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Chiral Phosphoric Acid Catalyzed Enantioselective Annulation of Acyclic Enecarbamates to In Situ-Generated *ortho*-Quinone Methides

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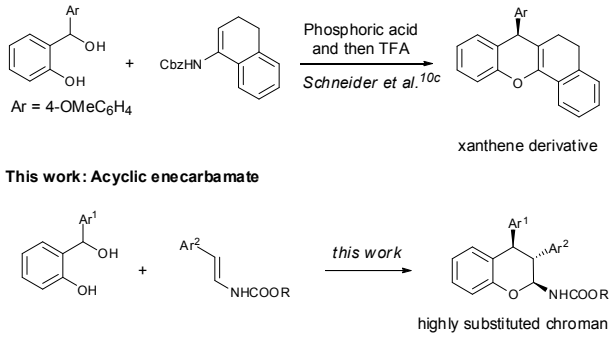
The first organocatalytic asymmetric reaction of acyclic enecarbamates with *o*-quinone methides is disclosed. BINOL-based phosphoric acid catalysts were found to be suitable for the annulation reaction. With 10 mol% of TRIP catalyst, high yields as well as excellent diastereo- and enantioselectivities are achieved for a variety of 2,3,4-trisubstituted chroman products.

Over the years, *o*-quinone methides have been established as important synthetic intermediates in organic synthesis and material chemistry and also in biological processes.[1] The interesting structural figure and inherent reactivity with highly electrophilic character have led to the development of a variety of reactions namely Michael additions, 6π electrocyclizations and [4 + 2] cycloadditions. Despite long history of *o*-quinone methides, the catalytic asymmetric versions have only been realized in recent years possibly due to transient nature of *o*-quinone methides.[2] The initial important contributions have been documented by the groups of Sigman,[3] Lectka,[4] Schaus,[5] Ye[6] and Scheidt[7] respectively on enantioselective palladium-, cinchona alkaloid-, BINOL-, and NHC catalysis with *o*-quinone methides. Later on, the groups of Bach,[8] Rueping,[9] Schneider[10], Sun[11] and others[12] have demonstrated the chiral Brønsted acid catalyzed generation of *o*-quinone methides from *o*-hydroxybenzyl alcohols/*o*-hydroxy styrenes and applied in a variety of nucleophilic additions and cyclization reactions. In a parallel way, few reports on bifunctional tertiary amine-thiourea/squaramide as well as metal catalyzed employment of *in situ* generated *o*-quinone methides have been disclosed.[13,14]

Densely functionalized chromans are important structural motifs that are present in many natural products and bioactive agents.[15] Though a range of organocatalytic asymmetric approaches have been documented in literature,[16,17] only two reports employing *o*-quinone methides are known as disclosed by Rueping[9a] and Shi[12b] for the synthesis of 2,4-disubstituted chromans using styrenes and vinyl indoles respectively.



Scheme 1 Enantioselective annulation of Enecarbamates with *in situ* Generated *o*-Quinone Methides.

Enamides and enecarbamates are also potential reactive nucleophiles that have been utilized in a wide range of C-C bond formation reactions.[18] Schneider *et al.* has elegantly employed cyclic enamides with *in situ* generated *o*-quinone methides for the asymmetric synthesis of xanthene based heterocycles.[10c-d] Though one example of reaction of cyclic enecarbamate has been demonstrated by Schneider and co-workers,[10c] to the best of our knowledge acyclic enacarbamates have not been studied. Realizing the importance of highly substituted diverse chromans in natural products and for other studies, we embarked in the Brønsted acid catalyzed reactions of acyclic enecarbamates and o-quinone methides.

We first attempted the reaction between *o*-hydroxybenzyl alcohol **1a** and enecarbamate **2a** using BINOL-phosphoric acid **I** in toluene at room temperature (Table 1, entry 1). Though the reaction led to the formation of chroman mixtures **3a**/**3a'** in high yield but the enantiomeric excess was low. The relative structures of **3a** and **3a'** were solved by 2D NMR experiments. Then we planned to screen 3,3'-substituted BINOL-phosphoric acids and the results are pleasing. For example, catalyst **II** and **III** having 1-naphthyl and 2-naphthyl substitutions provided the products **3a/3a'** in good enantioselectivities but the diastereoselectivity was not improved. Sterically demanding catalyst **IV** having bis *meta*-CF_3 groups on the 3,3'-phenyl

