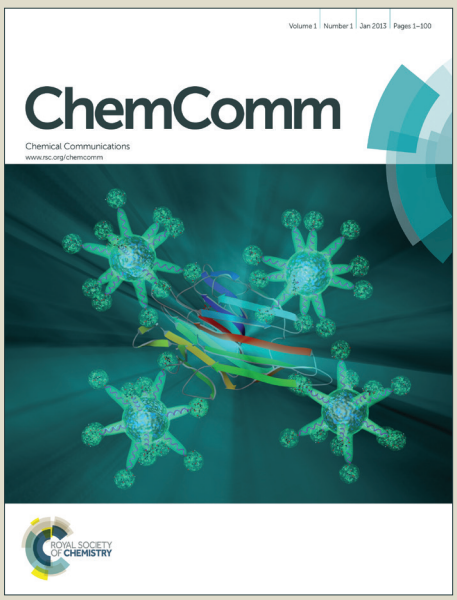
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Lu, J. Liu, C. Li, J. Lin, Y. Liang and P. Xu, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC00118H.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Dynamic Article Links ►
View Article Online
DOI: 10.1039/C5CC00118H

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A New Chiral C_1-Symmetric NHC-Catalyzed Addition to α-Aryl Substituted α,β-Disubstituted Enals: Enantioselective Synthesis of Fully Functionalized Dihydropyranones

Hong Lu, Jin-Yu Liu, Chen-Guang Li, Jun-Bing Lin, Yong-Min Liang and Peng-Fei Xu*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The first enantioselective NHC-catalyzed activation of α-aryl substituted α,β-disubstituted unsaturated aldehyde is successfully developed via a highly-active acyl azolium intermediate. The new C_1-symmetric biaryl-saturated imidazolium exhibits a superior ability to enable previously unavailable transformation, and the corresponding fully functionalized dihydropyranones are efficiently synthesized in high yields with excellent enantioselectivities.

Over the past decade, a large number of new catalysts and novel strategies have been developed to enable previously unavailable transformations.[1] Despite these significant improvements, however, the reaction of α-branched α,β-disubstituted unsaturated aldehydes, especially α-aryl substituted α,β-disubstituted enals, is still a long standing and challenging issue for asymmetric catalysis due to their steric hindrance and low reactivity.[2] Neither organocatalysis nor metal-based approaches have afforded to the stereoselective functionalization of these sterically congested substrates.[3] As a consequence, the activation of elusive α-aryl substituted α,β-disubstituted enals is still highly desired and will significantly extend the scope of asymmetric catalysis.

Due to the great potential for extending substrate scopes and achieving unprecedented transformations,[4] oxidative N-heterocyclic carbenes (NHCs) catalysis has received substantial attention and experienced very rapid development in the past decade.[5] Dozens of intriguing chemical entities with improved complexity and diversity have been readily constructed in a stereocontrolled fashion via α,β-unsaturated acyl azolium intermediates.[6,7] With our ongoing interest in the exploration of practical asymmetric organoctalysis,[8] we envisioned that the elusive asymmetric activation of challenging α-aryl substituted α,β-disubstituted enals might be achieved using C_1-symmetric biaryl-saturated imidazolium.[9] Herein we present the first asymmetric Michael addition to α-aryl substituted α,β-disubstituted enals through oxidative NHC catalysis, giving rise to fully substituted dihydropyranones which are otherwise difficult to obtain in high yields and excellent selectivities.

