

# Highly Enantioselective Michael Addition of Malonates to $\beta$ -CF<sub>3</sub>- $\beta$ -(3-Indolyl)-nitroalkenes: Construction of Trifluoromethylated All-Carbon Quaternary Stereogenic Centres

Chun-Hui Ma,<sup>[a]</sup> Tai-Ran Kang,<sup>\*[a]</sup> Long He,<sup>\*[a]</sup> and Quan-Zhong Liu<sup>\*[a]</sup>

**Keywords:** Enantioselectivity / Michael addition / Organocatalysis / Amino acids

A family of  $\gamma$ -nitrobutyric acid esters bearing an all-carbon quaternary stereogenic centre have been synthesized. Chiral thioureas catalysed the conjugate addition of malonates to nitroalkenes containing a trifluoromethyl and indole motif at the  $\beta$ -position to afford the corresponding  $\gamma$ -nitrobutyric acid

esters in good yields (up to 89 % yield) and with good to excellent enantioselectivities (up to 90 % ee). This protocol provides an efficient access to optically enriched  $\gamma$ -amino acids and  $\beta$ -disubstituted  $\gamma$ -butyrolactams.

## Introduction

Trifluoromethylated organic compounds, as an important class of halogen compounds, have received increasing attention because of their broad spectrum of intriguing physicochemical properties compared with isosteric dehalogenated analogues.<sup>[1]</sup> It is believed that the trifluoromethyl motif plays a pivotal role in the enhancement and modification of their original biological activities.<sup>[2]</sup> For example, nearly 20 % of all pharmaceuticals and 40 % of agrochemicals under development contain fluorine.<sup>[3]</sup> Therefore efficient approaches to such valuable CF<sub>3</sub>-bearing organic compounds are of considerable synthetic and biological importance. To date, many strategies have been developed to achieve the enantioselective synthesis of CF<sub>3</sub>-containing compounds with tertiary or quaternary stereogenic centre(s). Direct asymmetric trifluoromethylations involve the use of nucleophilic, electrophilic or radical trifluoromethylation reagents and enantioselective transformations of prochiral trifluoromethylated substrates.<sup>[4]</sup> However, the construction of all-carbon quaternary stereocentre(s) bearing a trifluoromethyl group has been a great challenge. Consequently, the development of novel and efficient methods to meet this challenge would be invaluable for asymmetric synthesis.<sup>[5]</sup>

## Results and Discussion

Recently, the enantioselective conjugate addition of nitroalkenes has been established as a versatile methodology in organic synthesis.<sup>[6]</sup> However, applications of this methodology for the synthesis of molecules bearing all-carbon quaternary stereocentre(s) are very limited.<sup>[7]</sup> Furthermore,  $\beta$ , $\beta$ -disubstituted nitroalkenes bearing CF<sub>3</sub> and indolyl as substrates have not yet been disclosed. Herein we wish to report the enantioselective conjugate addition of malonates to  $\beta$ -CF<sub>3</sub>- $\beta$ -(3-indolyl)nitroalkene catalysed by chiral thioureas,<sup>[8]</sup> which provided  $\gamma$ -nitrobutyric acid esters bearing all-carbon quaternary stereogenic centres in good yields and with good to excellent enantioselectivities.

The indole nucleus is found in numerous natural products and biologically active molecules, including commercial drugs.<sup>[9]</sup> For this reason,  $\beta$ -CF<sub>3</sub>- $\beta$ -(3-indolyl)nitroethylenes **2** were chosen for enantioselective conjugate addition reactions with malonates. Compounds **2** were readily prepared by a modified literature procedure.<sup>[7a,10]</sup> Indole derivatives were converted into **3** upon reaction with trifluoroacetic anhydride followed by treatment with TsCl in the presence of Et<sub>3</sub>N.<sup>[11]</sup> The nitro-aldol products **4** were obtained by nitro-Henry reactions of **3** and nitromethane in the presence of tetramethylguanidine (TMG) as base (Scheme 1). Note that other bases were not effective for the reaction. Finally, the desired  $\beta$ -CF<sub>3</sub>- $\beta$ -(3-indolyl)nitroalkenes **2** were obtained as single isomers in yields of 67–87 % (see the Supporting Information). The olefins were tentatively assigned the (*E*) configuration.<sup>[7a]</sup>

Initially, we explored the reaction of  $\beta$ -CF<sub>3</sub>- $\beta$ -(3-indolyl)nitroethylene (**2a**) and diethyl malonate (**5a**) in toluene at room temperature in the presence of 20 mol-% of Na<sub>2</sub>CO<sub>3</sub> as base and 10 mol-% of chiral thiourea **1** as catalyst (Figure 1); the results are summarized in Table 1. Encouragingly, the reaction proceeded smoothly to yield the corre-

[a] Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637009, P. R. China  
E-mail: quanzhongliu@cwnu.edu.cn  
longhe@cwnu.edu.cn  
http://210.41.193.83:555/lab

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.201402243>.

