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Highly diastereo- and enantioselective Michael addition of 3-substituted benzofuran-2(3*H*)-ones to 4-oxo-enoates catalyzed by lanthanide(III) complexes†

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An efficient lanthanide(III)-catalyzed diastereo- and enantioselective Michael addition of 3-substituted benzofuran-2(3*H*)-ones to 4-oxo-enoates was developed. The desired adducts with contiguous quaternary–tertiary stereocenters were obtained in up to 99% yield with up to >95/5 dr and 98% ee.

Chiral 3,3-disubstituted benzofuran-2(3*H*)-ones bearing a quaternary stereogenic center at the C3 position are extremely important building blocks[1] in organic synthesis due to their biological activities.[2] For their construction,[3] the Michael reactions of 3-substituted benzofuran-2(3*H*)-ones with various electrophiles are very efficient methods.[4] Since the pioneering work by Luo *et al.* and Melchiorre in 2010,[5] several such Michael reactions have been realized using chiral thioureas or amines as organocatalysts.[6] However, 4-oxo-enoates[7] have not yet been investigated as Michael acceptors in such reactions, which can afford optical benzofuranones with contiguous quaternary–tertiary stereocenters.[8] What's more, searching for new efficient catalytic systems to construct optical benzofuranone derivatives with both high diastereo- and enantiomeric excesses[5,6a] are still desirable. Herein, we present an efficient lanthanide(III)-catalyzed diastereo- and enantioselective Michael addition reaction of 3-substituted benzofuran-2(3*H*)-ones to 4-oxo-enoates. The corresponding benzofuranones featuring all-carbon or thioatom-substituted quaternary stereocenters at the C3 position were obtained in high yields with excellent diastereo- and enantiomeric excesses.

Initially, we examined various *N*,*N*′-dioxides[9] (Fig. 1) complexed with $Sc(OTf)_3$ to catalyze the model reaction of 3-phenylbenzofuran-2(3*H*)-one **1a** with ethyl (*E*)-4-oxo-4-phenylbutenoate **2a** in C_2H_5OH. It was found that the substituent at the amide moiety of the *N*,*N*′-dioxide ligands affected the selectivity of the reaction apparently (Table 1, entries 1–4). Compared with ligand **L1**, ligand **L2** having a methyl group at the *ortho* position of the aniline, could achieve higher diastereo- and enantioselectivities (Table 1, entry 2 *vs.* entry 1). However, upon further increasing the steric hindrance of the amide moiety led to poor results (Table 1, entry 2 *vs.*

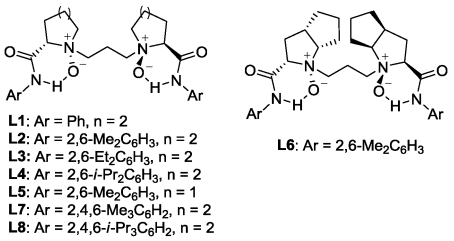
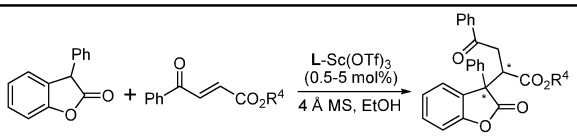


Fig. 1 Chiral ligands used in this study.

Table 1 Optimization of the reaction conditions[a]



1a 2a-e 3a-e

Entry	Ligand	R^4 (2)	Yield[b] (%)	dr[c]	ee[c] (%)
1	**L1**	Et (**2a**)	93 (**3a**)	83/17	87
2	**L2**	Et (**2a**)	92 (**3a**)	89/11	90
3	**L3**	Et (**2a**)	94 (**3a**)	90/10	87
4	**L4**	Et (**2a**)	90 (**3a**)	84/16	60
5	**L5**	Et (**2a**)	90 (**3a**)	91/9	68
6	**L6**	Et (**2a**)	85 (**3a**)	89/11	60
7[d]	**L7**	Et (**2a**)	98 (**3a**)	88/12[e]	91
8[d]	**L7**	Me (**2b**)	94 (**3b**)	78/22[e]	90
9[d]	**L7**	Bn (**2c**)	96 (**3c**)	86/14[e]	93
10[d]	**L7**	iPr (**2d**)	98 (**3d**)	93/7[e]	94
11[d]	**L7**	*t*Bu (**2e**)	97 (**3e**)	>95/5[e]	96
12[f]	**L7**	*t*Bu (**2e**)	96 (**3e**)	>95/5[e]	92
13[g]	**L7**	*t*Bu (**2e**)	97 (**3e**)	>95/5[e]	86

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and **2a–e** (0.11 mmol) in 1.0 mL EtOH with 5 mol% catalyst loading (metal : ligand = 1 : 1.2) and 20 mg 4 Å MS in air at 10 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC. [d] Reaction was performed at 0 °C for 5 h. [e] Determined by ^{1}H NMR of the crude products. [f] With 2 mol% catalyst at 23 °C for 8 h. [g] With 0.5 mol% catalyst at 23 °C for 12 h.