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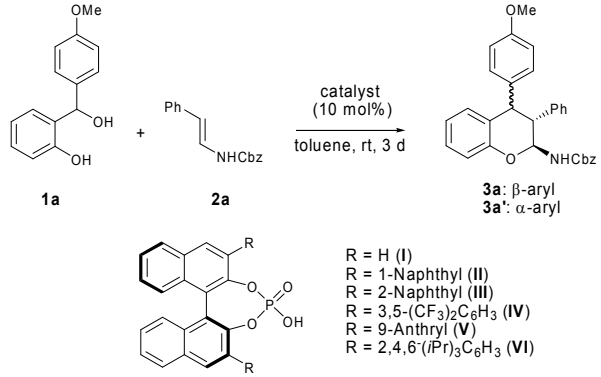
groups could not change the outcome of the reaction. An improvement in enantioselectivity was observed with catalyst **V** having 9-anthryl groups on the 3,3'-positions. Interestingly, more sterically demanding catalyst **VI** having 2,4,6-triisopropylated 3,3'-phenyl groups delivered the products in higher enantioselectivities and with higher diastereoselectivities (entry 6). The major diastereomer **3a** was obtained in 90% ee. The enantioselectivity did not improve after lowering the temperature. Other solvents were also screened but toluene was found to be the best solvent (see supporting information for details).

Table 1 Catalyst Screening and Optimization of Reaction Condition

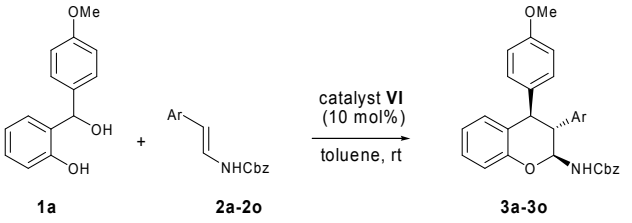


Entry[a]	Catalyst	Yield[b]	dr (**3a/3a'**)[c]	ee (**3a/3a'**)[d]
1	**I**	77	1:2	20/14
2	**II**	60	1:1.4	78/72
3	**III**	62	1:1	60/80
4	**IV**	65	1:1	54/70
5	**V**	71	1:2	88/74
6	**VI**	81	5.6:1	90/82

[a]Reaction condition: 0.04 mmol of **1a** and 0.06 mmol of **2a** in 0.2 mL toluene using 10 mol% catalyst at room temperature for 3 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by 1H NMR. [d]Determined by HPLC using stationary phase chiral column.

After the optimized conditions got established, the scope of the reaction was studied. Initially a variety of enecarbamates **2** having substitutions on the aryl group of the olefin was examined (Table 2). Delightfully, the reactions proceeded well in all cases and typically completed within 3-4 days at room temperature. At the beginning, different *para*-substitutions were screened and high yields as well as excellent enantioselectivities were achieved for the products **3a**-**3g** (Table 2, entries 1-7). To our delight, products **3e**-**3g** having 4-halo substitutions were obtained in acceptable yields and with high diastereo- and enantioselectivities (entries 5-7). Then different *meta*- and *ortho*-substitutions were studied and here also the products were attained in high yields as well as with high enantioselectivities (entries 8-14). Interestingly, here the products with halo functionalities **3l**-**3n** were isolated almost as single diastereomers (entries 12-14). A disubstituted enecarbamate also withstood the reaction condition and delivered the major product **3o** in 92% ee (entry 15).

Table 2 Scope of N-Cbz Enecarbamates



Entry[a]	Ar	**3**	Yield[b]	dr[c]	ee[d]
1	Ph	**3a**	81	5.6:1	90
2	4-MeC_6H_4	**3b**	84	5:1	92
3	4-$^{i}PrC_6H_4$	**3c**	85	8.3:1	88
4	4-$^{t}BuC_6H_4$	**3d**	87	9.1:1	88
5	4-FC_6H_4	**3e**	74	>20:1	84
6	4-ClC_6H_4	**3f**	48	8.3:1	92
7	4-BrC_6H_4	**3g**	53	9:1	94
8	3-MeC_6H_4	**3h**	70	10:1	92
9	3-ClC_6H_4	**3i**	48	5:1	94
10	3-BrC_6H_4	**3j**	80	20:1	94
11	2-MeC_6H_4	**3k**	72	4.2:1	88
12	2-FC_6H_4	**3l**	83	>20:1	94
13	2-ClC_6H_4	**3m**	88	>20:1	94
14	2-BrC_6H_4	**3n**	89	>20:1	94
15	2,4-$Me_2C_6H_3$	**3o**	63	4.3:1	92

[a]Reactions were carried out with catalyst **VI** in toluene at room temperature for 3-4 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by 1H NMR. [d]Determined by HPLC and of the major diastereomer.

