CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

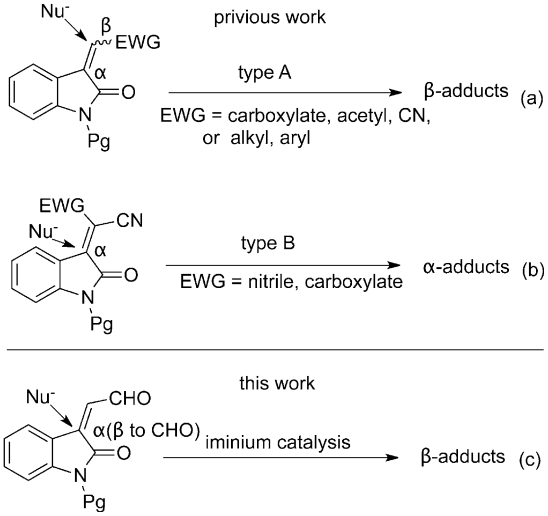
DOI: 10.1002/chem.201300977

Organocatalytic Michael Addition of Malonates to Isatylidene-3-acetaldehydes: Application to the Total Synthesis of (−)-Debromoflustramine E

Renrong Liu[a] and Junliang Zhang*[a, b]

Oxindoles bearing a quaternary carbon stereocenter at the 3-position are ubiquitous in nature and have been shown to be valuable building blocks for alkaloid synthesis.[1] Several strategies have been developed to achieve the enantioselective synthesis of 3,3′-disubstituted oxindoles, including 1) the direct functionalization of 3-substituted oxindoles;[2] 2) intramolecular coupling reactions (Heck[3] and arylation reactions[4]); 3) the rearrangement of indolyl acetates and carbonates;[5] and 4) the alkylation of 3-halooxindoles or 3-hydroxyoxindoles.[6]

In recent years, methyleneindolinones have attracted considerable attention as novel substrates for the enantioselective synthesis of 3,3′-dialkyloxindoles.[7] Trost and co-workers[7a] first reported an enantioselective palladium-catalyzed [3+2] cycloaddition reaction of 3-alkylideneoxindolin-2-ones with cyano-substituted trimethylenemethane to construct spirocyclic oxindolic cyclopentanes. The groups of Melchiorre,[7b] Barbas,[7c–e] Gong,[7f] Chen,[7g] Bencivenni,[7h] and Wang[7i,j] have developed several excellent organocatalytic methods to construct spirooxindoles by using methyleneindolinones in tandem reactions. Waldmann and co-workers[8] also developed a highly enantioselective Lewis acid catalyzed 1,3-dipolar cycloaddition reaction for the synthesis of 3,3′-pyrrolidinylspirooxindoles. However, all of these methods were initiated by a nucleophilic addition at the β-position, leading to β-adducts (type A, Scheme 1a) and the quaternary stereogenic centers were constructed in the second step by intramolecular functionalization of 3-substituted oxindoles. These methods are limited to cyclic quaternary stereogenic centers.



Scheme 1. Previous and proposed work.

In 1980, Kimio and co-workers[9a] reported a tandem reaction of 1,3-diones and isatylidene malononitriles to afford spirooxindoles, initiated by a conjugated addition at the α-position (Scheme 1b). However, recently, Yuan and co-workers[9b] reported the first enantioselective method for the synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives in a reaction catalyzed by cupreine. Shortly after this, Wang, Tao, and co-workers[9c] reported an efficient construction of the spirooxindole backbone in an optically pure form through a cascade Michael addition of isatylidene malononitriles with unsaturated ketones. Lu and co-workers[9d] also reported an elegant phosphine-catalyzed asymmentric [3+2] cycloaddition reaction of Morita–Baylis–Hillman adducts with isatylidene malononitriles leading to 3-spirocyclopentene-2-oxindoles. Recently, Wang and co-workers[9e,f] disclosed two organocatalytic, highly enantioselective conjugated addition reactions of ketones or nitroalkanes to isatylidine malononitriles and indolylidenecyanoacetates, leading to optically active α adducts. However, to synthesize these α adducts with a chiral quaternary stereocenter, these methods (Scheme 1b) require two electron-withdrawing groups, one of which must be a nitrile group,[10] limiting their use. Very recently, Arai and co-workers developed an elegant method to construct 3,3′-disubstituted oxindoles that is catalyzed by $Cu(OTf)_2$ using isatin-derived nitroalkenes as a novel methyleneindolinone.[11]

