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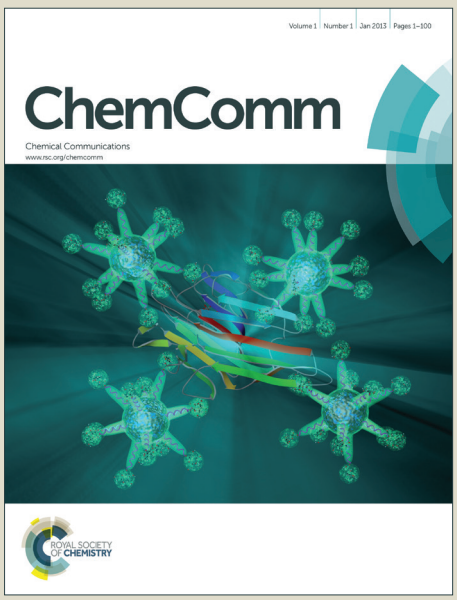

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N-Heterocyclic carbene-catalyzed enantioselective synthesis of functionalized cyclopentenes via α,β-unsaturated acyl azoliums†

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Highly enantioselective NHC-organocatalyzed synthesis of functionalized cyclopentenes proceeding via α,β-unsaturated acyl azolium intermediates is reported. The organocascade reaction of modified enals with malonic ester derivatives having a γ-benzoyl group involves the Michael-intramolecular aldol-β-lactonization-decarboxylation sequence to deliver cyclopentenes in good yields and excellent ee values.

Functionalized cyclopentenes are ubiquitous in various natural products and biologically relevant molecules. For instance, the natural product laurokamurene A is a rearranged aromatic sesquiterpene isolated from the Chinese marine organism *Laurencia*,[1] and sequosempervirin A is a spirocyclic cyclopentene natural product isolated from the branches and leaves of *Sequoia sempervirens* (Figure 1).[2] Moreover, vibralactone is a cyclopentene-fused β-lactone type metabolite, which is a pancreatic lipase inhibitor.[3] In addition, a wide variety of cyclopentenes serve as an intermediate in the total synthesis of natural and unnatural products.[4] Due to the widespread application of chiral cyclopentenes, development of enantioselective and flexible synthetic routes to these molecules is of paramount importance in organic synthesis.

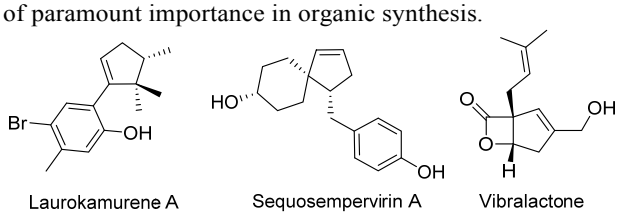
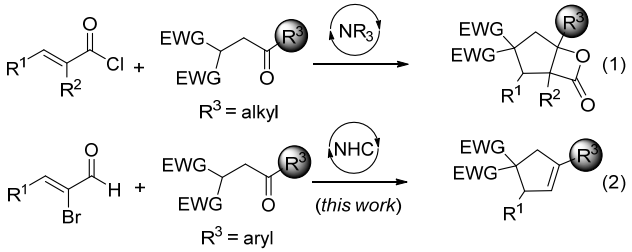


