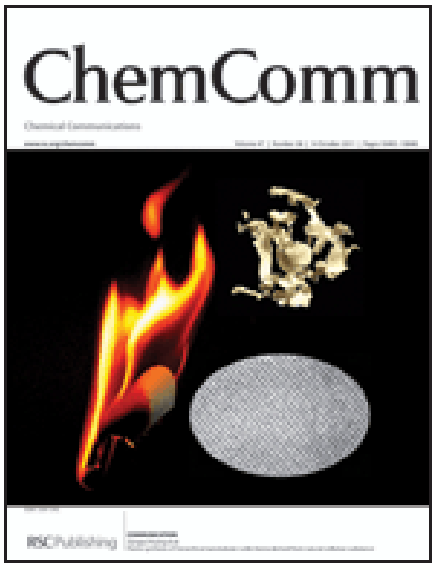

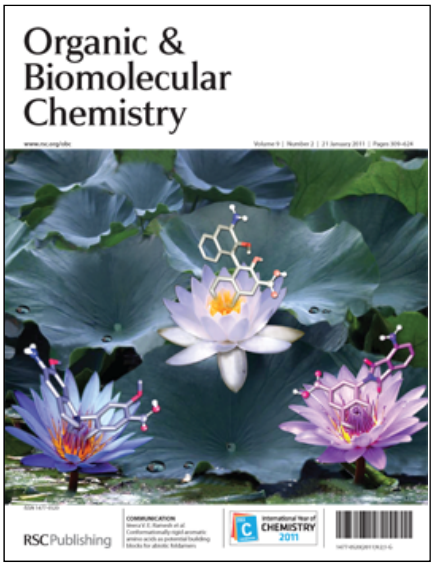

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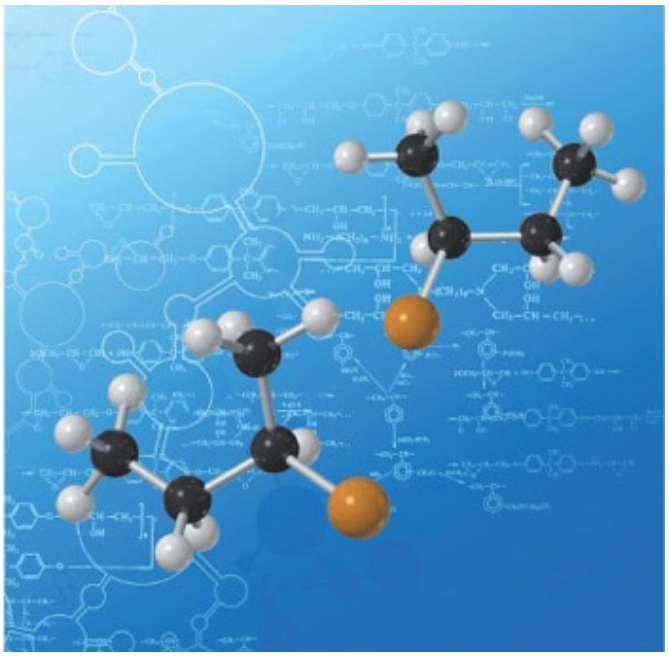

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COMMUNICATION

Enantioselective synthesis of substituted pyrans *via* amine-catalyzed Michael addition and subsequent enolization/cyclisation†‡

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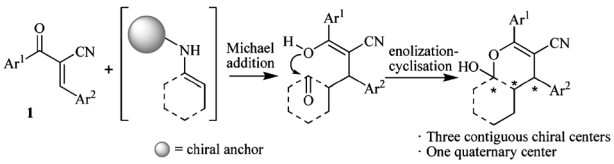
An organocatalytic construction of optically enriched substituted pyran derivatives *via* amine-catalyzed Michael addition and subsequent enolization/cyclisation has been described starting from electronically poor alkenes. Functionalized pyrans were obtained in high enantioselectivities (up to 96%) and good yields (up to 90%) having three contiguous chiral centers.