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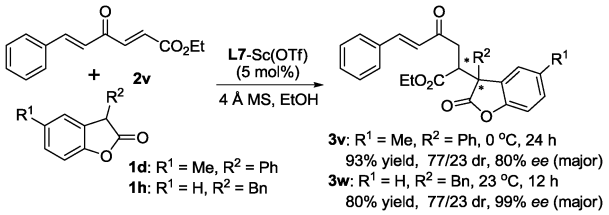
entries 3 and 4). As for the chiral backbone moiety, L-pipecolic acid derived ligand **L2** was superior to both L-proline derived **L5** and L-ramipril acid derived **L6** (Table 1, entry 2 *vs.* entries 5 and 6). *N*,*N*′-Dioxide **L7** derived from 2,4,6-trimethylaniline could give higher yield (98%) with 88/12 dr and 91% ee (Table 1, entry 7). Encouraged by the initial results, we next investigated the effect of ester groups of 4-oxo-4-arylbutenoates. As presented in Table 1, the more sterically hindered were the ester groups, the better were the diastereo- and enantioselectivities (Table 1, entries 7–11). To our delight, when (*E*)-*tert*-butyl 4-oxo-4-phenylbutenoate **2e** was employed, the product **3e** was obtained in 97% yield, with >95/5 dr and 96% ee (Table 1, entry 11). When the catalyst loading was reduced to 2 or 0.5 mol%, the diastereoselectivity was maintained, but the enantioselectivity was decreased (Table 1, entries 12 and 13).

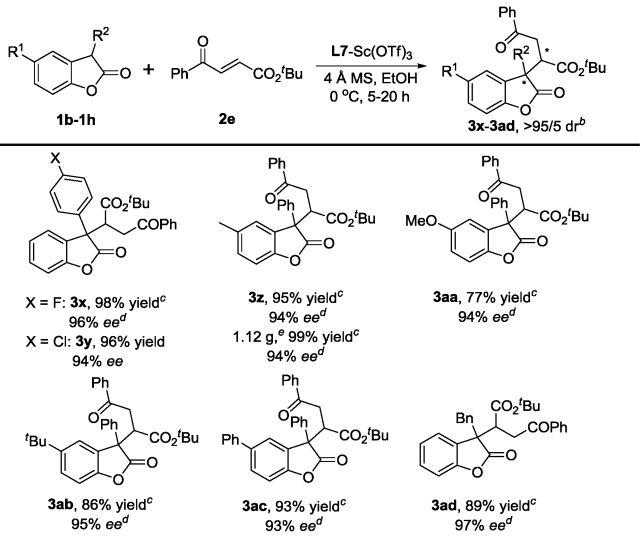
Under the optimal reaction conditions (Table 1, entry 11), the scope of the 4-oxo-enoates was examined. As summarized in Table 2, regardless of the electronic properties or steric hindrance of the substituents on the aromatic ring, the corresponding products were obtained in excellent yields with high diastereo- and enantiomeric excesses (Table 2, entries 1–9, 12–17). In addition, heteroaromatic, aliphatic and fused ring substrates were also well tolerated (Table 2, entries 10–11, 15–17). Furthermore, as 4-oxo-2,5-dienoate, the substrate **2v** with a cinnamyl group also gave good diastereo- and enantioselectivities (Scheme 1). The absolute configuration of **3n** was determined by X-ray crystallography to be (2*R*,3′*R*) (Table 2, entry 10).[10]

Then, the scope of benzofuran-2(3*H*)-ones was also examined. As shown in Table 3, a wide spectrum of 3-aryl benzofuran-2(3*H*)-ones bearing an electron-donating or an electron-withdrawing



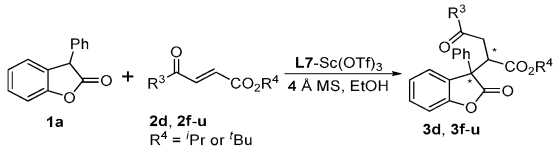
Scheme 1 Michael reactions of 4-oxo-2,5-dienoate **2v**.