[a] R. Liu, Prof. Dr. J. Zhang
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry
East China Normal University
3663 N. Zhongshan Road, Shanghai 200062 (P.R. China)
Fax: (+86) 21-6223-3213
E-mail: jlzhang@chem.ecnu.edu.cn

[b] Prof. Dr. J. Zhang
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (P.R. China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300977.

Iminium catalysis has now been established as one of the key catalytic concepts in organocatalysis.[12] We envisioned that isatylidene-3-acetaldehyde (Scheme 1c), the electrophilic position in which may convert from β to α through iminium catalysis by use of LUMO-lowering activation, may be a good candidate to construct the quaternary carbon stereocenter. However, asymmetric conjugate addition to a β,β-disubstituted α,β-unsaturated aldehyde is still a very challenging task.[13] We report herein a new enantioselective synthesis of 3,3′-disubstituted oxindoles by conjugate addition of malonates to isatylidene-3-acetaldehyde under iminium catalysis. This transformation provides a facile route for the enantioselective total synthesis of debromoflustramine E. To the best of our knowledge, this is the first example of the use of β-carbonyl-substituted α,β-unsaturated aldehydes to construct the quaternary stereocenter.[14–16]

In our initial study, we found, to our delight, that in the presence of catalyst **3a** and $PhCO_2H$, the Michael addition of dimethyl malonate **2a** to isatylidene-3-acetaldehyde ((*E*)-**1a**) gave the desired product **4a** with moderate enantioselectivity (Table 1, entry 1). Gratifyingly, the *Z* isomer of **1a** gave a higher enantioselectivity (Table 1, entry 2). A variety of α,α-diaryl prolinol derived catalysts were screened (Figure 1). With catalyst **3c**, we could obtain higher enantio-

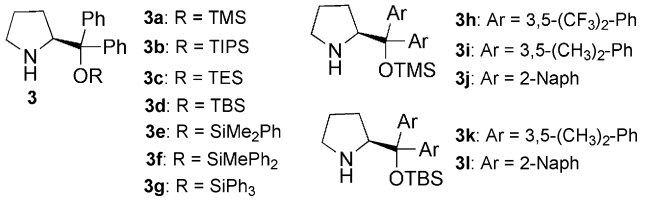
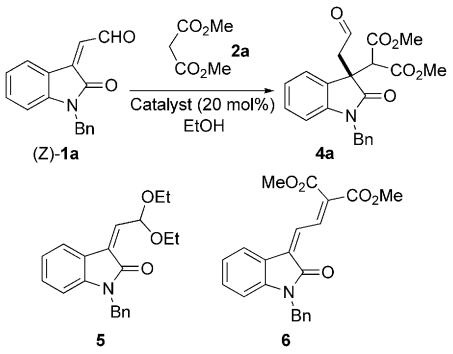


Figure 1. Screened catalysts (TMS = trimethylsilyl, TIPS = triisopropyldilyl, TES = triethylsilyl TBS = *tert*-butyldimethylsilyl,Naph = naphthyl).

selectivity, but in only 30% yield, and a significant amount of the condensation product **6** was isolated (Table 1, entry 4). To our delight, the reaction proceeded smoothly to afford the desired product in 81% yield and 88% enantiomeric excess (*ee*) at room temperature when the TBS-protected compound **3d** was employed as the catalyst (Table 1, entry 5). Unfortunately, no improvement in enantioselectivity was achieved by use of the other catalysts screened, which contain a variety of silyl ether (**3e**–**3g**), phenyl, and aryl groups (**3h**–**3j** and **3k**–**3l**; Table 1, entries 6-13). When a stronger acid was used, none of the desired product was formed. The acetal product **5** was obtained from reactions in EtOH (Table 1, entries 16 and 17). Further screening of the reaction conditions revealed that lowering the temperature to 0°C resulted in a slightly better enantioselectivity of 90% *ee* (Table 1, entry 18), and up to 93% *ee* could be achieved by lowing the temperature to −20°C (Table 1, entry 19). Indeed, the addition of 1.3 equivalents of water accelerated the reaction rate without loss of enantioselectivity (Table 1, entry 20). To our delight, reducing the catalyst loading did not alter the enantioselectivity or the efficiency