Substituted pyran rings are an important class of core structures found in a number of naturally occurring and biologically active molecules.[1] Accordingly, several methods have been developed for the synthesis of substituted pyrans.[2] In recent years organocatalysis has emerged as a promising synthetic tool in organic synthesis to challenge various synthetic problems.[3] Hence, the development of organocatalytic asymmetric approaches allowing the construction of these structural frameworks in optically active forms remains an attractive goal in organic synthesis.[4] Literature survey reveals that *trans*-trisubstituted electron-poor alkenes such as *trans*-2-aroyl-3-arylacrylonitriles[5] (**1**) are restricted substances in organocatalysis, given the fact that very limited literature reports are available on these substances although their functionalities offer possibility of additional transformations.

Herein, we wish to report a practical solution by using an organocatalyst to address the problem of using electron poor alkenes to construct pyran derivatives having three contiguous chiral centers. Our strategy was an amine-catalyzed Michael reaction of cyclohexanone (or anals) with *trans*-2-aroyl-3-aryl-acrylonitriles **1** and subsequent enolization and hemi-ketalization/acetalization to give pyran derivatives (Scheme 1).[6]

We began our investigation using *trans*-2-benzoyl-3-(4-benzonitrile)acrylonitrile (**1a**) and cyclohexanone (**2**) as the model substrates in the presence of *Cinchona*-based primary amine[7] catalysts (Fig. 1). Gratifyingly, substituted pyran **3a** was obtained with 80% ee in 79% yield (Table 1, entry 1) using **I** as catalyst. Encouraged by this result, a series of catalysts **II–V** (entries 2–5)



Scheme 1 A general strategy for the organocatalytic enantioselective synthesis of substituted pyrans.

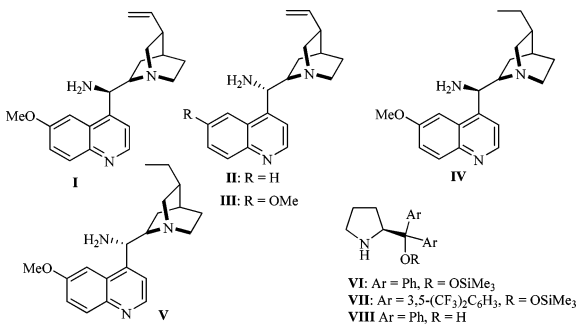


Fig. 1 Catalysts screened for this study.

were screened under the same conditions to find out the most suitable one. From the preliminary screening it was found that the catalyst **IV** was superior to others in terms of enantioselectivity and yield. Only a trace amount of the desired product could be detected when secondary amine catalyst **VI** was used in neat conditions (entry 6). To further optimize the reaction conditions, a series of solvents and additives were examined, and the key results are presented in Table 1. Although the reactions proceed readily in various solvents (for details see ESI‡) and also under solvent-free conditions, dichloromethane seems to be the better one. The use of various acidic co-catalysts (entries 9–11, for details see ESI‡) revealed that the enantioselectivity (96% ee) can be finely tuned using 2-fluorobenzoic acid (entry 10) accompanied by fair diastereoselectivity (5.4 : 1) and good yield. Importantly, the major diastereomer can be easily isolated by simple flash column chromatography. Using our protocol, it is also possible to obtain *ent*-**3** albeit with lower ee (87%, entry 3).

With an effective protocol for the enantioselective synthesis of pyran derivatives in hand, the substrate scope and generality of the method were examined (Table 2). A variety of substituents on both the aryl rings of **1** were well tolerated in our catalytic system, providing the desired substituted pyran adducts in

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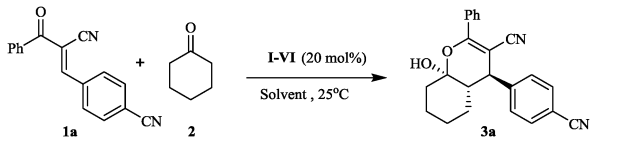
‡ Electronic supplementary information (ESI) available: Experimental procedure, spectral data of new compounds. CCDC 865351 (**3b**) and 865350 (**5d**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31445b

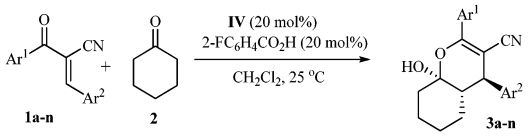
Table 1 Optimization of enantioselective synthesis of substituted pyrans[a]