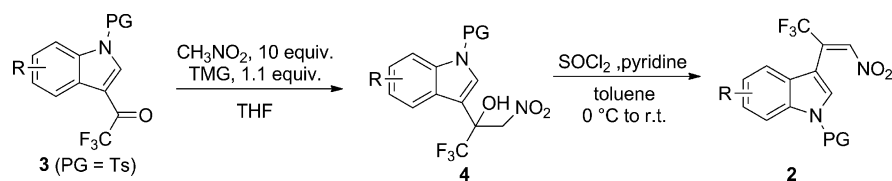
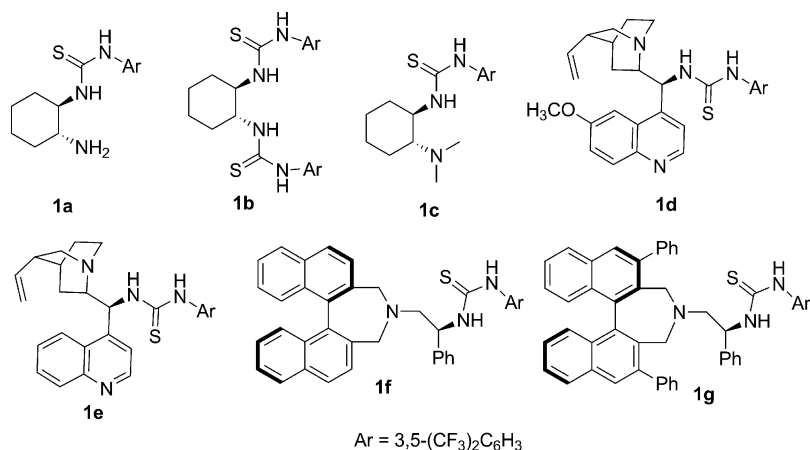

 Scheme 1. Preparation of  $\beta$ -trifluoromethyl- $\beta$ -(3-indolyl)nitroalkenes. TMG = tetramethylguanidine.


Figure 1. Chiral thioureas investigated in the work.

sponding  $\gamma$ -nitrobutyric acid ester **6a**, which bears an all-carbon quaternary stereogenic centre (Table 1), even though  $\beta,\beta$ -disubstituted nitroalkenes are much less reactive than *trans*- $\beta$ -nitrostyrene. Catalyst screening revealed that the catalyst employed had a significant effect on the reactivity and enantioselectivity of the Michael reaction (Entries 1–7). For example, the use of amino thiourea **1a** and bis-(thiourea) **1b** resulted in low yields and enantioselectivities (Entries 1 and 2). Alkaloid-derived thioureas **1d** and **1e** furnished poor yields and moderate enantioselectivities (17 and 12% yields, 73 and 50% *ee*, respectively; Entries 4 and 5). Catalyst **1c** afforded the Michael product with the highest enantioselectivity of 87%, but a yield of only 18% was observed (Entry 3). In particular, thiourea **1f** derived from a chiral amine developed by our group exhibited both poor reactivity and low enantioselectivity (Entry 6).<sup>[12]</sup> The introduction of phenyl substituents onto the naphthyl motifs of **1f**, as shown in **1g**, led to a much lower catalytic efficacy and stereocontrol than with **1f** (Entry 6 vs. 7). To further optimize the procedure, this Michael reaction was chosen to screen different bases and solvents. It was found that the yield and enantioselectivity were both greatly dependent on the base (Entries 8–13). Strong bases such as  $\text{Cs}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$  afforded excellent yields but with almost no enantioselectivity (Entries 8 and 9), whereas organic bases were not suitable, only providing traces of products (Entries 11 and 12). Of the bases screened,  $\text{AcONa}$  was the best choice in terms of yield and enantioselectivity (Entry 13). The screening of solvents indicated that toluene delivered the best enantioselectivity, but unfortunately all attempts to further improve the yield failed (Entries 13–17).

