{1}H NMR analysis of crude products. [c] Reaction run on 0.25 mmol scale.

Interestingly, challenging substituents such as heteroaromatic group and ferrocenyl moiety at β-position also furnished excellent yields of the tricyclic compound, further expanding the scope of this homoenolate annulation reaction (**3k,l**). Furthermore, it was observed that additional conjugation at β-position has no effect in the course of the reaction and the corresponding product **3m** was formed in 79% yield. Finally, the substitution at the benzoyl moiety of **1** was well tolerated leading to the formation of the desired products (**3n,o**) in good yields.

Next, we examined the effect of varying the substituents on the α,β-unsaturated aldehyde **2** (Scheme 3). Various electronically different substituents at the 4-position of the aromatic ring at β-position of **2** are well tolerated affording

the product in high yields (**3p−s**) maintaining the diastereoselectivity. Additionally, substitution at 3-position and 2-position as well as disubstitution resulted in smooth conversion to the desired product (**3t−v**). Interestingly, heterocyclic α,β-unsaturated aldehyde as well as alkyl substituents at the β-position of **2** resulted in the formation of the cyclopentane-fused coumarin derivatives thus demonstrating the versatility of the present reaction (**3w−y**). It may be noted that in the reaction with crotonaldehyde, the 2-phenylchroman-4-one **9** was also isolated in 22% yield.

Scheme 3. Variation of the Enal Moiety

[a] General reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **4** (10.0 mol %), DBU (20.0 mol %) in DME (4.0 mL) at 25 °C for 12 h. [b] Determined by ^{1}H NMR analysis of crude products. [c] Reaction run on 0.50 mmol scale. [d] Reaction run on 0.25 mmol scale. [e] 2-Phenylchroman-4-one **9** was isolated in 22% yield.

The mechanistic rationale for this homoenolate annulation reaction may be advanced as follows (Scheme 4). The reaction proceeds via the generation of homoenolate equivalent **A** from the enal and the NHC. The conjugate addition of **A** to the 2′-hydroxy chalcone **1** followed by the proton transfer generates the enolate **B**, which undergoes intramolecular aldol reaction generating intermediate **C**. The intermediate **C** instead of high energy β-lactonization[6a] may undergo a proton transfer to afford phenoxide **D** followed by δ-lactonization and dehydration to furnish the coumarin derivative **3**.

To gain mechanistic insight on this reaction, a series of experiments were carried out. When the −OH group at 2′-position was protected (substrate **10**), the reaction did not work at all under the optimized conditions. Interestingly, however, when the reaction was carried out at 45 °C, the cyclopentene derivative **11** was formed in 55% yield (Scheme 5, eq 3). No detectable formation of **3a** was observed and this indicates the importance of free −OH group at 2′-position for the δ-lactonization leading to **3a**. Moreover, to evaluate the role of an additional proton source in the proton transfer events, the reaction was
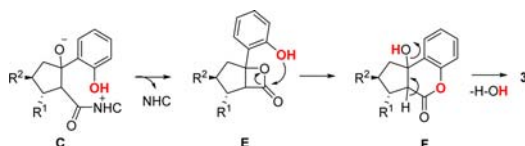
Scheme 4. Plausible Reaction Mechanism
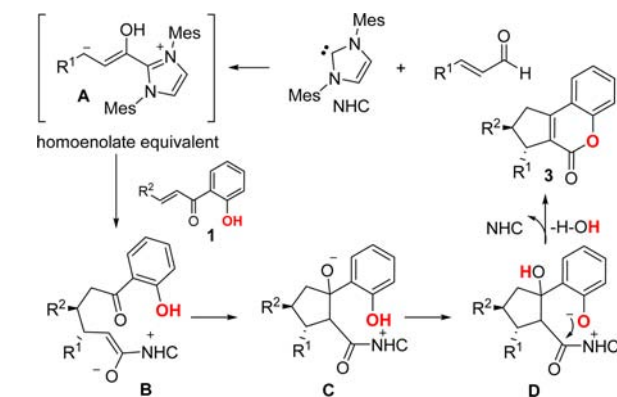
carried out with stoichiometric amounts of phenol. Gratifyingly, even in the presence of additional proton source, the desired product **3a** was formed in 52% yield and no detectable amounts of the redox esterification product **12** was observed (Scheme 5, eq 4).[12,16] This result tends to indicate that the proton transfer events are intramolecular (Scheme 4) and the nucleophilic attack of homoenolate equivalent **A** onto **1** is more important than its protonation (leading to redox-esterification product).[17]