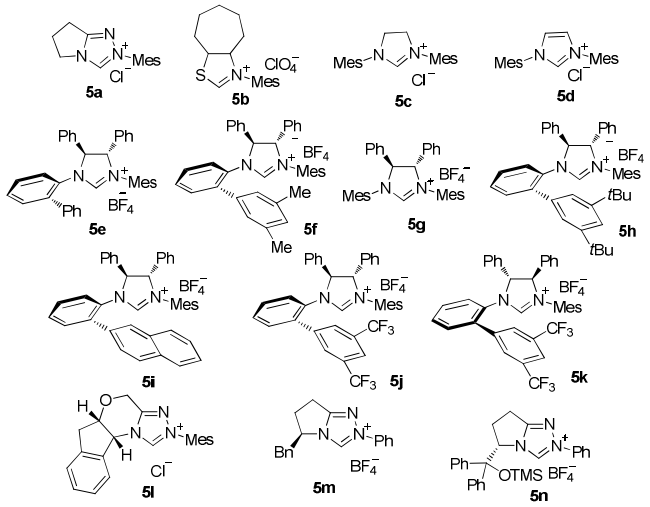


Fig.1 NHC catalysts examined in this study.

In our initial study, several achiral NHC catalysts were screened to evaluate their ability to promote the reaction of α-phenyl substituted enal **1a** and acetyl acetone **2a** by using diazabicyclo[5.4.0]undecene (DBU, 10 mol%) and oxidant **4** in THF at 10 °C (Fig. 1). To our delight, the saturated imidazolium catalyst **5c** could give the desired fully functionalized dihydropyranone **3a** in a short time (Table 1, entries 1–4). To uncover the asymmetric variants of this process, NHCs **5e** and **5f,** which had been used to formal [3+2] annulation of α,β-unsaturated aldehydes with acyl phosphonates, were screened (Table 1, entries 5 and 6).[10a] The reactions proceeded smoothly in high yield yet with a moderate stereocontrol. Further efforts toward improving catalyst performance revealed that NHCs with more electron-donating and bulkier substituents did not offer satisfactory results (Table 1, entries 7–9). Considering the superior ability of CF_3 group toward tuning the stereoelectronic effect in catalyst design, we expected that the introduction of CF_3 group into such type of catalysts would provide a beneficial effect toward reactivity and selectivity. Then catalyst **5j** and its enantiomer **5k** were synthesized and evaluated. Surprisingly, catalysts **5j** led to a very encouraging yield with good

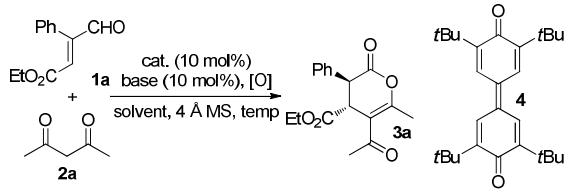
State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China.
E-mail: xupf@lzu.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental procedures and spectra of all new compounds. CCDC 1037041. See DOI: 10.1039/b000000x/

View Article Online
DOI: 10.1039/C5CC00118H

diastereoselectivity and excellent enantioselectivity while catalyst **5k** gave only slightly improved results (Table 1, entries 10 and 11). Next, different solvents were investigated and THF was found to be an optimal one (Table 1, entries 12–15). Further screening of the temperatures and bases showed 25 °C and DBU to be promising (Table 1, entries 16–22). When 3 equivalents of **2a** and 0.5 mL THF were used, a highly efficient and prominent selectivity was obtained (Table 1, entries 23–24). However, employing 5 mol% of **5k** led to a drop inefficiency and diastereoselectivity (Table 1, entry 25). Additionally, Bode's catalyst **5l**, which has been widely used in the synthesis of dihydropyranones, and other chiral triazolium precatalysts **5m** and **5n** were investigated, but only Bode's catalyst could give the product with good yield and moderate enantioselectivity after 12 hours (Table 1, entries 26–28).