Entry	Catalyst	Solvent	t/h	dr[b]	Yield[c] (%)	ee[d] (%)
1	**I**	CH_2Cl_2	36	4.6 : 1	79	80
2	**II**	CH_2Cl_2	18	2.8 : 1	72	−77
3	**III**	CH_2Cl_2	20	3.0 : 1	67	−87
4	**IV**	CH_2Cl_2	24	3.5 : 1	95	92
5	**V**	CH_2Cl_2	40	4.2 : 1	99	−83
6	**VI**	Neat	24	—	Trace	nd[e]
7	**IV**	$CHCl_3$	48[f]	2.7 : 1	70	93
8	**IV**	Toluene	48	4.6 : 1	95	90
9[g]	**IV**	CH_2Cl_2	36	5.6 : 1	94	90
10[h]	**IV**	$\mathbf{CH_2Cl_2}$	**60**	**5.4 : 1**	**97**	**96**
11[i]	**IV**	CH_2Cl_2	120	6.6 : 1	67	94

[a] **1a** (0.15 mmol), **2** (0.3 mmol) and cat. (20 mol%) were used in 0.15 mL solvent. [b] The diastereomeric ratio was measured by ^{1}H-NMR analysis of the crude reaction mixture. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [d] Enantiomeric excess determined by HPLC analysis. [e] Not determined. [f] 90% conversion. [g] $C_6H_5CO_2H$ (20 mol%) used as an additive. [h] 2-$FC_6H_4CO_2H$ (20 mol%) used as an additive (85% ee for the minor diastereomer).[8] [i] 2-$NO_2C_6H_4$-CO_2H (20 mol%) used as an additive.

Table 2 Enantioselective synthesis of substituted pyrans using **1** and **2**[a]



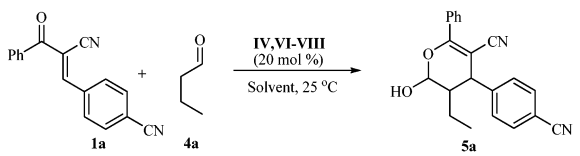
Entry	Ar^1	Ar^2	t/days	dr[b]	Yield of 3[c] (%)	ee[d] (%)
1	Ph	4-CNC_6H_4	2.5	5.4 : 1	90 (**3a**)	96
2	Ph	4-BrC_6H_4	2.5	4.8 : 1	84 (**3b**)	94
3	Ph	4-$NO_2C_6H_4$	2.0	5.6 : 1	77 (**3c**)	96
4	Ph	4-ClC_6H_4	2.5	3.7 : 1	85 (**3d**)	94
5	Ph	3-$NO_2C_6H_4$	4.0	5.4 : 1	79 (**3e**)	92
6	Ph	Ph	3.5	4.9 : 1	78 (**3f**)	95
7	Ph	4-MeC_6H_4	4.0	5.0 : 1	81 (**3g**)	93
8	Ph	4-$OMeC_6H_4$	4.0	4.5 : 1	78 (**3h**)	94
9	Ph	2-Furyl	1.0	5.2 : 1	88 (**3i**)	93
10	Ph	2-Thienyl	2.0	3.2 : 1	85 (**3j**)	95
11	Ph	2-Naphthyl	4.0	4.3 : 1	82 (**3k**)	60
12	Ph	2-BrC_6H_4	4.0	3.6 : 1	32 (**3l**)	86
13	4-BrC_6H_4	4-BrC_6H_4	2.0	4.6 : 1	81 (**3m**)	65
14	4-$OMeC_6H_4$	4-BrC_6H_4	4.0	9.0 : 1	86 (**3n**)	75

[a] **1** (0.25 mmol), **2** (0.5 mmol), **IV** (20 mol%) and 2-$FC_6H_4CO_2H$ (20 mol%) were used in 0.25 mL CH_2Cl_2. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.[8] [c] Isolated yields of the mixture of isomers. [d] Determined by HPLC analysis.