Table 1. Catalyst screening and optimization of the reaction conditions.[a]



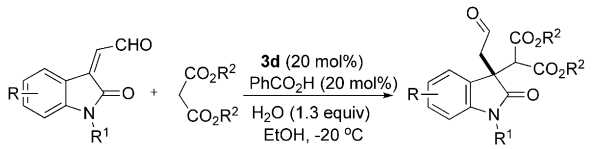
Entry	Catalyst	Additive	*t* [h]	Yield **4a** [%]	*ee* [%]
1	**3a**	$PhCO_2H$	3	72	50[b]
2	**3a**	$PhCO_2H$	3	75	66
3	**3b**	$PhCO_2H$	3	65	84
4	**3c**	$PhCO_2H$	3	30	91[c]
5	**3d**	$PhCO_2H$	3	81	88
6	**3e**	$PhCO_2H$	3	50	46
7	**3f**	$PhCO_2H$	3	45	41
8	**3g**	$PhCO_2H$	3	35	66
9	**3h**	$PhCO_2H$	3	–	–[d]
10	**3i**	$PhCO_2H$	3	62	50
11	**3j**	$PhCO_2H$	3	65	67
12	**3k**	$PhCO_2H$	3	78	78
13	**3l**	$PhCO_2H$	3	70	67
14	**3d**	2-F-$PhCO_2H$	1	80	79
15	**3d**	NaOAc	0.5	–	–[d]
16	**3d**	TsOH	0.5	0 (75)[e]	–
17	**3d**	TFA	0.5	0 (80)[e]	–
18[f]	**3d**	$PhCO_2H$	24	81	90
19[g]	**3d**	$PhCO_2H$	48	81	93
20[h]	**3d**	$PhCO_2H$	24	81	93
21[i]	**3d**	$PhCO_2H$	84	78	92
22[j]	**3d**	$PhCO_2H$	176	72	92

[a] Reaction conditions: **1a** (0.06 mmol, 1.0 equiv), **2a** (0.12 mmol, 2.0 equiv), catalyst (20 mol%), $PhCO_2H$ (20 mol%), H_2O (1.3 equiv) with the solvent indicated (0.1 M) at room temperature. [b] (*E*)-**1a** was used. [c] Compound **6** was formed as the major product. [d] Complex mixture of products. [e] The number in parentheses refers to the isolated yield of compound **5**. [f] The reaction was performed at 0°C. [g] The reaction was performed at −20°C. [h] The reaction was performed with H_2O (1.3 equiv) at −20°C. [i] The reaction was performed with the catalyst (10 mol%) and H_2O (1.3 equiv) at −20°C. [j] The reaction was performed with the catalyst (5 mol%) and H_2O (1.3 equiv) at −20°C.

too much, requiring only a longer reaction time (Table 1, entries 21–22).

With the optimal reaction conditions in hand, we investigated the reaction scope by varying two reaction components. Generally, both electron-withdrawing and -donating substituents on the oxindole moiety were tolerated, affording the corresponding products with ≥90% *ee* (Table 2, entries 1–11). The reaction of 4-Br substituted **1g** offered the highest enantioselectivity (99% *ee*) and yield (91%; Table 2, entry 7). In general, the substrates containing electron-withdrawing groups gave lower yields and enantiomeric excesses than those containing electron-donating groups, which may be due to the fact that these substrates are highly reactive and easily undergo side reactions. The substituent effect of

Table 2. Substrate scope of isatylidene-3-acetaldehyde and malonate.[a]