Table 1 Optimization of the reaction conditions[a]

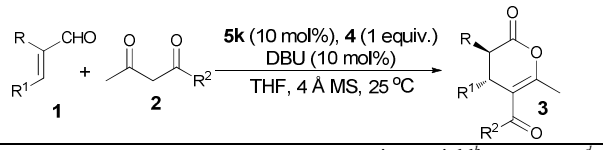


entry	cat.	temp (°C)	base	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**5a**	10	DBU	THF	24	64	2:1	-
2	**5b**	10	DBU	THF	24	NR	-	-
3	**5c**	10	DBU	THF	3	87	2:1	-
4	**5d**	10	DBU	THF	24	52	2:1	-
5	**5e**	10	DBU	THF	6	83	2:1	61
6	**5f**	10	DBU	THF	6	84	2:1	71
7	**5g**	10	DBU	THF	6	83	2:1	33
8	**5h**	10	DBU	THF	6	80	3:1	68
9	**5i**	10	DBU	THF	6	79	3:1	85/83
10	**5j**	10	DBU	THF	12	84	3:1	91/n.d.
11	**5k**	10	DBU	THF	12	86	4:1	93/83
12	**5k**	10	DBU	toluene	48	NR	-	-
13	**5k**	10	DBU	MeCN	48	NR	-	-
14	**5k**	10	DBU	dioxane	48	30	6:1	93
15	**5k**	10	DBU	DCM	48	trace	-	-
16	**5k**	25	DBU	THF	8	87	7:1	94
17	**5k**	40	DBU	THF	1.5	83	2:1	93
18	**5k**	25	DABCO	THF	12	67	2:1	92
19	**5k**	25	Cs_2CO_3	THF	12	64	3:1	92
20	**5k**	25	K_2CO_3	THF	12	76	3:1	93
21	**5k**	25	NaOAc	THF	12	78	7:1	92
22	**5k**	25	NEt_3	THF	12	59	5:1	92
23[e]	**5k**	25	DBU	THF	6	87	7:1	94
24[e,f]	**5k**	25	DBU	THF	3	87	8:1	96
25[g]	**5k**	25	DBU	THF	24	85	4:1	94
26[e,f]	**5l**	25	DBU	THF	12	80	2:1	86
27[e,f]	**5m**	25	DBU	THF	12	73	2:1	5
28[e,f]	**5n**	25	DBU	THF	12	30	2:1	26

[a] Conditions: Reactions performed with **1a** (0.1 mmol), **2a** (0.15 mmol), oxidant **4** (0.1 mmol), NHC (10 mol%) and DBU (10 mol%) in THF (1 mL) at 10 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by chiral-phase HPLC analysis. [e] 0.5 mL THF was used. [f] 3 equivalents of **2a** were used. [g] 5 mol% **5k** was used. n.d. = not determined.

With the optimal reaction conditions established, the scope of the reaction was also investigated. As shown in Table 2, in all the cases, the reaction proceeded smoothly to afford the corresponding fully decorated dihydropyranones in moderate to high yields with good diastereoselectivities and excellent enantioselectivities. The steric and electronic properties of the aryl at α-position of unsaturated aldehydes had noticeable effect on the outcome of the action. Only small substituent at the *ortho*-position of the phenyl group could give the desired result (Table 2, entry 2). But the steric influence of the substituents at *meta*- or *para*-position of the phenyl was not obvious (entries 3–7 versus entries 8–12). Electron-donating substituents gave higher levels of reactivity and enantioselectivity compared to those substrates with electron-withdrawing substituents (Table 2, entries 3–5, 8–10 versus entries 6–7, 11–17). Notably, satisfactory results could be obtained when the bulky substituent at the *para* position of the phenyl group or the α-position of enal (Table 2, entries 15 and 18). Furthermore, the reactions could be extended to benzyl carbonate (Table 2, entry 19). 1,3-dicarbonyl compounds with different substituents were also explored (Table 2, entries 20 and 21). The absolute configuration of the product **3v** was determined to be (3*S*, 4*R*) by X-ray crystallography (Table 2, entry 22).[11] In addition, the β-phenyl or α-methyl disubstituted enals could also give the product smoothly (Table 2, entries 23 and 24).