The next phase of experiments involved variation the carbamate moiety and gratifyingly, the fate of the reaction was unaffected (Table 3). Good to high yields as well as high enantioselectivities were maintained with S-benzyl carbamothioate **2p** and other enecarbamates **2q**-**2s** albeit slight less diastereoselectivity was obtained for product **3q** (Table 3).

The generality of the reaction was further shown by employing a range of *o*-hydroxybenzyl alcohols (Table 4). Gratifyingly, a range of *o*-hydroxybenzyl alcohols having variations both on the quinone methide fragment and *β*-aryl substituent could be engaged in the reaction and good results were produced. Initially different halo substitutions on the quinone methide component was screened and high enantioselectivities were attained for products **3t**-**3v** which can be further functinalized *via* metal catalyzed cross-coupling reactions. To our delight, excellent diastereoselectivity was observed for product **3u**. However, the reactions were sluggish for products **3u** and **3v** and needed to run for 6 days at room temperature and at 50 ^{o}C for 3 days respectively. The enantioselectivity was also high when the *β*-aryl substituent was varied and acceptable yields were observed for products **3w** and **3x** (Table 4). Then we investigated reaction with different *β*-alkyl substituents and

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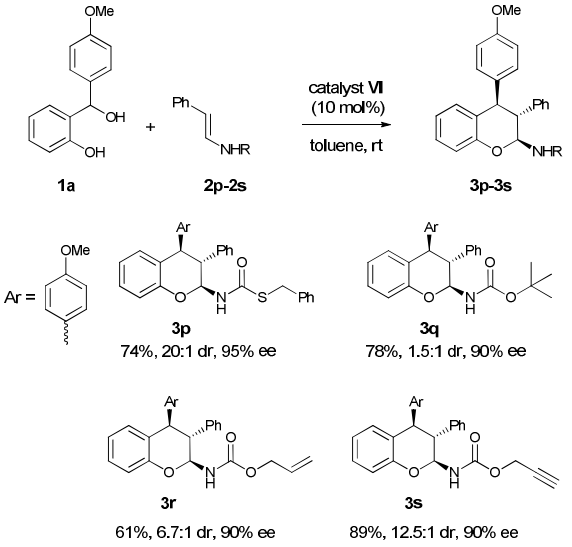
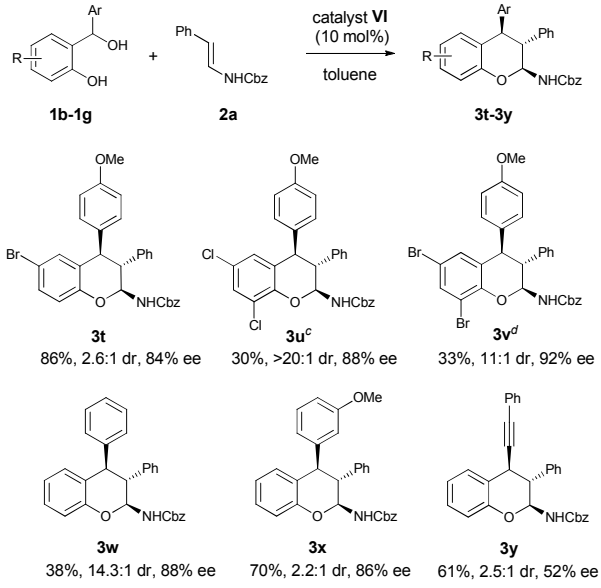
Table 3 Scope of Other Enecarbamates[a,b]



[a]Reaction was carried out with catalyst **VI** in toluene at room temperature for 3 days. [b]Isolated yield after silica gel column chromatography, diastereoselectivity was determined by 1H NMR and enantioselectivity was determined by HPLC using stationary phase chiral column.