Figure 1. Selected biologically active cyclopentene natural products

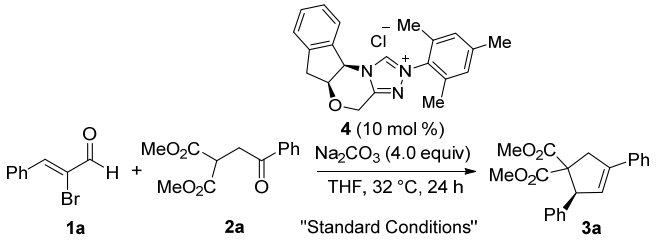
A highly efficient synthesis of cyclopentenes by the N-heterocyclic carbene (NHC)-catalyzed[5] annulation of enals with chalcones proceeding via the homoenolate equivalents[6] was uncovered by Nair and co-workers in 2006.[7,8] Moreover, highly enantioselective cyclopentannulation reaction under chiral NHC-catalysis was demonstrated by Bode and co-workers,[9] and a cooperative NHC/Lewis acid strategy was developed by Scheidt and co-workers for the synthesis of chiral cyclopentenes.[10] Additionally, Chi and co-workers realized the enantioselective synthesis of cyclopentenes by the NHC-catalyzed activation of saturated esters.[11] Recently, Romo and co-workers reported an elegant synthesis of cyclopentane-fused β-lactones by the isothiourea-catalyzed reaction of unsaturated acid chlorides with malonic ester bearing a β-oxyalkyl substituent proceeding via the chiral α,β-unsaturated acylammonium intermediates (eq 1).[12-14] Herein, we demonstrate the NHC-catalyzed enantioselective cascade reaction for the synthesis of functionalized cyclopentenes by the reaction of modified enals with malonic esters bearing a γ-aroyl group (eq 2).[15] The highly selective organocascade reaction proceeds via the chiral α,β-unsaturated acyl azolium intermediates[16-18] and takes place through a Michael-intramolecular aldol-β-lactonization-decarboxylation sequence. Notably, the reaction of α-unsubstituted β-diketones/β-ketoesters with α,β-unsaturated acyl azoliums under NHC-catalysis providing dihydropyranone derivatives was developed by the groups of Studer,[17m] Xiao,[17g, 17n] Ye,[18i] and Yao.[18h]



In a pilot experiment, treatment of α-bromocinnamaldehyde (**1a**) with the malonate **2a** in the presence of the triazolium salt **4**[19] and excess of Na_2CO_3 in THF resulted in the formation of the trisubstituted cyclopentene derivative **3a** in 52% yield and an excellent enantiomeric excess of 99% (Table 1, entry 1). Under this reaction conditions, the cyclopentane-fused β-

lactone derivative was not observed.[12] The yield of the product **3a** was increased to 65% (maintaining the 99% ee) upon increasing the reaction time to 60 h, whereas the reaction furnished only traces of **3a** when carried out at 60 °C (entries 2,3). Screening of different bases furnished the product in reduced yield and selectivity (entries 4-8). Among the various solvents screened, 1,4-dioxane and toluene returned inferior results (entry 9,10). Interestingly, when the reaction was carried out in DME, the functionalized cyclopentene **3a** was formed in an improved yield of 54% maintaining the 99% ee (entry 11). Further studies using DME as solvent showed that **3a** was formed in an improved yield of 75% maintaining the excellent ee value of 99% upon increasing the reaction time to 72 h (entry 12).[20]

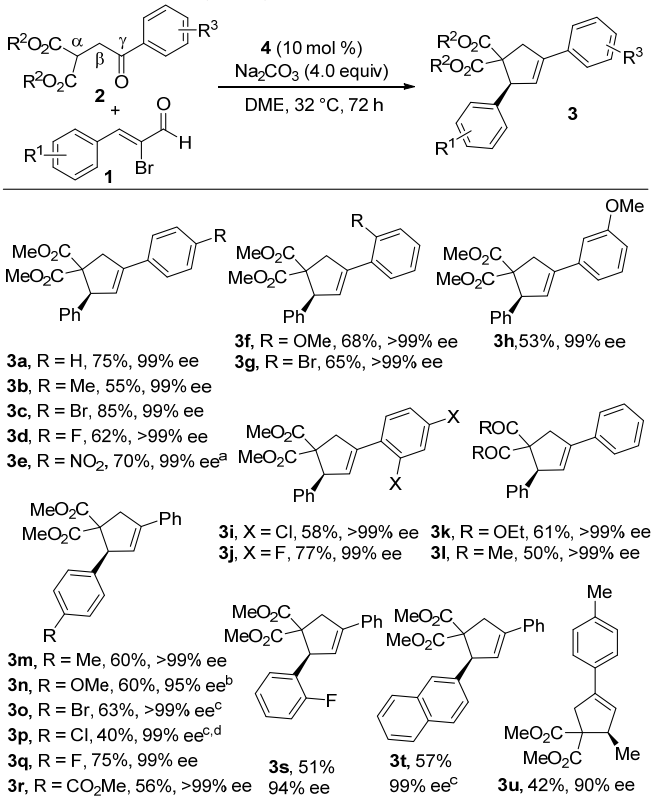
Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield **3a** (%)[b]	ee **3a** (%)[c]
1	none	52	99
2	reaction time 60 h instead of 24 h	65	99
3	reaction run at 60 °C instead of 32 °C	<5	n.d.
4	Cs_2CO_3 instead of Na_2CO_3	48	91
5	KO*t*-Bu instead of Na_2CO_3	<5	n.d.
6	DBU instead of Na_2CO_3	<5	n.d.
7	DABCO instead of Na_2CO_3	30	93
8	Et_3N instead of Na_2CO_3	10	86
9	1,4-dioxane instead of THF	<5	n.d.
10	toluene instead of THF	10	99
11	DME instead of THF	54	99
12	*DME instead of THF, run for 72 h*	*75*	*99*