moderate to high yields (up to 90%), high diastereoselectivity (up to 9.0 : 1) and excellent enantioselectivities (up to 96%). The electronic feature of the aryl substituents Ar^2 seems to have little effect on the stereoselectivity or the chemical yield. As a result, the compounds **3a–e** with electron-withdrawing substituents (entries 1–5) and the compounds **3g**, **h** (entries 7 and 8) having electron-donating substituents were obtained in excellent enantioselectivity ranging from 92 to 96% ee. Heteroaromatic residues as Ar^2 were also applied well in our optimized protocol, achieving high stereocontrol (93, 95% ee) in the products **3i**, **j** in much shorter time (entries 9 and 10). We have also observed slight decrease in ee but with significantly diminished yield when an *ortho*-Br substituent was used in Ar^2 compared to a *para*-Br substituent (entry 2 *vs.* 12). Poor enantioselectivity was also obtained in the case of *para* substituents in the benzoyl moiety (Ar^1) of **1** (entries 13 and 14). Instead of Ar^2, a less reactive group like cyclohexyl showed no product formation under the optimized reaction conditions.[9] Meanwhile, in preparative synthesis, the reaction (**3b**) can also be performed with a fourfold excess without any significant loss of selectivity (98% ee) or yield (80%). The absolute configuration of **3b**[10] was determined by single crystal X-ray data analysis and those of others were assigned by analogy.

After successfully demonstrating the utility of our protocol to synthesize substituted pyrans using cyclohexanone, we turned our attention towards anals for our study. We have chosen **1a** and butyraldehyde (**4a**) as reaction partners for optimization of reaction conditions (some representative results are summarized in Table 3; for details, see ESI‡). In our preliminary study, the use of catalyst **IV** was not encouraging as it led to very poor chemical yield of our desired product **5a** (Table 3, entry 1). Then we switched to a pyrrolidine based catalyst[11] and carried out the same reaction with the most promising diphenylprolinol trimethylsilyl ether as catalyst (**VI**) leading to the successful formation of product **5a** in good yield (73%) and ee (90, 80%) (entry 2). The catalytic ability was further examined by using α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**VII**), but surprisingly no product formation was observed (entry 3). The use of catalyst **VIII** was also not much interesting (entry 4). Further optimizations of the reaction conditions by changing molar ratio of reactants, solvents and employing neat conditions (entries 5–8, for details see ESI‡) were not beneficial. The screening of acidic co-catalysts revealed that both the amount and nature of the acid influenced the results (see ESI‡).

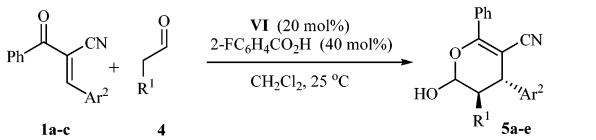
Table 3 Evaluation of the reaction condition[a]



Entry	Cat.	Solvent	t/days	dr[b]	Yield[c] (%)	ee[d] (%)
1	**IV**	CH_2Cl_2	3.0	1 : 1.2	21	nd[e]
2	**VI**	CH_2Cl_2	3.5	1 : 0.9	73	90, 80
3	**VII**	CH_2Cl_2	3.0	—	—	—
4	**VIII**	CH_2Cl_2	4.0	1 : 1.7	45	36, 86
5[f]	**VI**	CH_2Cl_2	3.0	1 : 1.1	69	88, 75
6	**VI**	Toluene	2.5	1 : 1.2	66	88, 72
7	**VI**	$CHCl_3$	2.5	1 : 1.1	63	88, 76
8	**VI**	Neat	3.5	1 : 1.0	40	84, 72
9[g]	**VI**	$\mathbf{CH_2Cl_2}$	**2.5**	**1 : 1.3**	**75**	**90, 87**
10[h]	**VI**	CH_2Cl_2	7.0	1 : 1.8	20	80, 60

[a] **1a** (0.1 mmol), **4a** (0.2 mmol), catalyst (20 mol%) and 2-$FC_6H_4CO_2H$ (20 mol%) were used in 0.1 mL solvent. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.[8] [c] Isolated yields of the mixture of isomers. [d] Determined by HPLC analysis. [e] Not determined. [f] 5 equiv. of **4a** was used. [g] 40 mol% 2-$FC_6H_4CO_2H$ was used. [h] 10 mol% **VI** and 20 mol% 2-$FC_6H_4CO_2H$ were used.