Table 4 Scope of *o*-HydroxyBenzyl Alcohols[a,b]

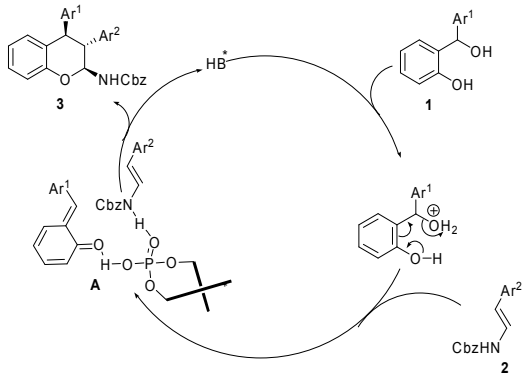


[a]Reaction was carried out with catalyst **VI** in toluene at room temperature for 3 days. [b]Isolated yield after silica gel column chromatography, diastereoselectivity was determined by 1H NMR and enantioselectivity was determined by HPLC using stationary phase chiral column. [c]Reaction was run at room temperature for 6 days. [d]At 50 °C for 3 days.

gratifyingly the reaction progressed well with alcohol **1g** having phenyl acetylene motif delivering product **3y** in 61% yield with 52% ee.

A plausible mechanism for the formation of chroman **3** has been depicted in Scheme 2. In the first step, protonation followed by dehydration of the o-hydroxybenzyl alcohol **1** catalyzed by phosphoric acid leads to the formation of o-quinone methide **A**. Then the bifunctional character of phosphoric acid plays a role in bringing o-quinone methide **A** and enecarbamate **2** together. Presumably, the catalyst is hydrogen-bonded to the oxygen atom of the o-quinone methide **A** through its acidic group O-H and simultaneously connected to the enecarbamate N-H moiety through an additional hydrogen bond from the basic phosphoryl oxygen atom (Scheme 2).[10c]

Also, the enecarbamate **2** adjusts in *endo* fashion and consequently the reaction occurs in a concerted pathway that explains the relative *trans*-structure of **3** (see supporting information for additional experiments). The absolute structure of compound **3q** was determined to be (2*S*,3*R*,4*R*) by Mosher amide method[19] and the other products are assumed to have same absolute configuration (see supporting information for details).



Scheme 2 Proposed Mechanism

In summary, this work represents a fascinating catalytic asymmetric reaction between *o*-quinone methides and acyclic enecarbamtes. The reaction is catalyzed by commercially available chiral phosphoric acid *TRIP*. The synthesis of chroman products having two aryl substitutions is difficult and thus our method is significant which allow for the synthesis of chromans having three stereogenic centres and could be applied in natural product synthesis.

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Notes and references

1 For selected recent reviews about *o*-QMs, see: (*a*) *Quinone Methides* (Ed.: S. E. Rokita), Wiley: Hoboken, 2009; (*b*) T. P. Pathak and M. S. Sigman, *J. Org. Chem*., 2011, **76**, 9210; (*c*) N. J. Willis and C. D. Bray, *Chem. Eur. J.,* 2012, **18**, 9160; (*d*) W. J. Bai, J. G. David, Z. G. Feng, M. G. Weaver, K. L. Wu and T. R. Pettus, *Acc. Chem. Res*., 2014, **47**, 3655; (*e*) L. Caruana, M. Fochi and L. Bernardi, *Molecules,* 2015, **20**, 11733.

2 For reviews, see: (*a*) Z. Wang and J. Sun, *Synthesis,* 2015, **47**, 3629; (*b*) A. A. Jaworski and A. A. Scheidt, *J. Org. Chem.,* 2016, **81**, 10145.

3 (*a*) Y. Zhang and M. S. Sigman, *J. Am. Chem. Soc*., 2007, **129**, 3076; (*b*) K. H. Jensen, T. P. Pathak, Y. Zhang and M. S. Sigman, *J. Am. Chem. Soc*., 2009, **131**, 17074; (*c*) T. P. Pathak, K. M. Gligorich, B. E. Welm and M. S. Sigman, *J. Am. Chem. Soc*., 2010, **132**, 7870; (*d*) K. H. Jensen, J. D. Webb and M. S. Sigman, *J. Am. Chem. Soc.,* 2010, **132**, 17471; (*e*) R. Jana, T. P. Pathak, K. H. Jensen and M. S. Sigman, *Org. Lett*., 2012, **14**, 4074.