[a] Standard conditions: **1a** (0.38 mmol), **2a** (0.25 mmol), **4** (10 mol %), Na_2CO_3 (4.0 equiv), THF (3.0 mL), 32 °C and 24 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on a chiral column.

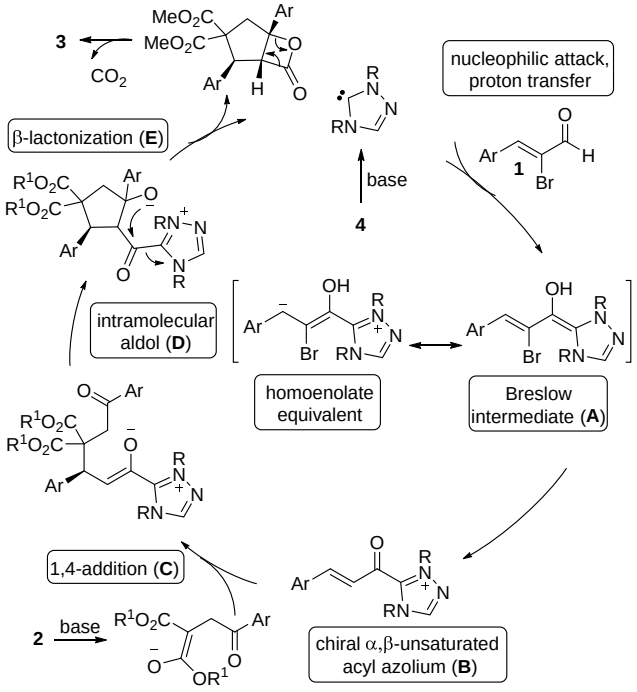
With the reaction condition in hand, we then evaluated the substrate scope of this reaction (Scheme 1). A series of malonic ester derivatives with electron releasing and -withdrawing groups at the 4-position of the benzene ring of γ-benzoyl moiety are well-tolerated, and the corresponding chiral cyclopentene derivatives are isolated in moderate to good yields and excellent ee of 99% in all cases (**3a-3e**). The structure and stereochemistry of **3c** was confirmed by single-crystal X-ray analysis.[22] Moreover, the malonic ester derivatives with substitution at the 2 and 3-position of γ-benzoyl functionality underwent smooth cyclopentannulation reaction leading to the formation of the desired product in good yields and excellent ee values (**3f-3h**). In addition, dihalogen substitution on the benzene ring of **2** also afforded the chiral cyclopentene derivative in moderate to good yield and high ee values (**3i-3j**). Furthermore, the alkoxy part on the malonic ester **2** can be easily varied, and the acetyl acetone-derived triketone can also be used as a nucleophile for addition to α,β-unsaturated acyl azoliums thus demonstrating the versatile nature of this annulation reaction (**3k-3l**).