Table 3 Substrate scope for benzofuran-2(3*H*)-ones[a]



[a] Please see the ESI for details. [b] Determined by ^{1}H NMR of the crude products. [c] Isolated yield. [d] Determined by HPLC. [e] The reaction was carried out on a 2.5 mmol scale with 2 mol% catalyst in 10.0 mL EtOH.

Table 2 Substrate scope for 4-oxo-enoates[a]



Entry	R^3	R^4	Prod.	dr[b]	Yield[c] (%)	ee[d] (%)
1	Ph	iPr	**3d**	93/7	98	94
2	2-FC_6H_4	iPr	**3f**	93/7	98	92
3	4-FC_6H_4	iPr	**3g**	92/8	97	96
4	4-ClC_6H_4	iPr	**3h**	94/6	98	96
5	4-BrC_6H_4	iPr	**3i**	93/7	98	97
6	3-ClC_6H_4	iPr	**3j**	94/6	98	96
7	3,4-$Cl_2C_6H_3$	iPr	**3k**	>95/5	96	97
8	4-MeC_6H_4	iPr	**3l**	89/11	98	96
9[e]	4-$MeOC_6H_4$	iPr	**3m**	91/9	95	93
10	2-Thienyl	iPr	**3n**	94/6	97	98[f]
11	2-Naphthyl	iPr	**3o**	93/7	98	96
12[e]	2-$MeOC_6H_4$	*t*Bu	**3p**	90/10	98	89
13[e]	4-$MeOC_6H_4$	*t*Bu	**3q**	>95/5	98	95
14	4-BrC_6H_4	*t*Bu	**3r**	>95/5	99	97
15	2-Furyl	*t*Bu	**3s**	>95/5	97	97
16	2-Naphthyl	*t*Bu	**3t**	>95/5	95	97
17	Cyclohexyl	*t*Bu	**3u**	>95/5	85	97

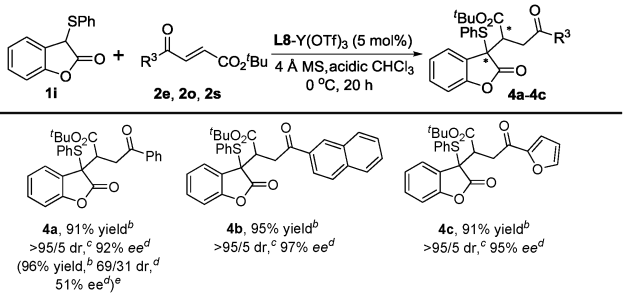
[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and **2** (0.11 mmol) in 1.0 mL EtOH with 5 mol% catalyst loading and 20 mg 4 Å MS in air at 0 °C for 5–20 h (see the ESI for details). [b] Determined by ^{1}H NMR of the crude products. [c] Isolated yield. [d] Determined by HPLC. [e] Reaction was performed at 25 °C. [f] The absolute configuration was determined to be (2*R*,3′*R*) by X-ray crystallographic analysis.

substituted aryl group could achieve excellent diastereo- and enantioselectivities (up to >95/5 dr, 98% ee). The benzyl substituted benzofuran-2(3*H*)-one **1h** also reacted well, generating the desired product **3ad** in high yield and with excellent diastereo- and enantioselectivities. Notably, by treatment of 2.5 mmol of starting material with 2 mol% catalyst, the optically active benzofuran-2(3*H*)-one **3z** was still obtained with excellent results (1.12 g, 98% yield, >95/5 dr, and 94% ee).

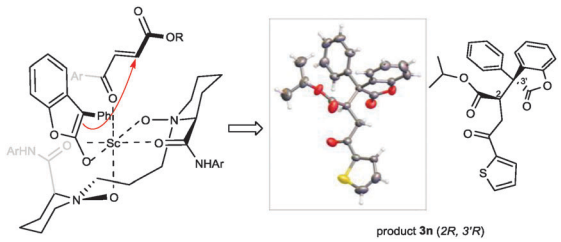
To further extend the application of this protocol,[11] 3-(phenylthio)-benzofuran-2(3*H*)-one **1i** was tested. However, only moderate results (**4a**; 96% yield, 69/31 dr, and 51% ee) were obtained using the present catalyst system, which is probably due to the interaction between thioatom and the scandium catalyst. Pleasingly, excellent results could be achieved (Table 4; up to 95% yield, >95/5 dr, and 97% ee) by employing a complex of $Y(OTf)_3$ with more sterically hindered ligand **L8** and acidic chloroform as a solvent (see the ESI† for details). This is the first example of asymmetric construction of chiral 3,3-disubstituted benzofuran-2(3*H*)-ones bearing a thioatom-substituted quaternary stereocenter at the C3 position.