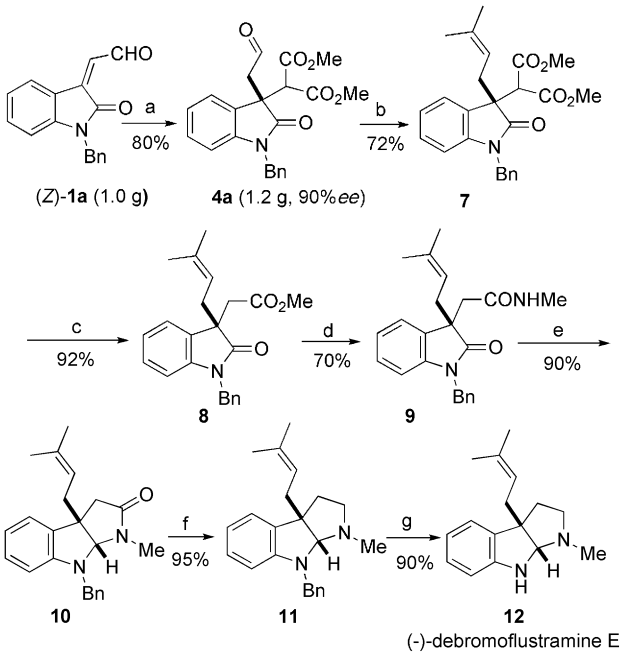


Entry	R/R^1 (**1**)	R^2 (**2**)	*t* [d]	Yield (**4**) [%][b]	*ee* [%][c]
1	H/Bn (**1a**)	Me (**2a**)	1.5	81 (**4a**)	93
2	5-Me/Bn (**1b**)	**2a**	2	83 (**4b**)	94
3	5-OMe/Bn (**1c**)	**2a**	2.5	80 (**4c**)	96
4	5-Br/Bn (**1d**)	**2a**	2	71 (**4d**)	95
5	5-Cl/Bn (**1e**)	**2a**	1	70 (**4e**)	92
6	5-F/Bn (**1f**)	**2a**	1.5	60 (**4f**)	90
7	4-Br/Bn (**1g**)	**2a**	1.5	91 (**4g**)	99
8	6-Br/Bn (**1h**)	**2a**	3	70 (**4h**)	94
9	7-Me/Bn (**1i**)	**2a**	2	73 (**4i**)	96
10	7-Cl/Bn (**1j**)	**2a**	2	70 (**4j**)	98
11	7-F/Bn (**1k**)	**2a**	2	63 (**4k**)	93
12	H/Me (**1l**)	**2a**	1.5	73 (**4l**)	88
13	H/allyl (**1m**)	**2a**	1.5	67 (**4m**)	90
14	H/prenyl (**1n**)	**2a**	1.5	61 (**4n**)	91
15	H/Ph (**1o**)	**2a**	1	70 (**4o**)	90
16	H/H (**1p**)	**2a**	2	82 (**4p**)	80
17	5-Me/allyl (**1q**)	**2a**	1.5	82 (**4q**)	91
18	5-OMe/allyl (**1r**)	**2a**	1.5	83 (**4r**)	97
19	**1r**	Bn (**2b**)	1.5	83 (**4s**)	97
20	**1a**	**2b**	1.5	81 (**4t**)	95
21	**1a**	allyl (**2c**)	1.5	88 (**4u**)	93
22	**1a**	Et (**2d**)	2.5	82 (**4v**)	93

[a] Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.0 equiv), catalyst **3d** (20 mol%), $PhCO_2H$ (20 mol%), H_2O (1.3 equiv) with EtOH (0.1 M) at −20 °C. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

N-protecting groups on the oxindole moiety was also investigated (Table 2, entries 12–15) and it was found that not only alkyl groups, such as methyl, allyl, and prenyl, but also aryl groups were compatible, efficiently yielding the desired products in high enantioselectivity. The N-unprotected compound **1p** could provide product **4p** in 82% yield but slightly lower *ee* (80%; Table 2, entry 16). Next, diethyl, dibenzyl, and diallyl malonates **2b–2d** were investigated and all of these malonates were applicable in this transformation, giving 81–88% yields of the products in 93–97% *ee* (Table 2, entries 19–22).