Scheme 1. Substrate scope for the asymmetric synthesis of functionalized cyclopentenes. General reaction conditions: **1** (0.75 mmol), **2** (0.50 mmol), **4** (10 mol %), Na_2CO_3 (4.0 equiv.), DME (6.0 mL) at 32 °C for 72 h. Given are isolated yields and the ee values were determined by HPLC analysis on a chiral column. [a] The reaction mixture stirred for 120 h. [b] The reaction was carried out in THF using Cs_2CO_3 (4.0 equiv) as base. [c] The reaction was run on 0.25 mmol scale. [d] The reaction was performed in THF.

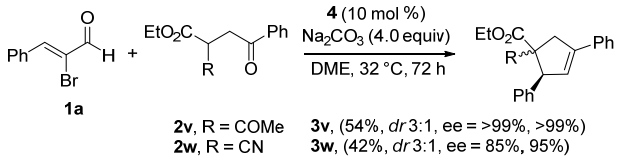
Then we studied the scope and limitation of the present methodology with 2-bromoenals. A number of 2-bromo enals with electron releasing and -withdrawing substituents at the 4-position of aryl ring underwent efficient annulation reaction affording the desired products in moderate to good yields and excellent ee values of 99% in all cases (**3m-3r**). In addition, substitution at the 2-position of the β-aryl ring as well as the 2-naphthyl substitution at the β-position are tolerated well and the corresponding products are formed in moderate yields and high ee values further expanding the scope of this reaction (**3s-3t**). It is noteworthy that the present method is not limited to aromatic 2-bromoenals. Interestingly, the (*Z*)-2-bromobut-2-enal can also be used as the aldehyde coupling partner thereby fixing the methyl group at the newly formed chiral centre, furnishing **3u** in 42% yield and 90% ee.

A tentative mechanism for this NHC-catalyzed cyclopentannulation reaction is shown in Scheme 2. The chiral NHC generated from **4** under basic condition undergo nucleophilic attack on 2-bromoenal **1** followed by a proton transfer generates the nucleophilic Breslow intermediate (**A**).[23] The intermediate **A** can also represented as a zwitterionic homoenolate equivalent. The intermediate **A** undergoes quick debromination to generate **B**, which is the key chiral α,β-unsaturated acyl azolium intermediate. Nucleophilic addition of anion generated from **2** onto intermediate **B** from below the plane containing the triazolium moiety results in the formation of the NHC-bound enolate intermediate **C**, which can undergo a highly selective intramolecular aldol reaction leading to the cyclopentane intermediate **D**. β-Lactonization of intermediate **D** followed by the release of carbene furnishes the cyclopentane-fused β-lactone E. Rapid decarboxylation of **E** results in the formation of the desired product **3**.[24] The installation of the styrenic double bond in **3** may be a reason for the immediate decarboxylation of **E**.[12] Notably, related rapid decarboxylation reactions leading to functionalized cyclopentenes were observed by groups of Nair,[7] Bode,[9] and Scheidt.[10]



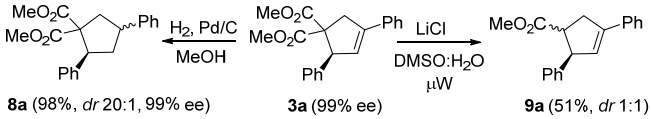
Scheme 2. Proposed Mechanism of the Reaction

We also studied the scope of the reaction using differently substituted nucleophilic component. When the ethyl acetoacetate-derived nucleophile **2v** was subjected to the reaction conditions, the reactions afforded the separable mixture of diastereomers **3v** in the ratio 3:1 and in 54% yield (Scheme 3). Interestingly, both the enantiomers are formed in excellent ee of 99%. Moreover, the cyanoester-derived nucleophile **2w** also afforded moderate yield of the separable mixture of cyclopentene derivatives **3w**, however, the major isomer was obtained in 85% ee only.



