EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201301860

Regio- and Enantioselective Organocascade Michael–Michael Reactions: Construction of Chiral Trisubstituted Indanes

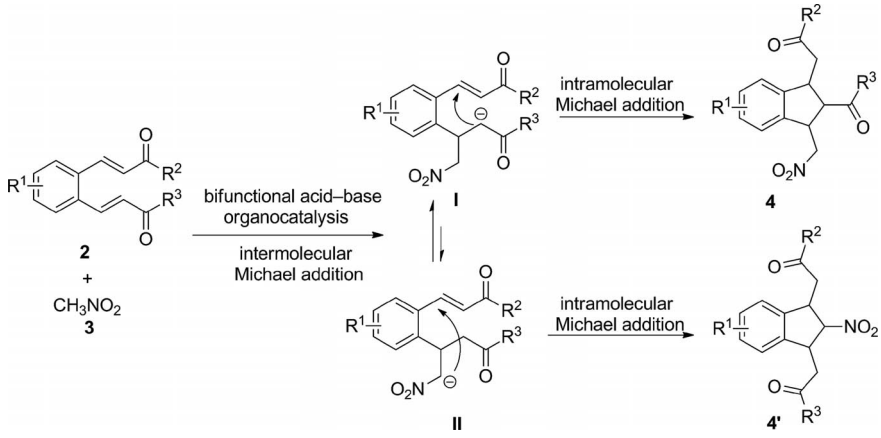
Ning Li,[a] Guo-Gui Liu,[a] Jian Chen,[a] Feng-Feng Pan,[a] Bing Wu,[a] and Xing-Wang Wang*[a]

Keywords: Domino reactions / Michael addition / Nitrogen heterocycles / Organocatalysis / Enantioselectivity

Given the importance of indane derivatives in both organic and medicinal chemistry, the development of an effective synthetic protocol for the preparation of multifunctionalized 1,2,3-trisubstituted indane derivatives is of considerable interest. In this paper, we developed a cascade regio- and enantioselective double Michael addition to construct challenging multifunctionalized chiral indane derivatives in the presence of a bifunctional acid–base organocatalyst. The resulting optically active indane derivatives with three alternating *trans* stereocenters were produced in moderate to good yields with excellent diastereoselectivities and excellent enantioselectivities. Remarkably, the resulting products were facilely converted into multifunctionalized optically active (1-indanylmethyl)amine and tetrahydroindeno-[2,1-*b*]pyrrole derivatives.

Introduction

Indane skeletons occur in various natural products and serve as valuable synthons for the synthesis of interesting complex organic compounds.[1] In particular, chiral indane units constitute core structural elements that are ubiquitous in a large number of biologically and pharmaceutically active molecules.[2] For example, indatraline is a drug used in the treatment of depression and addiction.[3] Indinavir is a protease inhibitor used as a component of highly active antiretroviral therapy to treat HIV infection and AIDS.[4] Rasagiline is an irreversible inhibitor of monoamine oxidase used as a monotherapy in early Parkinson's disease and as an adjunct therapy in more advanced cases.[5] PNU-99194A was reported to be a selective dopamine D3 receptor antagonist with potential antipsychotic properties in animal models.[6] Given the importance of indane derivatives in both organic and medicinal chemistry, the development of an effective synthetic protocol for the preparation of multifunctionalized substituted indane derivatives is of considerable interest.



Scheme 1. Proposed mechanism for cascade double Michael addition reactions between **2** and **3**.

Despite the great importance of chiral indane motifs, only a few methods have been developed for the stereoselec-

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China
E-mail: wangxw@suda.edu.cn
http://chemistry.suda.edu.cn/index.aspx?lanmuid=69&sublanmuid=604&id=111

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301860.