Table 2 Scope of the synthesis of fully functionalized δ-lactone[a]



entry	R	R^1	R^2	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	CO_2Et	Me	4	**3a**, 87	8:1	96
2	2-FC_6H_4	CO_2Et	Me	8	**3b**, 72	7:1	91
3	3-FC_6H_4	CO_2Et	Me	8	**3c**, 75	3:1	90
4	3-ClC_6H_4	CO_2Et	Me	8	**3d**, 70	3:1	93
5	3-BrC_6H_4	CO_2Et	Me	8	**3e**, 73	3:1	90
6	3-MeC_6H_4	CO_2Et	Me	3.5	**3f**, 90	11:1	94
7	3-$MeOC_6H_4$	CO_2Et	Me	3.5	**3g**, 92	9:1	94
8	4-FC_6H_4	CO_2Et	Me	6	**3h**, 80	5:1	90
9	4-ClC_6H_4	CO_2Et	Me	7	**3i**, 76	3:1	90
10	4-BrC_6H_4	CO_2Et	Me	7	**3j**, 74	3:1	93
11	4-MeC_6H_4	CO_2Et	Me	3.5	**3k**, 90	8:1	95
12	4-$MeOC_6H_4$	CO_2Et	Me	3.5	**3l**, 91	11:1	94
13	4-$EtOC_6H_4$	CO_2Et	Me	3.5	**3m**, 92	9:1	98
14	4-amylC_6H_4	CO_2Et	Me	3.5	**3n**, 89	10:1	97
15	4-cyclohexylC_6H_4	CO_2Et	Me	3.5	**3o**, 90	10:1	96
16	3,4-$Me_2C_6H_3$	CO_2Et	Me	3.5	**3p**, 91	9:1	96
17	3,4-$(MeO)_2C_6H_3$	CO_2Et	Me	3.5	**3q**, 92	10:1	96
18	2-naphthyl	CO_2Et	Me	3.5	**3r**, 87	7:1	96
19	4-$MeOC_6H_4$	CO_2Bn	Me	4	**3s**, 87	10:1	96
20	4-$MeOC_6H_4$	CO_2Et	OMe	4	**3t**, 86	10:1	95
21	4-$MeOC_6H_4$	CO_2Et	OEt	4	**3u**, 88	10:1	96
22[e]	3,4-$(MeO)_2C_6H_3$	4-$ClPhCH_2CO_2$	OMe	6	**3v**, 81	7:1	83
23	Ph	Ph	Me	36	**3w,** 65	7;1	69
24	Me	4-$ClPhCH_2CO_2$	Me	1	**3x,** 80	2:1	88

[a] Unless otherwise specified, the reaction was carried out with **1** (0.1 mmol), **2** (0.3 mmol), oxidant **4** (0.1 mmol), **5k** (10 mol%) and DBU (10 mol%) in THF (0.5 mL) at 25 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by chiral-phase HPLC analysis. [e] The absolute configurationof **3w** was determined by X-ray analysis (Fig. 2).

A plausible catalytic cycle is outlined in Scheme 1. We proposed that the reaction may be initiated by the combination of enal **1a** and imidazolium NHC, the Breslow intermediate is then oxidized to the key α-aryl substituted α,β-disubstituted acyl azolium **I**,[12] which undergoes Michael addition and generates intermediate **II**. After a tautomerization, the intermediate **III**

View Article Online
DOI: 10.1039/C5CC00118H

undergoes H-migration and O-acylation to afford desired product **3a** with the regeneration of the catalyst. [13]