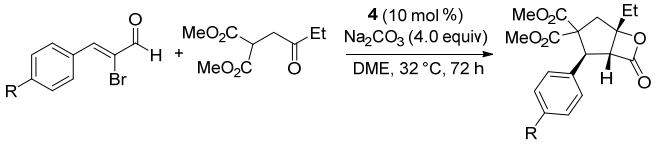
Scheme 3. Reactions Using Differently Substituted Nucleophiles

The functionalized cyclopentene **3a** can be converted into the trisubstituted cyclopentane derivative **8a** by a diastereoselective hydrogenation reaction furnishing the product **8a** in 98% yield and 99% ee (Scheme 4). Moreover, selective hydrolysis of **3a** using LiCl followed by decarboxylation under microwave conditions afforded the monoester **9a** in 51% yield and in 1:1 ratio.



Scheme 4. Synthetic Transformations

Interestingly, treatment of 2-bromoenals with malonate derivatives possessing an aliphatic keto group (**10**) under the chiral NHC-catalyzed conditions, the reaction resulted in the highly diastereoselective and enantioselective synthesis of cyclopentane-fused β-lactones **11** (Scheme 5). Thus, the parent 2-bromoenal **1a** upon reaction with **10** afforded the β-lactone **11a** in 46% yield, >20:1 dr, and 99% ee.[25] Similarly the substituted 2-bromoenal **1r** furnished the corresponding β-lactone **11r** in 72% yield, >20:1 dr, and 99% ee. The structure and stereochemistry of compound **11r** was confirmed by single-crystal X-ray analysis.[22] The highly selective formation of cyclopentane-fused β-lactone also sheds light on the proposed mechanism of the cyclopentene forming reaction (Scheme 2).



Scheme 5. Synthesis of Cyclopentane-fused β–lactones

In conclusion, we have developed the NHC-catalyzed enantioselective synthesis of cyclopentene derivatives by the reaction of modified enals with malonic ester-derived nucleophiles. Given the ubiquity of functionalized cyclopentenes, the protocol presented herein is a practical method to synthesize these molecules.

Generous financial support from CSIR-New Delhi (as part of 12th Five-Year plan program under ORIGIN-CSC0108), and CSIR-OSDD (HCP0001) is greatly acknowledged. S.M thanks UGC, and S.R.Y and A.P. thank CSIR-New Delhi for the research fellowship. We thank Mr. Anup Bhunia for helpful discussion, Dr. P. R. Rajamohanan for the excellent NMR support and Ms. B. Santhakumari for the HRMS data.

Notes and references

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† Details on experimental procedures, characterization data of all compounds, and single crystal X-ray data of compounds **3c**, and **11r**. See DOI: 10.1039/b000000x/

1 (*a*) S.-C. Mao, and Y.-W. Guo, *J. Nat. Prod.*, 2006, **69**, 1209; (*b*) A. Srikrishna, I. A. Khan, R. R. Babu, and A. Sajjanshetty, *Tetrahedron*, 2007, **63**, 12616.

2 (*a*) Y.-M. Zhang, N.-H. Tan, M. He, Y. Lu, S.-Q. Shang, and Q.-T. Zheng, *Tetrahedron Lett*., 2004, **45**, 4319; (*b*) Y. Ito, K. Takahashi, H. Nagase, and T. Honda, *Org. Lett*., 2011, **13**, 4640.

3 (*a*) D.-Z. Liu, F.Wang, T.-G. Liao, J.-G. Tang,W. Steglich, H.-J. Zhu, and J.-K. Liu, *Org. Lett*., 2006, **8**, 5749; (*b*) Q. Zhou, and B. B. Snider, *Org. Lett*., 2008, **10**, 1401.