Based on the absolute configuration of the product **3n** and our previous reports on *N*,*N*′-dioxide–lanthanide complexes,[9] a possible working model was proposed to explain the origin of the asymmetric induction of the Sc(III)-complex-catalyzed reaction (Scheme 2).

Table 4 Substrate scope for Michael reactions of 3-(phenylthio) benzofuran-2(3*H*)-one to 4-oxo-enoates[a]



[a] Please see the ESI for details. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude products. [d] Determined by HPLC. [e] Using **L7**-Sc(OTf)$_3$ as a catalyst in EtOH.



Scheme 2 Proposed transition state model and the X-ray crystallographic structure of **3n**.

In this transition state, the oxygens of *N*,*N*′-dioxides and amide oxygens coordinated to Sc(III) in a tetradentate manner. Benzofuran-2(3*H*)-one **1a** coordinated to the Sc(III) *via* oxygen to form the enolate **1a**′. Meanwhile, 4-oxo-enoate was attached to Sc(III) at the favorable equatorial position.[12] As a result, the *Si* face of benzofuranolate **1a**′ preferred to attack the *Si* face of 4-oxo-enoate **2n** to afford the desired Michael adduct **3n** with a (2*R*,3′*R*)-configuration.

In summary, we have developed a highly diastereo- and enantioselective Michael reaction of 3-substituted benzofuran-2(3*H*)-ones with 4-oxo-enoates promoted by 0.5–5 mol% *N*,*N*′-dioxide–lanthanide complexes. The protocol not only delivers a wide variety of enantiopure 3,3-disubstituted benzofuran-2(3*H*)-ones with excellent diastereo- and enantioselectivities (up to >95/5 dr, 98% ee), but also successfully constructs optical benzofuran-2(3*H*)-ones bearing thioatom-substituted quaternary stereocenters for the first time. Further application of the current method is currently underway.

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Notes and references

1 For selected examples of nature products: (*a*) N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303; (*b*) C. M. Passreiter, H. Weber, D. Bläser and R. Boese, *Tetrahedron*, 2002, **58**, 279; (*c*) B. Sontag, M. Rüth, P. Spiteller, N. Arnold, W. Steglich, M. Reichert and G. Bringmann, *Eur. J. Org. Chem.*, 2006, 1023; (*d*) Y.-J. Kwon, M.-J. Sohn, C.-J. Zheng and W.-G. Kim, *Org. Lett.*, 2007, **9**, 2449; (*e*) H. M. Ge, C. H. Zhu, D. H. Shi, L. D. Zhang, D. Q. Xie, J. Yang, S. W. Ng and R. X. Tan, *Chem. – Eur. J.*, 2008, **14**, 376.

2 (*a*) S. A. Adediran, D. Vabaret, B. Drouillat, R. F. Pratt and M. Wakselman, *Bioorg. Med. Chem.*, 2001, **9**, 1175; (*b*) E. K. Panisheva, L. M. Alekseeva, M. I. Evstratova, S. S. Kiselev and V. G. Granik, *Pharm. Chem. J.*, 2007, **41**, 549; (*c*) P. Nesvadba, S. Evans, C. Kröhnke and J. Zingg, *Ger. Offen.* 4432732, 1995; (*d*) H. S. Laver and P. Nesvadba, *Eur. Pat. Appl.* 857765, 1998; (*e*) M. Frenette, P. D. MacLean, R. C. Barclay and J. C. Scaiano, *J. Am. Chem. Soc.*, 2006, **128**, 16432; (*f*) Y. Li, A. J. Lampkins, M. B. Baker, B. G. Sumpter, J. Huang, K. A. Abboud and R. K. Castellano, *Org. Lett.*, 2009, **11**, 4314.