Pyrrolidinoindolines bearing a prenyl substitutent at C3 of the hexahydropyrrolo[2,3-*b*]indole ring system have been obtained from a diverse array of natural sources.[17] The efficient and enantioselective construction of the prenyl-substituted quaternary carbon center at the C3 position offers an interesting synthetic problem.[18] The utility of the conjugate addition of malonates to isatylidene-3-acetaldehyde is demonstrated by a total synthesis of (−)-debromoflustramine E (Scheme 2). The enantioselective Michael addition gave **4a** in 80% yield and 90% *ee*, running with 1.0 g of **1a** and 10 mol% catalyst **3d**. The Wittig reaction of **4a** furnished compound **7** in 72% yield, which was subjected to Krapcho decarboxylation to give the desired product **8** in 92% yield. The amidation reaction of **8** with methylamine produced the



Scheme 2. The total synthesis of (−)-debromoflustramine E. Reaction conditions: a) **2a** (2.0 equiv), **3d** (10 mol%), $PhCO_2H$ (20 mol%), H_2O (1.3 equiv), EtOH, −20 °C; b) *n*BuLi, $Ph_3P^+CHMe_2I^-$, THF, 0 °C; c) NaCl, DMSO/H_2O, 160 °C; d) $MeNH_2$(EtOH), 60 °C; e) $LiAlH_4$, THF, 0 °C; f) $LiAlH_4$, THF, reflux; g) $Na/NH_{3(l)}$, −78 °C (Bn = benzyl).

methyl amide **9**, which was then reduced with $LiAlH_4$ over two steps, first at 0 °C and then at reflux, to yield compound **11**. Under the Na/NH_3 conditions, deprotection of the benzyl group easily took place to afford (−)-debromoflustramine E (**12**) in 90% yield (7 steps, 29% overall yield from isatylidene-3-acetaldehyde, **1a**). The absolute configuration was determined by comparison of the optical rotation with that reported in the literature.[18e,j] This absolute configuration is reasonable considering that the malonate component approaches opposite the face of the bulky diphenyl(*tert*-butyldimethylsiloxy)methyl group (Figure 2).

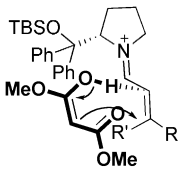
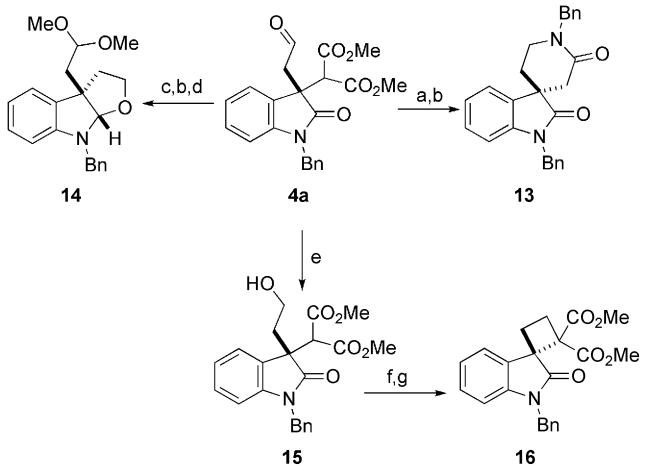


Figure 2. The transition state of the reaction.

As well as hexahydropyrrolo[2,3-*b*]indoles, the spirooxindole and hexahydrofurano[2,3-*b*]indole cores also frequently appear in bioactive naturally occurring alkaloids and medicinally relevant compounds.[19] To further demonstrate the synthetic importance of this reaction, we enantioselectively constructed several different oxindole cores that feature in alkaloids (Scheme 3). Reductive amination of **4a** with benzylamine, followed by condensative cyclization yielded the lactam in 70% overall yield, which was then decarboxylated by use of the Krapcho reaction to give a 96% yield of spirooxindole **13**, the core structure of communesin.[19c] Through protection of the aldehyde, Krapcho decarboxylation, and reduction, **4a** could be efficiently converted into