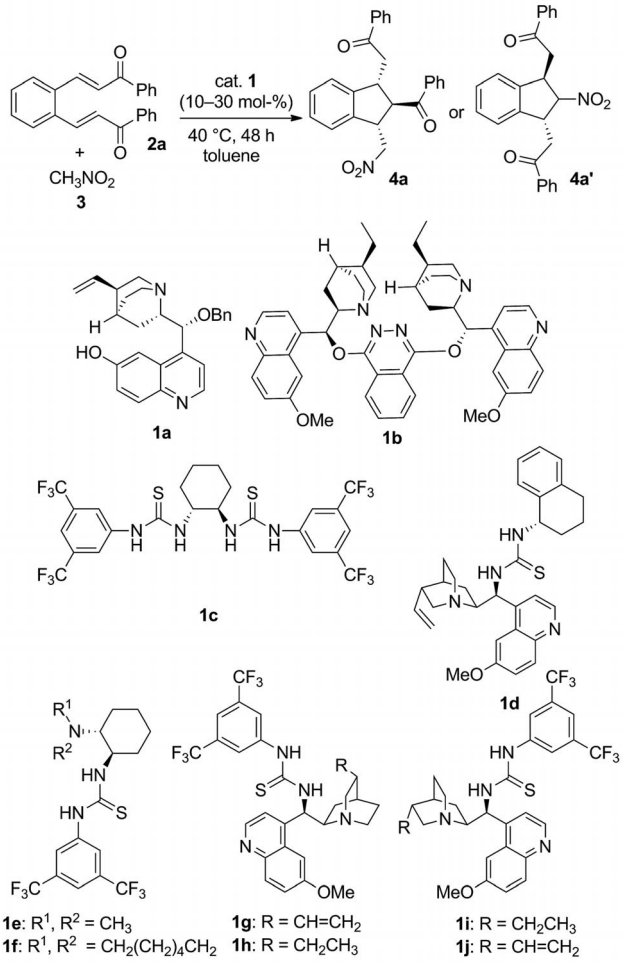
tive construction of disubstituted and/or trisubstituted indanes by the use of chiral secondary amines,[7] chiral transition-metal complexes,[8] and N-heterocyclic carbenes (NHCs) as catalysts.[9] In addition, the Studer group reported the highly enantioselective synthesis of 1,2,3-trisubstituted indanes through asymmetric oxidative NHC catalysis in 2011.[10,11] Very recently, Enders et al. reported an asymmetric organocatalytic Michael/Henry domino reaction and successfully generated *cis*-vicinal trisubstituted indane derivatives with high enantioselectivities.[12] In this context, the development of new methodology for the generation of *trans*-1,2,3-trisubstituted indanes with multiple stereogenic carbon centers in a cascade manner[13] remains challenging and is still in great demand. Herein, we report our preliminary results on the highly enantioselective synthesis of 1,2,3-trisubstituted indanes through an asymmetric intermolecular and intramolecular tandem double Michael addition approach in the presence of a bifunctional acid–base organocatalyst.[14]

As illustrated in Scheme 1, we envisaged that *o*-divinylbenzenes **2** would react with an active methylene-containing Michael donor, such as nitromethane (**3**), to form mono-Michael adducts through activation of an appropriate enantiopure bifunctional acid–base organocatalyst. The resulting mono-Michael adducts would be in situ deprotonated to yield enolate **I** or nitroenolate **II** under Brønsted base catalysis. Subsequently, two possible cyclization pathways could take place through the rapid reaction of the enols with other electron-poor olefin acceptors, which would generate multifunctionalized indane derivatives **4** and **4′**.

Results and Discussion

Initially, we examined the model reaction between **2a** and **3** in the presence of acidic and/or basic organocatalysts **1a**–**d** (10 mol-%) in toluene, and almost no reaction occurred (Table 1, Entries 1–4). If chiral thiourea **1e** or **1f** was employed for the cascade Michael addition reaction, desired product **4a** was obtained in low yield (31 and 36% yield, respectively), albeit with a high diastereomeric ratio (*dr*) and a high enantiomeric excess (*ee*) (>20:1 *dr*, 88 and 94% *ee*, respectively; Table 1, Entries 5 and 6). Encouraged by these promising results, thiourea-modified cinchona alkaloid catalysts **1g**, **1h**, and **1j** were examined (Table 1, Entries 7–9). To our delight, if chiral thiourea **1h** derived from hydroquinidine was used as the catalyst, both the stereoselectivity and the yield were improved (40% yield, >20:1 *dr*, 96% *ee*; Table 1, Entry 8). After further delicate optimization of other parameters, including reaction medium, catalyst loading, the addition of molecular sieves (MS), reaction temperature, molar ratio of the reactants, as well as their concentrations, we finally found that the **1h**-catalyzed cascade double Michael addition of **2a** and **3** provided desired product **4a** in 77% yield, with >20:1 *dr* and 97% *ee* by using 5 equiv. of **3** and 4 Å MS (20 mg) with a reaction concentration of 0.125 M relative to **2a** at 40 °C in toluene (Table 1,