4 T. Hudlicky, and J. W. Reed, *Angew. Chem. Int. Ed*., 2010, **49**, 4864.

5 For recent reviews on NHC catalysis: (*a*) M. N. Hopkinson, C. Richter, M. Schedler, and F. Glorius, *Nature*, 2014, **510**, 485; (*b*) J. Mahatthananchai, and J.W. Bode, *Acc. Chem. Res.*, 2014, **47**, 696; (*c*) S. J. Ryan, L. Candish, and D.W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906; (*d*) A. Grossmann, and D. Enders, *Angew. Chem. Int. Ed.*, 2012, **51**, 314; (*e*) X. Bugaut, and F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 351; (*f*) J. Izquierdo, G. E. Hutson, D. T. Cohen, and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2012, **51**, 11686; (*g*) D. T. Cohen, and K. A. Scheidt, *Chem. Sci.*, 2012, **3**, 53; (*h*) H. U. Vora, P. Wheeler, and T. Rovis, *Adv. Synth. Catal.*, 2012, **354**, 1617;

6 For reviews, see: (*a*) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, and V. Sreekumar, *Chem. Soc. Rev.*, 2011, **40**, 5336; (*b*) V. Nair, S. Vellalath, and B. P. Babu, *Chem. Soc. Rev*., 2008, **37**, 2691; (*c*) K. Zeitler, *Angew. Chem. Int. Ed.*, 2005, **44**, 7506.

7 V. Nair, S. Vellalath, M. Poonoth, and E. Suresh, *J. Am. Chem. Soc.*, 2006, **128**, 8736.

8 For related reports, see (*a*) A. Bhunia, A. Patra, V. G. Puranik, and A. T. Biju, *Org. Lett*., 2013, **15**, 1756; (*b*) Z. Fu, K. Jiang, T. Zhu, J. Torres, and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2014, **53**, 6506.

9 (*a*) P.-C. Chiang, J. Kaeobamrung, and J. W. Bode, *J. Am. Chem. Soc.*, 2007, **129**, 3520; (*b*) M. He, and J. W. Bode, *J. Am. Chem. Soc.*, 2008, **130**, 418.

10 For selected reports, see: (*a*) M. Wadamoto, E. M. Phillips, T. E. Reynolds, and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 10098; (*b*) B. Cardinal-David, D. E. A. Raup, and K. A. Scheidt, *J. Am. Chem. Soc.*, 2010, **132**, 5345; (*c*) D. Cohen, B. Cardinal-David, and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2011, **50**, 1678.

11 Z. Fu, J. Xu, T. Zhu, W.W. Y. Leong, and Y. R. Chi, *Nat. Chem.*, 2013, **5**, 835.

12 G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin, and D. Romo, *Nat. Chem*., 2013, **5**, 1049.

13 For related β-lactone synthesis, see: (*a*) L. Candish, C. M. Forsyth, and D. W. Lupton, *Angew. Chem. Int. Ed.*, 2013, **52**, 9149. (*b*) L. Candish, and D.W. Lupton, *J. Am. Chem. Soc.*, 2013, **135**, 58.

14 For selected recent reports on α,β-unsaturated acyl ammonium chemistry, see: (*a*) M. E. Abbasov, B. M. Hudson, D. J. Tantillo, and D. Romo, *J. Am. Chem. Soc*., 2014, **136**, 4492; (*b*) S. Vellalath, K. N. Van, and D. Romo, *Angew. Chem. Int. Ed.*, 2013, **52**, 13688; (*c*) B. Ranieri, O. Robles, and D. Romo, *J. Org. Chem*., 2013, **78**, 6291; (*d*) E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin, and A. D. Smith, *Chem. Sci.*, 2013, **4**, 2193.

15 While this manuscript was under preparation, Studer and co-workers reported the enantioselective synthesis of highly substituted β–lactones proceeding via the α,β-unsaturated acyl azoliums under oxidative NHC-catalysis. For details see: S. Bera, R. C. Samanta, C. G. Daniliuc, and A. Studer, *Angew. Chem. Int. Ed.*, 2014, **53**, 9622.

16 For reviews, see: (*a*) S. De Sarkar, A. Biswas, R. C. Samanta, and A. Studer, *Chem. Eur. J.*, 2013, **19**, 4664; (*b*) C. E. I. Knappke, A. Imami, and A. J. vonWangelin, *ChemCatChem*, 2012, **4**, 937.