Scheme 3. The synthesis of spirooxindole and hexahydrofurano[2,3-*b*]indole. Reaction conditions: a) $BnNH_2$, $Na(OAc)_3BH$, dioxane, 70%; b) NaCl, DMSO/H_2O, 160°C, 96%; c) TsOH, $CH(OCH_3)_3$, quantitative; d) LAH, 94%; e) $NaBH_4$, MeOH, −20°C, 95%; f) MsCl, Et_3N, 95%; g) NaH, THF, quantitative (Ts = tosyl, LAH = lithium aluminum hydride).

hexahydrofurano[2,3-*b*]indole **14**, the core structure of physovenine.[19d] Finally, we synthesized the four-membered-ring-containing spirooxindole **16** in a three step sequence, the structure of which can be found in welwitindolinone A.[19e]

In summary, we have developed an enantioselective synthesis of 3,3′-disubstituted oxindoles by conjugate addition of malonates to isatylidene-3-acetaldehyde in high yield and excellent enantioselectivity. This transformation is easily scaled up to the gram scale, and its synthetic applications have been showcased by the enantioselective synthesis of core skeletons of three indoline-derived alkaloids and the asymmetric total synthesis of debromoflustramine E in a relatively short route. Further studies, including synthesis of other hexahydropyrrolo[2,3-*b*]indole alkaloids and other nucleophiles, are being conducted in this laboratory and will be reported in due course.

Experimental Section

Typical procedure for the organocatalytic addition of malonates to α,β-unsaturated aldehydes: Malonate **2a** (0.5 mmol, 2.0 equiv) was added to a solution of **3d** (18.35 mg, 0.05 mmol, 0.2 equiv), $PhCO_2H$ (6.2 mg, 0.05 mmol, 0.2 equiv), and **1a** (0.25 mmol, 67.75 mg, 1.0 equiv) in EtOH (2.5 mL) containing H_2O (1.3 equiv) at −20°C. The reaction mixture was stirred for 36 h at −20°C and then filtered through a 1–2 cm pad of silica, washing through with EtOAc and CH_2Cl_2. The solvents were evaporated under vacuum. The crude product was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 15:1) to yield the desired product **4a** (79.9 mg, 81%).

Acknowledgements

Financial support from the 973 program (2011CB808600), the National Natural Science Foundation of China, the Ministry of Educationof China, and the Ying Tung Education Foundation (121014) is acknowledged. This research is also supported by the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning.

Keywords: asymmetric synthesis · enantioselectivity · Michael addition · organocatalysis · oxindoles

[1] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; b) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; c) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38; *Angew. Chem. Int. Ed.* **2003**, *42*, 36; d) K. Shen, X. Liu, L. Lin, X. Feng, *Chem. Sci.* **2012**, *3*, 327; e) F. Zhou, Y. L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381.

[2] a) R. He, C. Ding, K. Maruoka, *Angew. Chem.* **2009**, *121*, 4629; *Angew. Chem. Int. Ed.* **2009**, *48*, 4559; b) P. Galzerano, G. Bencivenni, F. Pesciaioli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2009**, *15*, 7846; c) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 4590; d) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 14548; e) B. M. Trost, M. U. Frederiksen, *Angew. Chem.* **2005**, *117*, 312; *Angew. Chem. Int. Ed.* **2005**, *44*, 308; f) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2007**, *119*, 8820; *Angew. Chem. Int. Ed.* **2007**, *46*, 8666; g) X. Tian, K. Jiang, J. Peng, W. Du, Y.-C. Chen, *Org. Lett.* **2008**, *10*, 3583; h) T. Bui, S. Syed, C. F. Barbas II, *J. Am. Chem. Soc.* **2009**, *131*, 8758; i) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168; j) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620; k) X. Li, S.-Z. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 14290; l) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; m) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339; n) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhou, *Chem. Sci.* **2011**, *2*, 2035; o) H. Mitsunuma, M. Shibasaki, M. Kanai, S. Matsunaga, *Angew. Chem.* **2012**, *124*, 5307; *Angew. Chem. Int. Ed.* **2012**, *51*, 5217; p) C. Wang, X. Yang, D. Enders, *Chem. Eur. J.* **2012**, *18*, 4832.