Table 1. Optimization of the reaction conditions.[a]



Entry	Cat. (mol-%)	Solvent	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**1a** (10)	toluene	trace	–	–
2	**1b** (10)	toluene	trace	–	–
3	**1c** (10)	toluene	trace	–	–
4	**1d** (10)	toluene	trace	–	–
5	**1e** (10)	toluene	31	>20:1	88
6	**1f** (10)	toluene	36	>20:1	94
7	**1g** (10)	toluene	26	>20:1	97
8	**1h** (10)	toluene	40	>20:1	96
9	**1j** (10)	toluene	36	>20:1	–96
10	**1h** (20)	toluene	47	>20:1	96
11	**1h** (30)	toluene	45	>20:1	96
12[e]	**1h** (20)	toluene	52	>20:1	96
13[f]	**1h** (20)	toluene	60	>20:1	96
14[f]	**1h** (20)	*o*-xylene	48	>20:1	96
15[f]	**1h** (20)	benzene	54	>20:1	96
16[f]	**1h** (20)	PhCl	56	>20:1	96
17[f]	**1h** (20)	mesitylene	48	>20:1	97
18[f,g]	**1h** (20)	toluene	68	>20:1	97
19[f,h]	**1h** (20)	toluene	77	>20:1	97
20[f,h]	**1i** (20)	toluene	80	>20:1	–97

[a] Unless noted, the reactions were performed with toluene (1.0 mL), **2a** (0.1 mmol, 1.0 equiv.), **3** (2.0 mmol, 20 equiv.). [b] Yield of isolated **4a**. [c] Determined by analysis of the crude products by ^{1}H NMR spectroscopy. [d] Determined by HPLC, *ent*-**4a** for Entries 9 and 20. [e] 3 Å MS (20 mg) were added. [f] 4 Å MS (20 mg) were added. [g] Compound **3** (5 equiv.). [h] Toluene (0.8 mL).

Entry 19 vs. Entries 14–18). In addition, hydroquinine-derived thiourea catalyst **1i** as a pseudoenantiomer of **1h** was also investigated in this reaction under otherwise identical conditions, and its use led to the enantiomer of **4a** in 80% yield with >20:1 *dr* and 97% *ee* (Table 1, Entry 20). Notably, Michael product **4a′** was not observed on the basis of TLC stains and ^{1}H NMR spectroscopy analysis, wherein enolate **I** was unambiguously proven to be the active intermediate of the cyclic Michael addition reaction.

The substrate scope of this cascade asymmetric double Michael addition reaction was then investigated with **1h** and **1i** as the catalysts under the optimized reaction conditions. The results are summarized in Table 2. All the reactions between dienones **2a**–**o** and **3** proceeded smoothly with the cascade catalytic actions to afford corresponding optically active 1,2,3-trisubstituted indanes **4** in moderate to high yields with good to excellent stereoselectivities. Apparently, substrates **2b**–**k** bearing halogen substituents (2-F, 3-F, 4-F, 4-Cl, 4-Br, 4-I, 3,4-Cl_2) and electron-donating substituents (4-Me, 3-OMe, 4-OMe, 4-*n*-pentyl) on the phenyl rings had a very small influence on the enantioselectivity of the corresponding reactions (Table 2, Entries 2–12). Dienones **2m** and **2n** containing biphenyl and a heteroaromatic ring were also suitable substrates for the **1h**- and **1i**-catalyzed cascade double Michael additions, and desired products **4m**, *ent*-**4m**, **4n**, and *ent*-**4n** were obtained in 73–82% yield with >20:1 *dr* and 86–96% *ee* (Table 2, Entries 13 and 14). In addition, unsymmetrical dienone **2o** was also examined, and it provided the desired product in moderate yield with excellent diastereoselectivity, albeit with inferior regioselectivity (Table 2, Entry 15), which presumably resulted from difficulties in differentiating the two enantiofaces of the substrate attacked by the nucleophile in the first Michael addition step. Furthermore, dienone **2r** bearing two methyl groups was subjected to the reaction conditions. However, no reaction occurred for this transformation after 48 h (Table 2, Entry 16). To our delight, X-ray crystallographic analysis (Figure 1) of a single crystal of *ent*-**4h** obtained by recrystallization allowed us to make an