3 For a recent review, see: (*a*) Y. Li, X. Li and J.-P. Cheng, *Adv. Synth. Catal.*, DOI: 10.1002/adsc.201301038. For selected examples of other strategies, such as asymmetric Black rearrangement, amination, allylation *etc.*, see: (*b*) I. D. Hills and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 3921; (*c*) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va and E. Vedejs, *J. Am. Chem. Soc.*, 2006, **128**, 925; (*d*) C.-L. Zhu, F.-G. Zhang, W. Meng, J. Nie, D. Cahard and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2011, **50**, 5869; (*e*) K. Ohmatsu, M. Ito, T. Kunieda and T. Ooi, *J. Am. Chem. Soc.*, 2013, **135**, 590; (*f*) C. Liu, B. Tan, J.-L. Jin, Y.-Y. Zhang, N. Dong, X. Li and J.-P. Cheng, *J. Org. Chem.*, 2011, **76**, 5838; (*g*) C. L. Zhu, X. Y. Fu, A. J. Wei, D. Cahard and J. A. Ma, *J. Fluorine Chem.*, 2013, **150**, 60; (*h*) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; (*i*) M. L. Wang, Z. F. Zhang, S. Liu, F. Xie and W. B. Zhang, *Chem. Commun.*, 2014, **50**, 1227.

4 For books and recent reviews of Michael reaction, see: (*a*) E. N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer, New York, 1999; (*b*) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033; (*c*) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri and M. Petrini, *Chem. Rev.*, 2005, **105**, 933.

5 (*a*) X. Li, Z. Xi, S. Luo and J.-P. Cheng, *Adv. Synth. Catal.*, 2010, **352**, 1097; (*b*) F. Pesciaioli, X. Tian, G. Bencivenni, G. Bartoli and P. Melchiorre, *Synlett*, 2010, 1704.

6 (*a*) X. Li, S. S. Hu, Z. G. Xi, L. Zhang, S. Luo and J.-P. Cheng, *J. Org. Chem.*, 2010, **75**, 8697; (*b*) C. Cassani, X. Tian, E. C. Escudero-Adán and P. Melchiorre, *Chem. Commun.*, 2011, **47**, 233; (*c*) X. Li, X. Xue, C. Liu, B. Wang, B. Tan, J. L. Jin, Y. Y. Zhang, N. Dong and J.-P. Cheng, *Org. Biomol. Chem.*, 2012, **10**, 413; (*d*) X. Li, Y. Y. Zhang, X. Xue, J. L. Jin, B. Tan, C. Liu, N. Dong and J.-P. Cheng, *Eur. J. Org. Chem.*, 2012, 1774; (*e*) J. H. Chen, Y. P. Cai and G. Zhao, *Adv. Synth. Catal.*, 2014, **356**, 359.

7 For selected examples, see: (*a*) Z. Jiang, Y. Yang, Y. Pan, Y. Zhao, H. Liu and C.-H. Tan, *Chem. – Eur. J.*, 2009, **15**, 4925; (*b*) H. Lu, X. Wang, C. Yao, J. Zhang, H. Wu and W.-J. Xiao, *Chem. Commun.*, 2009, 4251; (*c*) Z. Wang, D. H. Chen, Z. G. Yang, S. Bai, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. – Eur. J.*, 2010, **16**, 10130.

8 For selected reviews, see: (*a*) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (*b*) D. J. Ramón and M. Yus, *Curr. Org. Chem.*, 2004, **8**, 149; (*c*) J. Christoffers and A. Baro, *Angew. Chem., Int. Ed.*, 2003, **42**, 1688.

9 For our own work in this field, see: (*a*) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; (*b*) L. Zhou, X. H. Liu, J. Ji, Y. H. Zhang, X. L. Hu, L. L. Lin and X. M. Feng, *J. Am. Chem. Soc.*, 2012, **134**, 17023; (*c*) K. Shen, X. H. Liu, G. Wang, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2011, **50**, 4684; (*d*) Y. F. Cai, X. H. Liu, Y. H. Hui, J. Jiang, W. T. Wang, W. L. Chen, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2010, **49**, 6160.

10 CCDC 983289 (**3n**).

11 The current catalytic system was not efficient for the reaction with chalcone. Only 9% yield, 86/14 dr, 69% ee was obtained when **1b** reacted with chalcone (see the ESI† for details).

12 T. C. Wabnitz, J.-Q. Yu and J. B. Spencer, *Chem. – Eur. J.*, 2004, **10**, 484.