Table 4 Enantioselective synthesis of substituted pyrans using **1** and **4**[a]



1a-c 4 5a-e

Entry	R^1	Ar^2	t/days	dr[b]	Yield of **5**[c] (%)	ee[d] (%)
1	Et	4-CNC_6H_4	2.5	1 : 1.3	75 (**5a**)	90, 87
2	Et	4-BrC_6H_4	2.5	1 : 1.6	87 (**5b**)	89, 83
3	Et	4-$NO_2C_6H_4$	3.0	1 : 1.6	84 (**5c**)	88, 87
4	Me	4-BrC_6H_4	1.5	1 : 3.0	81 (**5d**)	55, 95
5	Me	4-CNC_6H_4	1.5	1 : 3.0	79 (**5e**)	61, 87

[a] **1** (0.25 mmol), **4** (0.5 mmol), **VI** (20 mol%) and 2-$FC_6H_4CO_2H$ (40 mol%) were used in 0.25 mL CH_2Cl_2. [b] Determined by ^1H NMR analysis of the crude reaction mixture.[8] [c] Isolated yields of the mixture of isomers. [d] Determined by HPLC analysis.

In fact, higher loading of 2-fluorobenzoic acid (40 mol%) led to slight increase in ee for both the diastereomers (90%, 87%) and yield (75%) in shorter time, but reducing the catalyst loading led to considerable loss of selectivity and yield (entries 9 and 10).

Having suitable conditions, the scope of the enantioselective synthesis of pyran derivatives using aldehydes (**4a**,**b**) and *trans*-2-aroyl-3-arylacrylonitriles (**1a–c**) was further demonstrated and is given in Table 4. Both butyraldehyde (**4a**) and propionaldehyde (**4b**) were successfully employed with the differently aryl-substituted **1** thus affording desired products **5a–e** in high chemical yields (up to 87%) and enantiomeric excess (up to 95% ee). Although the products **5a–c** generated from **4a** were afforded with poor diastereomeric ratios, the enantioselectivities of both isomers were comparably good (entries 1–3). But in the case of **4b**, the products **5d** and **5e** were obtained in better diastereomeric ratios and high enantioselectivities (95%, 87%) only for major isomers (entries 4 and 5). The absolute configuration of **5d**[10] was determined by single crystal X-ray data analysis and those of others were assigned by analogy.

In conclusion, we have demonstrated an efficient enantioselective cascade Michael addition–cyclisation reaction sequence to generate highly functionalized pyrans of synthetic and biological importance. Cyclohexanone and aliphatic aldehydes were successfully employed for the scope of the reaction with various *trans*-trisubstituted alkenes (**1a–n**) to provide the corresponding adducts in very high enantioselectivities (up to 96%) and very good yields (up to 90%) having three contiguous chiral centers one of which is quaternary (**3a–n**). The synthetic usefulness of this method lies in the fact that electron-poor alkenes were efficiently functionalized to access pyrans derivatives.

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Notes and references

1 For reviews, see: (*a*) K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237; (*b*) E. J. Kang and E. Lee, *Chem. Rev.*, 2005, **105**, 4348; (*c*) J. E. Aho, P. M. Pihko and T. K. Rissa, *Chem. Rev.*, 2005, **105**, 4406; (*d*) T. Nakata, *Chem. Rev.*, 2005, **105**, 4314; (*e*) A. Goel and V. J. Ram, *Tetrahedron*, 2009, **65**, 7865; (*f*) N. Bai, K. He, A. Ibarra, A. Bily, M. Roller, X. Chen and R. Ruhl, *J. Nat. Prod.*, 2010, **73**, 2.

2 For reviews, see: (*a*) I. Larrosa, P. Romea and F. Urpi, *Tetrahedron*, 2008, **64**, 2683; (*b*) P. A. Clarke and S. Santos, *Eur. J. Org. Chem.*, 2006, 2045.

3 For reviews, see: (*a*) F. Giacalone, M. Gruttadauria, P. Agrigento and R. Noto, *Chem. Soc. Rev*, DOI: 10.1039/c1cs15206h; (*b*) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703; (*c*) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen and K. A. Jørgensen, *Chem. Commun.*, 2011, **47**, 632; (*d*) D. R. Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry*, 2010, **21**, 2561; (*e*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*f*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (*g*) B. List, *Chem. Rev.*, 2007, **107**, 5413; (*h*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138.