 Table 1. Optimization of reaction conditions.<sup>[a]</sup>

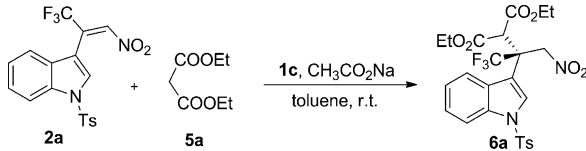
Entry	1	Base	Solvent	Yield [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	<b>1a</b>	$\text{Na}_2\text{CO}_3$	toluene	27	4
2	<b>1b</b>	$\text{Na}_2\text{CO}_3$	toluene	13	4
3	<b>1c</b>	$\text{Na}_2\text{CO}_3$	toluene	18	87
4	<b>1d</b>	$\text{Na}_2\text{CO}_3$	toluene	17	73 <sup>[d]</sup>
5	<b>1e</b>	$\text{Na}_2\text{CO}_3$	toluene	12	50 <sup>[d]</sup>
6	<b>1f</b>	$\text{Na}_2\text{CO}_3$	toluene	18	20 <sup>[d]</sup>
7	<b>1g</b>	$\text{Na}_2\text{CO}_3$	toluene	9	2
8	<b>1c</b>	$\text{Cs}_2\text{CO}_3$	toluene	99	0
9	<b>1c</b>	$\text{K}_2\text{CO}_3$	toluene	98	2
10	<b>1c</b>	$\text{Na}_3\text{PO}_4$	toluene	23	63
11	<b>1c</b>	$\text{Et}_3\text{N}$	toluene	9	86
12	<b>1c</b>	DABCO	toluene	8	65
13	<b>1c</b>	$\text{CH}_3\text{CO}_2\text{Na}$	toluene	24	94
14	<b>1c</b>	$\text{CH}_3\text{CO}_2\text{Na}$	$\text{CH}_2\text{Cl}_2$	5	86
15	<b>1c</b>	$\text{CH}_3\text{CO}_2\text{Na}$	$\text{CHCl}_3$	24	91
16	<b>1c</b>	$\text{CH}_3\text{CO}_2\text{Na}$	$\text{Et}_2\text{O}$	13	67
17	<b>1c</b>	$\text{CH}_3\text{CO}_2\text{Na}$	THF	21	10

<sup>[a]</sup> Reaction conditions: **2a** (0.05 mmol), **5a** (0.3 mmol), catalysts **1** (10 mol-%), solvent (0.5 mL), base (20 mol-%), room temp., 24–72 h. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> Determined by chiral HPLC. <sup>[d]</sup> The opposite enantiomer was obtained as the major enantiomer.

To further optimize the procedure, we investigated the influence of the amount of  $\text{AcONa}$  and the ratio of **2a**/**5a** on the reaction outcome (Table 2). Pleasingly, when the

reaction was carried out in the presence of 80 mol-% AcONa with a ratio of **2a**/**5a** of 1:20, the desired product **6a** was obtained in 54% yield and with 92% *ee* (Table 2, Entry 6). Both the yield and *ee* were almost unchanged when the amount of AcONa was increased to 1 equiv. with respect to **2a** (Entry 4). The reaction performed with 20 equiv. of malonate with respect to **2a** was sufficient to achieve the best selectivity (Entry 6 vs. 7). Further studies on catalyst loading indicated that 20 mol-% of **1c** afforded the desired Michael product in 72% yield with a slight erosion of enantioselectivity (90% *ee*; Entry 8). In addition, lower enantioselectivity was observed when the reaction was carried out at a higher temperature, although the yield was increased (Entry 9 vs. 6).

Table 2. Effects of the amount of base and substrate ratio on the reaction.<sup>[a]</sup>



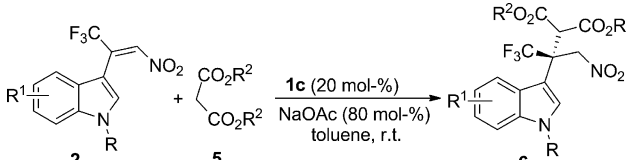
Entry	Base (amount [%]) <sup>[b]</sup>	<b>2a</b> / <b>5a</b>	Yield [%] <sup>[c]</sup>	<i>ee</i> [%] <sup>[d]</sup>
1	AcONa (40)	1:6	29	92
2	AcONa (60)	1:6	34	92
3	AcONa (80)	1:6	45	92
4	AcONa (100)	1:6	44	91
5	AcONa (80)	1:10	50	92
6	AcONa (80)	1:20	54	92
7	AcONa (80)	1:30	71	75
8	AcONa (80)	1:20	72	90 <sup>[e]</sup>
9	AcONa (80)	1:20	72	85 <sup>[f]</sup>

[a] The reaction was carried out with **2a** (0.05 mmol), ethyl malonate (**5a**), and catalyst **1c** (10 mol-%) in toluene (0.5 mL) at room temp. for 24–96 h, unless indicated otherwise. [b] Molar ratio with respect to nitro olefin **2a**. [c] Isolated yield. [d] Determined by chiral HPLC. [e] 20 mol-% of **1c** was used. [f] The reaction was carried out at 35 °C.