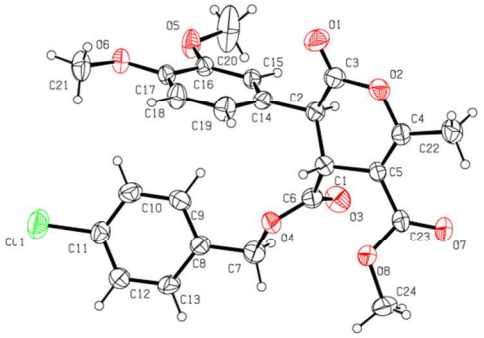
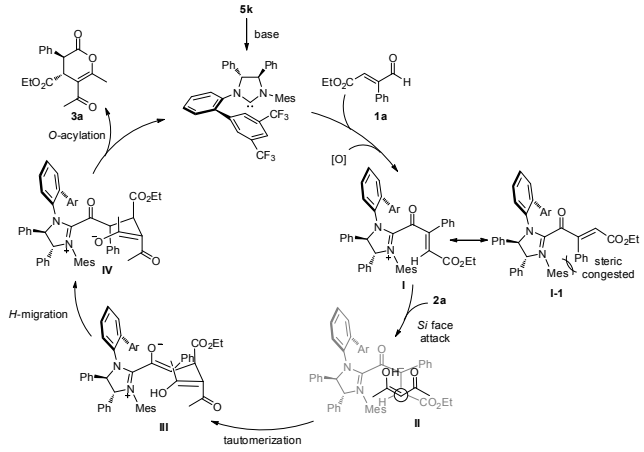
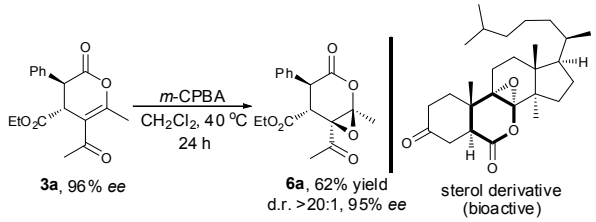


Fig. 2 X-ray crystal structure of compound **3v**.



Scheme 1 Proposed Reaction Mechanism

To further demonstrate the synthetic value of this oxidative addition reaction, product **3a** with a tetrasubstituted olefin moiety was subjected to a mild epoxidation process. Gratifyingly, the desired δ-lactone epoxide **6a,** a scaffold widely existed in numerous biologically active compounds,[14] was readily achieved with moderate yield but excellent diastereo- and enantioselectivity (Scheme 2).



Scheme 2 Synthetic Application of the Chiral δ-lactone **3a**

In summary, we have developed a practical and efficient approach for the activation of challenging α-aryl substituted α,β-disubstituted unsaturated aldehydes via a newly developed NHC catalyst, and a series of fully substituted dihydropyranones were obtained in high yields with excellent enantioselectivities. Notably, the C_1-symmetric biaryl-saturated imidazolium, as a robust organocatalyst, has shown powerful potential for the activation of previously unavailable reactions and inactive substrates. Further studies and applications of the novel NHC catalyst are currently underway.

We are grateful to the NSFC (21172097, 21202070 and 21372105), the International S&T Cooperation Program of China (2013DFR70580), the National Natural Science Foundation from Gansu Province of China (no. 1204WCGA015), and the "111" program from MOE of P. R. China.