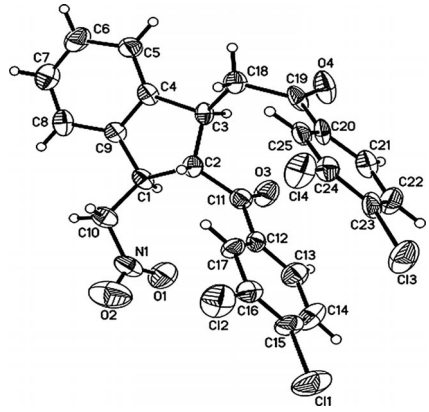
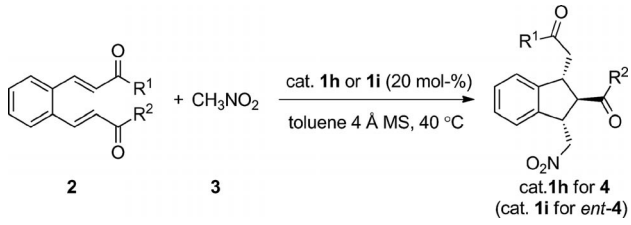


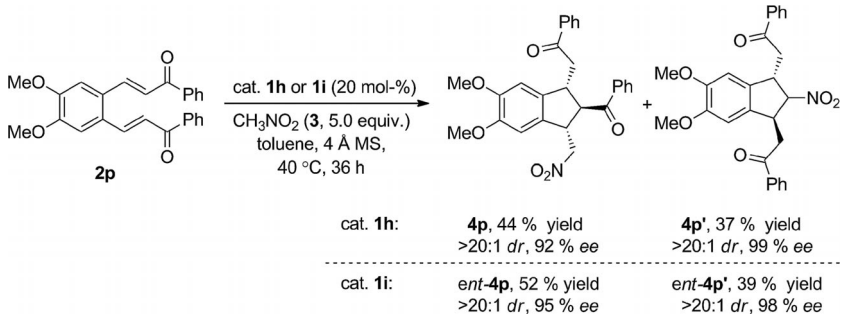
Figure 1. X-ray crystal structure of *ent*-**4h**.

Table 2. Substrate scope.[a]



Entry	2	R^1	R^2	*t* [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**2a**	Ph	Ph	48	77 (80)	>20:1	97 (97)
2	**2b**	2-FC_6H_4	2-FC_6H_4	36	55 (71)	>20:1	88 (93)
3	**2c**	3-FC_6H_4	3-FC_6H_4	36	72 (82)	>20:1	94 (98)
4	**2d**	4-FC_6H_4	4-FC_6H_4	36	72 (76)	>20:1	99 (99)
5	**2e**	4-ClC_6H_4	4-ClC_6H_4	36	81 (73)	>20:1	99 (99)
6	**2f**	4-BrC_6H_4	4-BrC_6H_4	36	77 (78)	>20:1	94 (98)
7	**2g**	4-IC_6H_4	4-IC_6H_4	36	87 (85)	>20:1	98 (99)
8	**2h**	3,4-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3$	36	91 (87)	>20:1	98 (99)
9	**2i**	4-MeC_6H_4	4-MeC_6H_4	48	69 (68)	>20:1	97 (97)
10	**2j**	3-$MeOC_6H_4$	3-$MeOC_6H_4$	36	55 (71)	>20:1	94 (97)
11	**2k**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	48	51 (53)	>20:1	96 (97)
12	**2l**	4-*n*-pentylC_6H_4	4-*n*-pentylC_6H_4	36	61 (60)	>20:1	95 (97)
13	**2m**	4-PhC_6H_4	4-PhC_6H_4	48	73 (74)	>20:1	90 (94)
14	**2n**	2-furyl	2-furyl	24	81 (82)	>20:1	86 (96)
15[e]	**2o**	Ph	4-$MeOC_6H_4$	48	64 (65)		96/97 (95:95)
16	**2r**	Me	Me	48	–	–	–

[a] Unless noted, the reactions were performed with **2a** (0.2 mmol), **3** (1.0 mmol), and **1h** or **1i** (20 mol-%) in toluene (1.6 mL). PMP = *p*-methoxyphenyl. [b] Yield of isolated product with the use of **1h**. The yield of the isolated product obtained with the use of **1i** is given in parentheses. [c] Determined by analysis of the crude products by ^{1}H NMR spectroscopy. [d] Determined by HPLC. The *ee* value for the product obtained with the use of **1i** is given in parentheses. [e] The regioselectivity was 2:1; >20:1 *dr* for both isomers.