4 For selected examples on organocatalytic stereoselective formation of pyran rings, see: (*a*) X. Wang, T. Fang and X. Tong, *Angew. Chem., Int. Ed.*, 2011, **50**, 5361; (*b*) H. Uehara, R. Imashiro, G. H. Torres and C. F. Barbas III, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20672; (*c*) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin and X. Feng, *J. Am. Chem. Soc.*, 2010, **132**, 10650; (*d*) J. Kaeobamrung, J. Mahatthananchai, P. Zheng and J. W. Bode, *J. Am. Chem. Soc.*, 2010, **132**, 8810; (*e*) H. Gotoh, D. Okamura, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2009, **11**, 4056; (*f*) D. Hazelard, H. Ishikawa, D. Hashizume, H. Koshino and Y. Hayashi, *Org. Lett.*, 2008, **10**, 1445; (*g*) T. Tozawa, H. Nagao, Y. Yamane and T. Mukaiyama, *Chem.–Asian J.*, 2007, **2**, 123; (*h*) K. Juhl and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 1498; (*i*) Y. Huang, A. K. Unni, A. N. Thadani and V. H. Rawal, *Nature*, 2003, **424**, 146.

5 For selected examples, (*a*) Ref. 4*a*; (*b*) C. D. Fusco, C. Tedesco and A. Lattanzi, *J. Org. Chem.*, 2011, **76**, 676.

6 We believe that the reaction proceeds through Michael reaction followed by enolization and cyclization. However hetero-Diels–Alder reaction described by Juhl and Jørgensen [see ref. 4*h*] cannot be excluded.

7 For reviews, see: (*a*) L. Jiang and Y.-C. Chen, *Catal. Sci. Technol.*, 2011, **1**, 354; (*b*) M. Tommaso and H. Henk, *Synthesis*, 2010, 1229; (*c*) L.-W. Xu, J. Luo and Y. Lu, *Chem. Commun.*, 2009, 1807; for selected recent examples; (*d*) L. Liu, D. Wu, X. Li, S. Wang, H. Li, J. Li and W. Wang, *Chem. Commun.*, 2012, **48**, 1692; (*e*) L.-L. Wang, L. Peng, J.-F. Bai, L.-N. Jia, X.-Y. Luo, Q.-C. Huang, X.-Y. Xu and L.-X. Wang, *Chem. Commun.*, 2011, **47**, 5593; (*f*) P. Kwiatkowski, T. D. Beeson, J. C. Conrad and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2011, **133**, 1738; (*g*) Q. Cai, C. Zheng, J.-W. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2011, **50**, 8665, and ref. 11 cited therein; (*h*) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7196; (*i*) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200.

8 The minor diastereomer of **3** or **5** which is observed in the crude reaction mixture has the structure with *syn* stereochemistry resulting from the Michael addition step.

9 We found that cyclopentanone and cycloheptanone were much less reactive in our optimized reaction conditions. There was even no product formation in the case of α-tetralone and 3-pentanone.

10 CCDC 865351 (**3b**) and 865350 (**5d**) contains supplementary crystallographic data for this paper (ESI‡).

11 For reviews, see: (*a*) A. Mielgo and C. Palomo, *Chem.–Asian J.*, 2008, **3**, 922; (*b*) C. Palomo and A. Mielgo, *Angew. Chem., Int. Ed.*, 2006, **45**, 7876; for selected recent examples; (*c*) J. Deng, F. Wang, W. Yan, J. Zhu, H. Jiang, W. Wang and J. Li, *Chem. Commun.*, 2012, **48**, 148; (*d*) B.-C. Hong, N. S. Dange, C.-S. Hsu, J.-H. Liao and G.-H. Lee, *Org. Lett.*, 2011, **13**, 1338; (*e*) V. Coeffard, A. Desmarchelier, B. Morel, X. Moreau and C. Greck, *Org. Lett.*, 2011, **13**, 5778; (*f*) K. L. Jensen, G. Dickmeiss, B. S. Donslund, P. H. Poulsen and K. A. Jørgensen, *Org. Lett.*, 2011, **13**, 3678; (*g*) H. Ishikawa, S. Sawano, Y. Yasui, Y. Shibata and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2011, **50**, 3774; (*h*) D. Enders, C. Wang, M. Mukanova and A. Greb, *Chem. Commun.*, 2010, **46**, 2447; (*i*) X. Companyo, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano and R. Rios, *Chem. Commun.*, 2010, **46**, 6953; (*j*) J. Jiang, L. He, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *Chem. Commun.*, 2007, 736.