Notes and references

1. For seclected examples, see: (a) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.*, 2011, **44**, 1182; (b) D. T. Cohen and K. A. Scheidt, *Chem. Sci.*, 2012, **3**, 53; (c) Z, Du and Z, Shao, *Chem. Soc. Rev.*, 2013, **42**, 1337; (d) G. Masson, C. Lalli, M. Benohoud and G. Dagousset, *Chem. Soc. Rev.*, 2013, **42**, 902; (e) I. D. Jurberg, I. Chatterjee, R. Tannerta and P. Melchiorre, *Chem. Commun.*, 2013, **49**, 4869; (f) Y. C. Fan and O. Kwon, *Chem. Commun.*, 2013, **49**, 11588; (g) M. T. Hovey, C. T. Check, A. F. Sipher and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2014, **53**, 9603.
2. For α-alky substitueted α,β-disubstituted enals, see: (a) S. Karlsson and H.-E. Högberg, *Eur. J. Org. Chem.*, 2003, 2782;(b) H. D. King, Z. Meng, D. Denhart, R. Mattson, R. Kimura, D. Wu, Q. Gao and J. E. Macor, *Org. Lett.*, 2005, **7**, 3437; (c) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2009, **48**, 7892; (d) A. Ma and D. Ma, *Org. Lett.*, 2010, **12**, 3634; (e) O. Lifchits, C. M. Reisinger and B. List, *J. Am. Chem. Soc*., 2010, **132**, 10227; (f) P. Melchiorre, *Angew. Chem. Int. Ed.*, 2012, **51**, 9748; (g) A. Pou and A. Moyano, *Eur. J. Org. Chem.*, 2013, 3103; (h) O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Farès, I. Polyak, G. Gopakumar, W. Thiel and B. List, *J. Am. Chem. Soc*., 2013, **135**, 6677; for α-branched enones, see: (i) K. Nishide, M. Ozeki, H. Kunishige, Y. Shigeta, P. K. Patra, Y. Hagimoto and M. Node, *Angew. Chem. Int. Ed.*, 2003, **42**, 4515; (j) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo and P. Melchiorre, *J. Am. Chem. Soc.*, 2011, **133**, 17934; (k) A. T. Davies, P. M. Pickett, A. M. Z. Slawin and A. D. Smith, *ACS Catal.*, 2014, **4**, 2696.
3. (a) T. Kano, Y. Tanaka, K. Osawa, T. Yurino and K. Maruoka, *Chem. Commun.*, 2009, 1956; (b) A. Quintard, A. Lefranc and A. Alexakis, *Org. Lett.*, 2011, **13**, 1540; (c) M. P. Sibi, J. Coulomb and L. M. Stanley, *Angew. Chem. Int. Ed.*, 2008, **47**, 9913.
4. For selected examples, see: (a) S. D. Sarkar and A. Studer, *Angew. Chem. Int. Ed.*, 2010, **49**, 9266; (b) Z.-Q. Rong, M.-Q. Jia and S.-L. You, *Org. Lett.*, 2011, **13**, 4080; (c) X. Zhao, K. E. Ruhl and T. Rovis, *Angew. Chem. Int. Ed.*, 2012, **51**, 12330; (d) J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc.*, 2012, **134**, 8810; (e) A. G. Kravina, J. Mahatthananchai and J. W. Bode, *Angew. Chem. Int. Ed.*, 2012, **51**, 9433; (f) E. G. Delany, C.-L. Fagan, S. Gundala, A. Mari, T. Broja, K. Zeitler and S. J. Connon, *Chem. Commun.*, 2013, **49**, 6510; (g) J. Mo, L. Shen and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2013, **52**, 8588; (h) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong and Y. R. Chi, *Nat. Chem.*, 2013, **5**, 839; (i) X. Chen, S. Yang, B.-A. Song and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2013, **52**, 11134; (j) S. Bera, R. C. Samanta, C. G. Daniliuc and A. Studer, *Angew. Chem. Int. Ed.*, 2014, **53**, 9622; (k) Z. Fu, K. Jiang, T. Zhu, J. Torres and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2014, **53**, 650; (l) O. Bortolini, C. Chiappe, M. Fogagnolo, P. P. Giovannini, A. Massi, C. S. Pomellib and D. Ragno, *Chem. Commun.*, 2014, **50**, 2008; (m) S. W. Youn, H. S. Song and J. H. Park, *Org. Lett.*, 2014, **16**, 1028.
5. For reviews on the oxidative N-heterocyclic carbenes catalysis, see: (a) C. E. I. Knappke, A. Imami and A. J. Wangelin, *ChemCatChem*, 2012, **4**, 937; (b) S. D. Sarkar, A. Biswas, R. C. Samanta and A. Studer, *Chem. Eur. J*., 2013, **19**, 4664.