4 E. Alden-Danforth, M. T. Scerba and T. Lectka, *Org. Lett.,* 2008, **10**, 4951.

5 Y. Luan and S. E. Schaus, *J. Am. Chem. Soc.,* 2012, **134**, 19965.

6 (*a*) H. Lv, L. You and S. Ye, *Adv. Synth. Catal*., 2009, **351**, 2822; (*b*) H. Lv, W. Q. Jia, L. H. Sun and S. Ye, *Angew. Chem. Int. Ed*., 2013, **125**, 8769.

7 (*a*) A. E. Mattson and K. A. Scheidt, *J. Am. Chem. Soc*., 2007, **129**, 4508; (*b*) J. Izquierdo, A. Orue and K. A. Scheidt, *J. Am. Chem. Soc*., 2013, **135**, 10634; (c) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra and K. A. Scheidt, *J. Am. Chem. Soc*., 2014, **136**, 10589.

8 D. Wilcke, E. Herdtweck and T. Bach, *Synlett,* 2011, **22**, 1235.

9 (*a*) C.-C. Hsiao, H.-H. Liao and M. Rueping, *Angew. Chem. Int. Ed.,* 2014, **53**, 13258; (*b*) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei and M. Rueping, *Angew. Chem. Int. Ed*., 2015, **54**, 1910.

10 (*a*) O. El-Sepelgy, S. Haseloff, S. K. Alamsetti and C. Schneider, *Angew. Chem. Int. Ed*., 2014, **53**, 7923; (*b*) S. Saha, S. K. Alamsetti and C. Schneider, *Chem. Commun*., 2015, **51**, 1461; (*c*) S. Saha and C. Schneider, *Chem. –Eur. J*., 2015, **21**, 2348; (*d*) S. Saha and C. Schneider, *Org. Lett*., 2015, **17**, 648; For a Rh/Brønsted acid catalysis, see: S. K. Alamsetti, M. Spanka and C. Schneider, *Angew. Chem. Int. Ed*., 2016, **55**, 2392.

11 (*a*) W. Zhao, Z. Wang, B. Chu and J. Sun, *Angew. Chem. Int. Ed*., 2015, **54**, 1910; (*b*) Z. Wang, F. Ali, Z. Wang, W. Zhao, G. Zhu, Z. Lin and J. Sun, *J. Am. Chem. Soc*., 2015, **137**, 383; (*c*) Z. Lai, Z. Wang and J. Sun, *Org. Lett*., 2015, **17**, 6058; (*d*) Z. Lai and J. Sun, *Synlett,* 2016, **27**, 555.

12 (*a*) R.-Y. Zhu, C.-S. Wang, J. Zheng, F. Shi and S.-J. Tu, *J. Org. Chem.,* 2014, **79**, 9305; (*b*) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu and F. Shi, *Angew. Chem. Int. Ed*., 2015, **54**, 5460; (*c*) Y.-C. Zhang, Q.-N. Zhu, X. Yang, L.-J. Zhou and F. *J.* Shi, *Org. Chem*., 2016, **81**, 1681; (*d*) Q. Wu, C. Ma, X.-h. Du, Y. Chen, T.-z Huang, X.-q. Shi, S.-j. Tu and P.-j. Cai, *Tetrahedron: Asymmetry,* 2016, **27**, 307; (*e*) M. Tang, J.-J. Zhao, Q. Wu, M. S. Tu, F. Shi, *Synthesis,* 2017, **49**, 2035; For *o*-QM intermediate in Prins reaction, see: (*f*) G. C. Tsui, L. Liu and B. List, *Angew. Chem. Int. Ed*., 2015, **54**, 7703.

13 For selected examples, see: (*a*) W. Guo, B. Wu, X. Zhou, P. Chen, X. Wang, Y.-G. Zhou, Y. Liu and C. Li, *Angew. Chem. Int. Ed*., 2015, **54**, 4522; (*b*) L. Carruna, M. Mondatori, V. Corti, S. Morales, A. Mazzanti, M. Fochi and L. Bernardi, *Chem. -Eur. J*., 2015, **21**, 6037; (*c*) B. Wu, X. Gao, Z. Yan, W.-X. Huang and Y.-G. Zhou, *Tetrahedron Lett*., 2015, **56**, 4334; (*d*) Y. Wang, C. Zhang, H. Wamg, Y. Jiang, X. Du and D. Xu, *Adv. Synth. Catal.,* 2017, **359**, 791; (*e*) B. Wu, Z. Yu, X. Gao, Y. Lan and Y.-G. Zhou, *Angew. Chem. Int. Ed*., 2017, **129**, 4064; For primary amine catalyzed addition to *o*-QMs, see: (*f*) Y. Zhu, L. Zhang and S. Luo, *J. Am. Chem. Soc*., 2016, **138**, 3978; For a recent report using NHC, see: (*g*) Y. Wang, J. Pan, J. Dong, C. Yu, T. Li, X.-S. Wang, S. Shen and C. Yao, *J. Org. Chem*., 2017, **82**, 1790.