To get insight into the kinetics of the reaction as well as to investigate the ease of δ-lactonization over β-lactonization, competition experiments were carried out. Intermolecular competition experiments carried out between 2′-hydroxy chalcone **1a** and chalcone **1a′** revealed that **1a** reacted ∼75 times faster than **1a′** indicating the preferential formation of **3a** (Scheme 5, eq 5). The low rate of formation of **3a′** may be due to the fact that this reaction proceeds via the high energy β-lactone intermediate. These observations indicate that the thermodynamically

Scheme 5. Mechanistic Experiments

more feasible δ-lactonization proceeds over the high energy β-lactonization.[18,19] Alternatively, the H-bonding interaction in **1** can also enhance its reactivity with homoenolate equivalent **A**.

In conclusion, we have developed a metal-free and scalable NHC-organocatalyzed homoenolate annulation with hydroxy chalcones to furnish functionalized coumarin derivatives in good to excellent yields. The key to success of the present reaction is the ease of δ-lactonization over the β-lactonization. Moreover, broad substrate scope, high yields of products, and mild reaction conditions are the notable features of the present reaction. Further studies on developing an enantioselective version of this reaction and the related NHC-organocatalyzed annulation reactions are ongoing in our laboratory.

Supporting Information Available. Detailed experimental procedures, single-crystal X-ray data of **3a**, mechanistic experiments, and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) When the reaction was performed in methanol, intramolecular cyclization of **1a** leading to 2-phenyl chroman-4-one **9** was observed. Interestingly, just stirring **1a** in methanol in the presence of 20 mol % DBU for 12 h afforded **9** in 62% yield indicating that this cyclization is catalyzed by base only. Moreover, in DME the blank reaction afforded 20% of **9**.
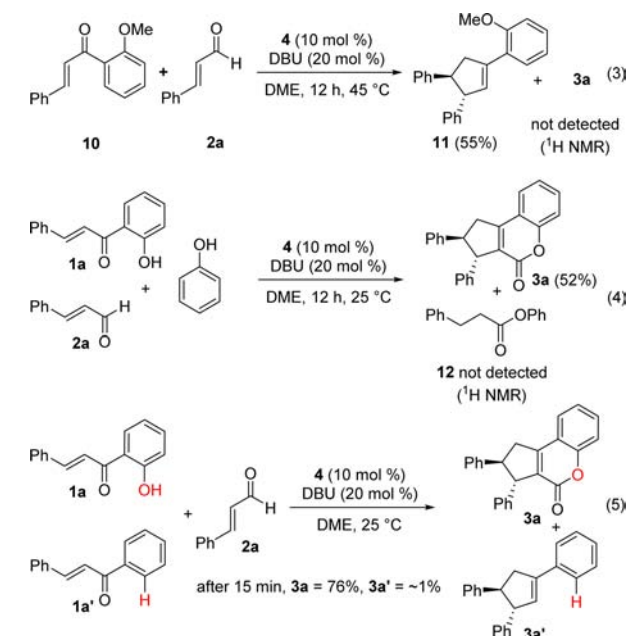
(17) For a related report on interception of homoenolates with chalcones in methanol, see: Nair, V.; Babu, B. P.; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507.

(18) Notably, the formation of functionalized coumarin **3** can also be rationalized by invoking the β-lactone intermediate **E** generated from cyclopentane intermediate **C** (Scheme 4) followed by the intramolecular opening of the β-lactone **E** to generate δ-lactone **F** and subsequent elimination of water. However, based on the apparent preference of δ-lactonization over β-lactonization as revealed by the competition experiments, this possibility can be ruled out at this point. For a related report, see: Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677

(19) Monitoring the kinetics of the reaction revealed that **3a** was formed in 11% yield after 15 min and 25% after 30 min under optimized conditions. For details, see the Supporting Information.