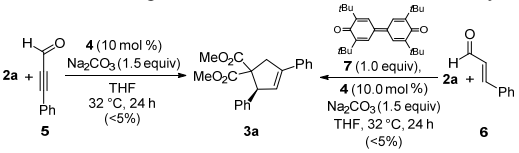
17 For selected recent reports, see: (*a*) J. Cheng, Z. Huang, and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2013, **52**, 8592; (*b*) R. C. Samantha, B. Maji, S. De Sarkar, K. Bergander, R. Fröhlich, C. Mück-Lichtenfeld, H. Mayr, and A. Studer, *Angew. Chem. Int., Ed.*, 2012, **51**, 5234; (*c*) A. G. Kravina, J. Mahatthananchai, and J. W. Bode, *Angew. Chem. Int. Ed.*, 2012, **51**, 9433; (*d*) J. Mahatthananchai, J. Kaeobamrung, and J. W. Bode, *ACS Catal.*, 2012, **2**, 494; (*e*) E. Lyngvi, J. W. Bode, and F. Schoenebeck, *Chem. Sci.*, 2012, **3**, 2346; (*f*) B. Wanner, J. Mahatthananchai, and J. W. Bode, *Org. Lett.*, 2011, **13**, 5378; (*g*) Z.-Q. Zhu, X.-L. Zheng, N.-F. Jiang, X. Wan, and J.-C. Xiao, *Chem. Commun*., 2011, **47**, 8670; (*h*) Z.-Q. Rong, M.-Q. Jia, and S.-L. You, *Org. Lett*., 2011, **13**, 4080; (*i*) J. Mahatthananchai, P. Zheng, and J. W. Bode, *Angew. Chem., Int. Ed*., 2011, **50**, 1673; (*j*) A. Biswas, S. De Sarkar, R. Fröhlich, and A. Studer, *Org. Lett.*, 2011, **13**, 4966; (*k*) S. J. Ryan, L. Candish, and D. W. Lupton, *J. Am. Chem. Soc.*, 2011, **133**, 4694.

18 For selected reports, see: (*a*) Q. Ni, X. Song, G. Raabe, and D. Enders, *Chem. Asian J.*, 2014, **9**, 1535; (*b*) S. R. Yetra, T. Roy, A. Bhunia, D. Porwal, and A. T. Biju, *J. Org. Chem.*, 2014, **79**, 4245; (*c*) S. R. Yetra, T. Kaicharla, S. S. Kunte, R. G. Gonnade, and A. T. Biju, *Org. Lett.*, 2013, **15**, 5202; (*d*) S. R. Yetra, A. Bhunia, A. Patra, M. V. Mane, K. Vanka, and A. T. Biju, *Adv. Synth. Catal*., 2013, **355**, 1089; (*e*) B. Zhang, P. Feng, Y. Cui, and N. Jiao, *Chem. Commun*., 2012, **48**, 7280; (*f*) C. Yao, D. Wang, J. Lu, T. Li, W. Jiao, and C. Yu, *Chem. Eur. J*., 2012, **18**, 1914; (g) F.-G. Sun, L.-H. Sun, and S. Ye, *Adv. Synth. Catal*., 2011, **353**, 3134.

19 J. R. Struble, and J. W. Bode, *Org. Synth.*, 2010, **87**, 362.

20 For details, see the Supporting Information.

21 Notably, the reaction of ynal **5** with **2a**, and the reaction of enal **6** with **2a** in the presence of oxidant **7** furnished only traces of **3a**.



22 CCDC-1013561 (**3c**), and CCDC-1021576 (**11r**).

23 R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719.

24 For theoretical studies on related process, see: L. R. Domingo, R. J. Zaragozá and M. Arnó, *Org. Biomol. Chem*., 2010, **8**, 4884.

25 For selected reports on NHC-catalyzed β–lactone synthesis, see: (*a*) J. Douglas, J. E. Taylor, G. Churchill, A. M. Z. Slawin, and A. D. Smith, *J. Org. Chem*., 2013, **78**, 3925; (*b*) X.-N. Wang, P.-L. Shao, H. Lv, and Song Ye, *Org. Lett.*, 2009, **11**, 4029.