[3] a) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945, and references therein; c) A. Ashimori, B. Bachand, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6477; d) A. Ashimori, T. Matsuura, L. E. Overman, D. J. Poon, *J. Org. Chem.* **1993**, *58*, 6949; e) C. A. Busacca, D. Grossbach, R. C. So, E. M. O Brien, E. M. Spinelli, *Org. Lett.* **2003**, *5*, 595.

[4] E. P. Kündig, T. M. Seidel, Y.-X. Jia, G. Bernardinelli, *Angew. Chem.* **2007**, *119*, 8636; *Angew. Chem. Int. Ed.* **2007**, *46*, 8484.

[5] a) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921; b) T. A. Duffey, S. A. Shaw, E. Vedejs, *J. Am. Chem. Soc.* **2009**, *131*, 14; c) B. M. Trost, M. K. Brennan, *Org. Lett.* **2006**, *8*, 2027; d) S. Adhikari, S. Caille, M. Hanbauer, V. X. Ngo, L. E. Overman, *Org. Lett.* **2005**, *7*, 2795; e) L. E. Overman, Y. Shin, *Org. Lett.* **2007**, *9*, 339; f) E. C. Linton, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 16162; g) T. Cao, J. Deitch, E. C. Linton, M. C. Kozlowski, *Angew. Chem.* **2012**, *124*, 2498; *Angew. Chem. Int. Ed.* **2012**, *51*, 2448.

[6] a) S. Ma, X. Han, S. Krishnan, S. C. Virgil, B. M. Stoltz, *Angew. Chem.* **2009**, *121*, 8181; *Angew. Chem. Int. Ed.* **2009**, *48*, 8037; b) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 1070; *Angew. Chem. Int. Ed.* **2012**, *51*, 1046.

[7] a) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396; b) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200; c) B. Tan,

N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672; d) B. Tan, G. Hernández-Torres, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 12354; e) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473; f) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819; g) K. Jiang, Z.-J. Jia, S. Chen, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 2852; h) F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli, G. Bencivenni, *Chem. Eur. J.* **2011**, *17*, 2842; i) Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 9290; *Angew. Chem. Int. Ed.* **2011**, *50*, 9124; j) W. Sun, G. Zhu, C. Wu, L. Hong, R. Wang, *Chem. Eur. J.* **2012**, *18*, 6737.

[8] A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735.

[9] a) K. Higashiyama, H. Otomasu, *Chem. Pharm. Bull.* **1980**, *28*, 1540, and references therein; b) W.-B. Chen, Z.-J. Wu, Q.-L. Pei, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2010**, *12*, 3132; c) Y.-B. Lan, H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao, X.-W. Wang, *Org. Lett.* **2011**, *13*, 4866; d) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem.* **2011**, *123*, 7983; *Angew. Chem. Int. Ed.* **2011**, *50*, 7837; e) L. Liu, D. Wu, X. Li, S. Wang, H. Li, J. Li, W. Wang, *Chem. Commun.* **2012**, *48*, 1692; f) L. Liu, D. Wu, S. Zheng, T. Li, X. Li, S. Wang, J. Li, H. Li, W. Wang, *Org. Lett.* **2012**, *14*, 134.

[10] For two ester groups, Shi and co-workers have reported a Lewis base catalyzed, highly regioselective cycloaddition reaction first initiated at the β-position: X.-C. Zhang, S.-H. Cao, Y. Wei, M. Shi, *Org. Lett.* **2011**, *13*, 1142.

[11] T. Arai, Y. Yamamoto, A. Awata, K. Kamiya, M. Ishibashi, M. A. Arai, *Angew. Chem.* **2013**, *125*, 2546; *Angew. Chem. Int. Ed.* **2013**, *52*, 2486.

[12] a) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248; b) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79; c) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.

[13] a) A. E. Asato, C. Watanabe, X.-Y. Li, R. S. H. Liu, *Tetrahedron Lett.* **1992**, *33*, 3105; b) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; c) A. Ma, D. Ma, *Org. Lett.* **2010**, *12*, 3634; d) M. G. Banwell, D. A. S. Beck, A. C. Willis, *ARKIVOC (Gainesville, FL, U.S.)* **2006**, *iii*, 163; e) K. Akagawa, K. Kudo, *Angew. Chem.* **2012**, *124*, 12958; *Angew. Chem. Int. Ed.* **2012**, *51*, 12786.