14 For metal catalyzed reports, see: (*a*) H. Xu, Y. Liu, J. Guo, L. Lin, Y. Xu, X. Liu and X. Feng, *Chem. Commun*., 2015, **51**, 3835; (*b*) Y. Huang and T. Hayashi, *J. Am. Chem. Soc*., 2015, **137**, 7556; (*c*) M. Liang, S. Zhang, J. Jia, C.-H. Tung, J. Wang and Z. Xu, *Org. Lett.,* 2017, **19**, 2526.

15 For selected examples, see: (*a*) S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev*., 2004, **104**, 3059; (*b*) M. C. Breschi, V. Calderone, A. Martelli, F. Minutolo, S. Rapposelli, L. Testai, F. Tonelli and A. Balsamo, *J. Med. Chem*., 2006, **49**, 7600; (*c*) S. Khelili, X. Florence, M. Bouhadja, S. Abdelaziz, N. Mechouch, Y. Mohamed, P. D. de Tullio, P. Lebrun and B. Pirotte, *Bioorg. Med. Chem*., 2008, **16**, 6124; (*d*) A. Coi, A. M. Bianucci, V. Calderone, L. Tstai, M. Digiacomo, S. Rapposelli and A. Balsamo, *Bioorg. Med. Chem.,* 2009, **17**, 5565.

16 For selected recent examples, see: (*a*) H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson and A. Córdova, *Chem. –Eur. J*., 2007, **13**, 574; (*b*) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.,* 2009, **11**, 1627; (*c*) B.-C. Hong, P. Kotame, C.-W. Tsai and J.-H. Liao, *Org. Lett.,* 2010, **12**, 776; (*d*) X.-F. Wang, Q.-L. Hua, Y. Cheng, A.-L. An, Q.-Q. Yang, J.-R. Chen and W.-J. Xiao, *Angew. Chem. Int. Ed*., 2010, **49**, 8379; (*e*) X.-F. Wang, J. An, X.-X. Zhang, F. Tan, J.-R. Chen and W.-J. Xiao, *Org. Lett.,* 2011, **13**, 808; (*f*) D. B. Ramachary, M. S. Shiva Prasad and R. Madhavachary, *Org. Biomol. Chem*., 2011, **9**, 2715; (*g*) Z.-X. Jia, Y.-C. Luo, X.-N. Cheng, P.-F. Xu and Y.-C. *J.* Gu, *Org. Chem*., 2013, **78**, 6488; (*h*) P. H. Poulsen, K. S. Feu, B. M. Paz, F. Jensen and K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2015, **54**, 8203; (*i*) P. Saha, A. Biswas, N. Molletti and V. A. Singh, *J. Org. Chem*., 2015, **80**, 11115; (*j*) Y. Zhu, X. Li, Q. Chen, J. Su, F. Jia, S. Qiu, M. Ma, Q. Sun, W. Yan, K. Wang and R. Wang, *Org. Lett.,* 2015, **17**, 3826.

17 For selected reviews on the synthesis of chroman derivatives using organocatalysts, see: (*a*) M. G. Núńez, P. García, R. F. Moro and D. Díez, *Tetrahedron,* 2010, **66**, 2089; (*b*) C. Bhanja, S. Jena, S. Nayak and S. Mohapatra, *Beilstein J. Org. Chem*., 2012, **8**, 1668; (*c*) C. F. Nising and S. Brase, *Chem. Soc. Rev*., 2012, **41**, 988.

18 For a review, see: K. Gopalaiah and H. B. Kagan, *Chem. Rev*., 2011, **111**, 4599.

19 For a review, see: J. M. Seco, E. Quinoa and R. Riguera, *Chem. Rev*., 2004, **104**, 17.