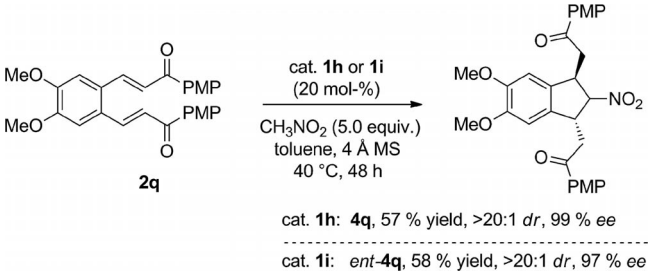


Scheme 2. Domino Michael–Michael reaction of **2p** and **3**.

unambiguous assignment of the relative and absolute configuration.[15]

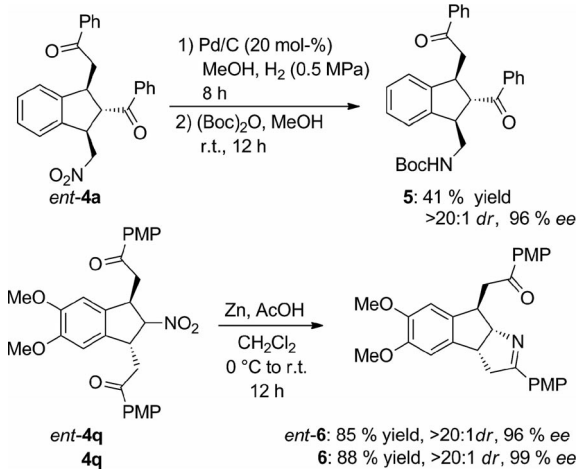
Upon using dienone **2p** bearing two contiguous methoxy groups on the parent benzene ring as the substrate for this transformation, a regioselective Michael cyclization pathway was observed with the use of catalysts **1h** and **1i** under otherwise identical reaction conditions, which generated multifunctionalized 1,2,3-trisubstituted indane derivatives **4p** and **4p′** or *ent*-**4p** and *ent*-**4p′** in 37–52% yield with 92–99%*ee* and >20:1 *dr* (Scheme 2).

Substrate **2q** containing additionally two methoxy groups on the dienone moiety was further employed as a substrate to investigate the regioselectivity of this transformation. Intriguingly, we found that only **4q** and *ent*-**4q** were produced in 57 and 58% yield with 99 and 97%*ee*, respectively, with >20:1 *dr* after 48 h of reaction (Scheme 3), which thus indicates that the regioselective reaction pathway is determined by the electronic properties of the substituents attached to the parent phenyl ring.



Scheme 3. Cascade double Michael reaction of **2q** and **3**.

(1-Indanylmethyl)amine and 2-aminoindane derivatives show a broad spectrum of pharmacological actions, including hypotensive, analgesic, antipsychotic, and muscle-relaxant activities.[16] Multifunctionalized 1,2,3-trisubstituted indane derivatives **4** containing nitro groups can be facilely converted into optically active (1-indanylmethyl)amine and tetrahydroindeno[2,1-*b*]pyrrole derivatives. Multifunctionalized indane derivative **4a** was reduced in the presence of Pd/C in anhydrous methanol, followed by *tert*-butoxycarbonyl (Boc) protection of the NH group to furnish enantiomerically enriched (1-indanylmethyl)amine derivative **5** in 41% yield over the two steps with >20:1 *dr* and 96%*ee*. In addition, resulting 2-nitro-2,3-dihydro-1*H*-indenes **4q** and *ent*-**4q** were readily converted into enantioenriched tetrahydroindeno[2,1-*b*]pyrrole derivatives **6** and *ent*-**6** by cascade reductive amination in 88 and 85% yield with 99 and 96%*ee*, respectively, and >20:1 *dr* (Scheme 4).[17]



Scheme 4. Synthesis of optically active (1-indanylmethyl)amine and indenopyrrole compounds.

Conclusions

We developed a new type of organocatalytic cascade asymmetric double Michael addition to construct challenging multifunctionalized chiral indane derivatives with three alternating *trans* stereocenters in moderate to good yields with excellent diastereoselectivities and excellent enantioselectivities. Remarkably, the resulting products were readily converted into optically active (1-indanylmethyl)amine and tetrahydroindeno[2,1-*b*]pyrrole derivatives. Further expansion of the substrate scope of this catalytic system, as well as biological evaluation of the resulting products, are in progress in our laboratory.