[14] a) S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305; b) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431; c) Y. Wang, P. Li, X. Liang, J. Ye, *Adv. Synth. Catal.* **2008**, *350*, 1383; d) A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075; e) I. Fleischer, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 95.

[15] Kwiatkowski recently reported the construction of β-carbonyl-substituted quaternary stereogenic centers from α,β-unsaturated enones at high pressure with low to moderate *ee*: D. Łyżwa, K. Dudziński, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 1540.

[16] For reviews of the catalytic asymmetric construction of all-carbon quaternary stereocenters, see: a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; b) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; c) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; d) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969.

[17] For reviews, see: a) U. Anthoni, C. Christophersen, P. H. Nielsen in *Alkaloids: Chemical and Biological Perspectives, Vol. 13* (Ed.: S. W. Pelletier), Pergamon Press, New York, **1999**, 163; b) M. S. Morales-Rios, O. R. Suarez-Castillo, *Nat. Prod. Commun.* **2008**, *3*, 629.

[18] For the asymmetric syntheses of these alkaloids, see: a) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; b) M. S. Morales-Ríos, E. Rivera-Becerril, P. Joseph-Nathan, *Tetrahedron: Asymmetry* **2005**, *16*, 2493; c) T. Kawasaki, M. Shinada, D. Kamimura, M. Ohzono, A. Ogawa, *Chem. Commun.* **2006**, 420; d) T. Kawasaki, M. Shinada, M. Ohzono, A. Ogawa, R. Terashima, M. Sakamoto, *J. Org. Chem.* **2008**, *73*, 5959; e) A. V. Dix, C. M. Meseck, A. J. Lowe, M. O. Mitchell, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2522; f) T. Hirano, K. Iwakiri, H. Miyamota, A. Nakazaki, S. Kobayashi, *Heterocycles* **2009**, *79*, 805; g) E. Rivera-Becerril, P. Joseph-Nathan, V. M. Pérez-Álvarez, M. S. Morales-Ríos, *J. Med. Chem.* **2008**, *51*, 5271; h) B. M. Trost, Y. Zhang, *Chem. Eur. J.* **2011**, *17*, 2916; i) B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328; j) Y. Zhou, Y. Xi, J. Zhao, X. Sheng, S. Zhang, H. Zhang, *Org. Lett.* **2012**, *14*, 3116.

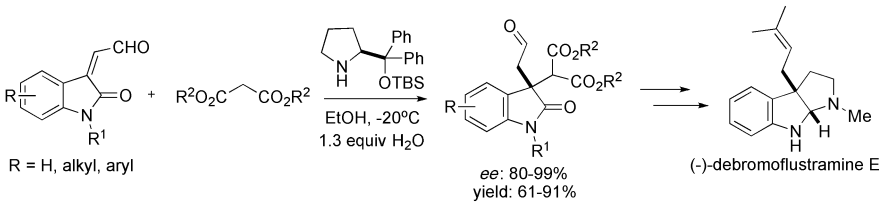
[19] a) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; b) J. J. Badillo, N. V. Hanhan, A. K. Franz, *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758; c) P. Siengalewicz, T. Gaich, J. Mulzer, *Angew. Chem.* **2008**, *120*, 8290; *Angew. Chem. Int. Ed.* **2008**, *47*, 8170; d) T. Matsuura, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6500; e) K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935.

Received: March 14, 2013
Published online: ■■ ▮▮, 0000

Organocatalysis

*R. Liu, J. Zhang** ..... ▮▮▮▮–▮▮▮▮

Organocatalytic Michael Addition of Malonates to Isatylidene-3-acetaldehydes: Application to the Total Synthesis of (−)-Debromoflustramine E



Flustering oxindoles: An enantioselective synthesis of 3,3′-disubstituted oxindoles by conjugate addition of malonates to isatylidene-3-acetaldehydes in high yield and enantioselectivity is developed (see scheme). The synthetic utility of this reaction is demonstrated by the synthesis of three oxindole core structures and the asymmetric total synthesis of debromoflustramine E.