View Article Online
DOI: 10.1039/C5CC00118H

6. For reviews on acyl azolium intermediate, see: J. Mahatthananchaiand and J. W. Bode, *Acc. Chem. Res.*, 2014, **47**, 696.
7. For selected examples, see: (a) J. Mahatthananchai, P. Zheng and J. W. Bode, *Angew. Chem. Int. Ed.*, 2011, **50**, 1673; (b) Z.-Q. Zhu, X.-L. Zheng, N.-F. Jiang, X. Wan and J.-C. Xiao, *Chem. Commun.*, 2011, **47**, 8670; (c) J. Mahatthananchai, J. Kaeobamrung and J. W. Bode, *ACS Catal.*, 2012, **2**, 494; (d) E. Lyngvi, J. W. Bode and F. Schoenebeck, *Chem. Sci.*, 2012, **3**, 2346; (e) R. C. Samanta, B. Maji, S. D. Sarkar, K. Bergander, R. Frçhlich, C. Mück-Lichtenfeld, H. Mayr and A. Studer, *Angew. Chem. Int. Ed.*, 2012, **51**, 5234; (f) G. Wang, X. Chen, G. Miao, W. Yao and C. Ma, *J. Org. Chem.*, 2013, **78**, 6223; (g) C. Yao, Z. Xiao, R. Liu, T. Li, W. Jiao and C. Yu, *Chem. Eur. J.*, 2013, **19**, 456; (h) S. R. Yetra, T. Kaicharla, S. S. Kunte, R. G. Gonnade and A. T. Biju, *Org. Lett.*, 2013, **15**, 5202; (i) Z. Xiao, C. Yu, T. Li, X.-S. Wang and C. Yao, *Org. Lett.*, 2014, **16**, 3632; (j) S. Mondal, S. R. Yetra, A. Patra, S. S. Kunte, R. G. Gonnadeb and A. T. Biju, *Chem. Commun.*, 2014, **50**, 14539.
8. For selected examples, see: (a) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu and D. J. Dixon, *Angew. Chem. Int. Ed.*, 2009, **48**, 9834; (b) Y. Wang, T.-Y. Yu, H.-B. Zhang, Y.-C. Luo and P.-F. Xu, *Angew. Chem. Int. Ed.*, 2012, **51**, 12339; (c) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang and P.-F. Xu, *Angew. Chem. Int. Ed.*, 2014, **53**, 14128; (d) S. Zhao, J.-B. Lin, Y.-Y. Zhao, Y.-M. Liang and P.-F. Xu, *Org. Lett.*, 2014, **16**, 1802; (e) Y.-L. Zhao, Y. Wang, J. Cao, Y.-M. Liang and P.-F. Xu, *Org. Lett.*, 2014, **16**, 2438; (f) L. Tian, G.-Q.Xu, Y.-H. Li, Y.-M. Liang and P.-F. Xu, *Chem. Commun.*, 2014, **50**, 2428; (g) H. Lu, J.-B. Lin, J.-Y. Liu and P.-F. Xu, *Chem. Eur. J.*, 2014, **20**, 11659; (h) T.-P. Gao, J.-B. Lin, X.-Q. Hu and P.-F. Xu, *Chem. Commun.*, 2014, **50**, 8934.
9. The catalyst was often used as aligand, for selected examples, see; (a) E. M. Vieira, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 3332; (b) F. Meng, H. Jang and A. H. Hoveyda, *Chem. Eur. J.*, 2013, **19**, 3204; (c) V. Pace, J. P. Rae and D. J. Procter, *Org. Lett.*, 2014, **16**, 476; (d) N. W. Mszar, F. Haeffner and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2014, **136**, 3362.
10. For examples on organocatalysis, see: (a) K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H.-Y. Cheong and K. A. Scheidt, *J. Am. Chem. Soc.*, 2014, **136**, 76; (b) A. Lee and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2014, **53**, 7594.
11. CCDC 1037041 (**3v**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
12. Owing to the steric congestion of intermediates **I-1**, we suspect that only the transition **I** could participate the reaction readily.
13. With regard to the mechanism, at current stage, the pathway involving the direct addition of enone and subsequent Claisen rearrangement proposed by Bode *et al* can not be ruled out. To see ref 7c and 7d.
14. K. Uchida, T. Agatsuma, K. Hibino, S. Sasho, K. Iida, H. Onodera, PCT WO 2011/010682A1, **2011**.