Experimental Section

General Procedure for the Addition of Nitromethane to Dienones: A powder of activated 4 Å molecular sieve (40 mg) was added to a solution of **2** (0.2 mmol), **3** (1.0 mmol), and the organocatalyst (20 mol-%) in anhydrous toluene (1.6 mL). The reaction mixture was stirred at 40 °C for 1–2 d, and the solvent was then removed

under vacuum. The residue was purified by silica gel chromatography to yield desired products **4a**–**q**.

Supporting Information (see footnote on the first page of this article): Experimental details and spectroscopic data.

Acknowledgments

We are grateful for financial support from the National Natural Science Foundation of China (21272166), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (13KJA150004) and the Program for New Century Excellent Talents in University (NCET-12-0743).

[1] For some representative examples, see: a) W. M. Clark, A. M. Tickner-Eldridge, G. K. Huang, L. N. Pridgen, M. A. Olsen, R. J. Mills, I. Lantos, N. H. Baine, *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551; b) B.-C. Hong, S. Sarshar, *Org. Prep. Proced. Int.* **1999**, *31*, 1–86; c) H. M. C. Ferraz, A. M. Aguilar, L. F. Silva Jr., M. V. Craveiro, *Quim. Nova* **2005**, *28*, 703–712; d) J. Duan, B. Jiang, WO 2007073503A2, **2007**.

[2] For some representative examples, see: a) H. Hong, S. P. Hollinshead, S. E. Hall, K. Kalter, L. M. Ballas, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973–978; b) S. Ulmschneider, U. Müller-Vieira, C. D. Klein, I. Antes, T. Lengauer, R. W. Hartmann, *J. Med. Chem.* **2005**, *48*, 1563–1575; c) M. F. Gross, S. Beaudoin, G. McNaughton-Smith, G. S. Amato, N. A. Castle, C. Huang, A. Zou, W. Yu, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849–2853.

[3] a) X.-H. Gu, H. Yu, A. E. Jacobson, R. B. Rothman, C. M. Dersch, C. George, J. L. Flippen-Anderson, K. C. Rice, *J. Med. Chem.* **2000**, *43*, 4868–4876; b) L. F. Silva, F. A. Siqueira, E. C. Pedrozo, F. Y. M. Vieira, A. C. Doriguetto, *Org. Lett.* **2007**, *9*, 1433–1436.

[4] a) J. K. Ekegren, T. Unge, M. Z. Safa, H. Wallberg, B. Samuelsson, A. Hallberg, *J. Med. Chem.* **2005**, *48*, 8098–8102; b) S. S. Shankar, M. P. Dube, J. C. Gorski, J. E. Klaunig, H. O. Steinberg, *Am. Heart J.* **2005**, *150*, e933/931–e933/937.

[5] a) F. Hubálek, C. Binda, M. Li, Y. Herzig, J. Sterling, M. B. H. Youdim, A. Mattevi, D. E. Edmondson, *J. Med. Chem.* **2004**, *47*, 1760–1766; b) D. A. Gallagher, A. Schrag, *CNS Drugs* **2008**, *22*, 563–586.

[6] a) J. G. Cannon, J. A. Perez, R. K. Bhatnagar, J. P. Long, F. M. Sharabi, *J. Med. Chem.* **1982**, *25*, 1442–1446; b) S. R. Haadsma-Svensson, K. A. Cleek, D. M. Dinh, J. N. Duncan, C. L. Haber, R. M. Huff, M. E. Lajiness, N. F. Nichols, M. W. Smith, K. A. Svensson, M. J. Zaya, A. Carlsson, C.-H. Lin, *J. Med. Chem.* **2001**, *44*, 4716–4732.

[7] J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.

[8] For the construction of chiral indanones and indenes, see: a) K. Kundu, J. V. McCullagh, A. T. Morehead, *J. Am. Chem. Soc.* **2005**, *127*, 16042–16043; b) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483; c) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379–3381; d) A. Minatti, X. Zheng, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 9253–9258; e) R. Shintani, K. Takatsu, T. Hayashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 3735–3737; *Angew. Chem.* **2007**, *119*, 3809–3811; f) M. P. Watson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 12594–12595; g) C. L. Oswald, J. A. Peterson, H. W. Lam, *Org. Lett.* **2009**, *11*, 4504–4507; h) J. A. Brekan, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 1472–1473; i) X.-H. Li, B.-H. Zheng, C.-H. Ding, X.-L. Hou, *Org. Lett.* **2013**, *15*, 6086–6089.

[9] a) E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3107–3110; *Angew. Chem.* **2007**, *119*, 3167–3170; b) Y. Li, X.-Q. Wang, C. Zheng, S.-L. You, *Chem. Commun.* **2009**, 5823–5825; c) X. Fang, K. Jiang, C. Xing, L. Hao, Y. R. Chi, *Angew. Chem. Int. Ed.* **2011**, *50*, 1910–1913; *Angew. Chem.* **2011**, *123*, 1950–1953; d) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2011**, *133*, 2714–2720.

[10] A. Biswas, S. D. Sarkar, R. Fröhlich, A. Studer, *Org. Lett.* **2011**, *13*, 4966–4969.

[11] For the diastereoselective synthesis of 1,2,3-trisubstituted indanes by means of synthetic procedures that take place through cascade transition-metal or NHC catalysis, see: a) C. Navarro, A. G. Csaky, *Org. Lett.* **2007**, *9*, 217–219; b) E. Sánchez-Larios, M. Gravel, *J. Org. Chem.* **2009**, *74*, 7536–7539; c) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 6877–6880; *Angew. Chem.* **2010**, *122*, 7029–7032; d) Á. Rincón, V. Carmona, M. R. Torres, A. G. Csákÿ, *Synlett* **2012**, *23*, 2653–2656.

[12] C. C. J. Loh, I. Atodiresei, D. Enders, *Chem. Eur. J.* **2013**, *19*, 10822–10826.

[13] For some representative reviews, see: a) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431.

[14] Nitro-Michael reaction with the use of α,β-unsaturated compounds: a) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; some representative acid–base catalysis: b) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; c) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; d) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; *Angew. Chem.* **2005**, *117*, 6525–6528; e) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603–606; f) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; *Angew. Chem.* **2006**, *118*, 1550–1573; g) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160; h) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; i) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; j) X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 8379–8383; *Angew. Chem.* **2010**, *122*, 8557–8561; k) T. Ogawa, S. Mouri, R. Yazaki, N. Kumagai, M. Shibasaki, *Org. Lett.* **2011**, *13*, 110–113; l) Z.-X. Jia, Y.-C. Luo, Y. Wang, L. Chen, P.-F. Xu, B. Wang, *Chem. Eur. J.* **2012**, *18*, 12958–12961; m) Z.-X. Jia, Y.-C. Luo, X.-N. Cheng, P.-F. Xu, Y.-C. Gu, *J. Org. Chem.* **2013**, *78*, 6488–6494.

[15] CCDC-913190 (for *ent*-**4h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Data for *ent*-**4h**: block crystal ($0.60 \times 0.25 \times 0.20$ mm), $T = 293(2)$ K, λ(Mo-K_α) = 0.71070 Å, monoclinic, space group $P2_12_12_1$, $a = 9.944(5)$ Å, $b = 11.239(5)$ Å, $c = 20.791(12)$ Å, $V = 2324(2)$ Å^3, 9236 total reflections, 4207 unique, $R_{int} = 0.0884$, $R_1 = 0.0927$ [$I > 2\sigma(I)$], $wR_2 = 0.1960$.

[16] a) J. G. Cannon, J. C. Kim, M. A. Aleem, J. P. Long, *J. Med. Chem.* **1972**, *15*, 348–350; b) J. G. Cannon, J. A. Perez, J. P. Pease, J. P. Long, J. R. Flynn, D. B. Rusterholz, S. E. Dryer, *J. Med. Chem.* **1980**, *23*, 745–749; c) M. Casarrubea, F. Sorbera, G. Crescimanno, *Physiol. Behav.* **2006**, *89*, 552–562.

[17] CCDC-947252 (for *ent*-**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Data for *ent*-**6**: block crystal ($0.6 \times 0.18 \times 0.1$ mm), $T = 293(2)$ K, λ(Mo-K_α) = 1.54184 Å, monoclinic, space group $P12_11$, $a = 12.8630(3)$ Å, $b = 6.02461(13)$ Å, $c = 15.3155(3)$ Å, $V = 1155.91(4)$ Å^3, 18218 total reflections, 4104 unique, $R_{int} = 0.0341$, $R_1 = 0.0333$ [$I > 2\sigma(I)$], $wR_2 = 0.0852$.

Received: December 13, 2013
Published Online: March 27, 2014