Having optimized the reaction as outlined above, we then explored the generality of the protocol for different malonates and nitroalkenes under the optimal conditions. As shown in Table 3, malonates with various ester moieties, such as methyl, isopropyl and benzyl, were investigated. In all cases, chiral  $\gamma$ -nitrobutyric acid esters were obtained with the same levels of yields and enantioselectivities (Entries 1–4), although the enantioselectivity was slightly reduced with dimethyl malonate. Various  $\beta,\beta$ -disubstituted nitroalkene derivatives with electron-withdrawing as well as -donating substituents at the 5-, 6- and 7-positions of the indole motif proved to be suitable substrates, giving the Michael products in good yields and with high enantioselectivities (Entries 5–13). Substitution at the 4-position of the indole motif afforded no product (Entry 14). Note also that *N*-Boc-protected nitroalkenes afforded better yields and enantioselectivities than the corresponding *N*-Ts derivatives (Entries 15 and 16 vs. 1 and 2). The absolute configurations of the nitroalkanes were unambiguously assigned to be (*R*) by single-crystal X-ray diffraction analysis of **6k** (see

the Supporting Information).<sup>[13]</sup> On the basis of the observed stereochemistry, a plausible transition state was proposed (Figure 2). The thiourea **1c** coordinates to the nitro olefin **2a** through two hydrogen bonds to form an eight-membered transition state in which the tertiary amine motif acts as a base to deprotonate the malonate. The resulting enolate approaches the nitro olefin **2a** from the *Si* face to yield the (*R*) product as the major enantiomer.

Table 3. Scope of the enantioselective Michael addition reaction.<sup>[a]</sup>



Entry	R	R <sup>1</sup>	R <sup>2</sup>	<b>6</b>	Yield [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	Ts	H	Et	<b>6a</b>	72	90
2	Ts	H	Me	<b>6b</b>	75	82
3	Ts	H	Bn	<b>6c</b>	78	90
4	Ts	H	<i>i</i> Pr	<b>6d</b>	49	90
5	Ts	5-Br	Et	<b>6e</b>	64	85
6	Ts	5-MeO	Et	<b>6f</b>	62	84
7	Ts	5-Me	Et	<b>6g</b>	61	83
8	Ts	5-Cl	Et	<b>6h</b>	67	84
9	Ts	6-Cl	Et	<b>6i</b>	70	82
10	Ts	6-F	Et	<b>6j</b>	74	82
11	Ts	7-Br	Et	<b>6k</b>	63	84
12	Ts	6-F	Bn	<b>6l</b>	93	88
13	Ts	5-Me	Bn	<b>6m</b>	77	90
14	Ts	4-Br	Et	<b>6n</b>	0	–
15	Boc	H	Et	<b>6o</b>	89	90
16	Boc	H	Me	<b>6p</b>	82	90

[a] Unless stated otherwise, the reaction was carried out with **2** (0.05 mmol), malonate **5** (1 mmol) and **1c** (20 mol-%) using NaOAc (80 mol-%) as base in toluene (0.5 mL) at room temperature for 24–96 h. [b] Isolated yield. [c] Determined by chiral HPLC.

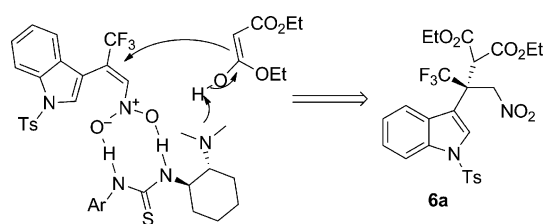


Figure 2. Possible transition state for the Michael addition reaction.

With the optically enriched  $\gamma$ -nitrobutyric acid esters **6** in hand, we turned our attention to the further transformation of **6a** into a  $\gamma$ -butyrolactam and  $\gamma$ -aminobutyric acid (GABA).  $\gamma$ -Aminobutyric acid derivatives are important inhibitory neurotransmitters of mammalian central nervous systems. Moreover, they also serve as chiral building blocks or intermediates in the synthesis of medically relevant compounds (Figure 3).<sup>[14]</sup> First, **6a** was reduced to the expected ester **7a** as a single isomer by using NaBH<sub>4</sub> as the reducing agent (Scheme 2). The absolute configuration at C-2 was not assigned, because the newly formed stereocentre was removed in a later transformation. No erosion of

optical purity was observed during the reduction (64% yield, 90% *ee*).<sup>[15]</sup> Saponification of the ester **7a** with alcoholic sodium hydroxide and subsequent acidification gave the corresponding acid, which was decarboxylated upon heating in xylene at reflux to afford the corresponding  $\gamma$ -butyrolactam **8a**, with trifluoromethyl and 3-indolyl both attached to the  $\beta$ -position, in a total yield of 84% over three steps with no erosion of enantioselectivity (see the Supporting Information).<sup>[16]</sup> Note that the tosyl group was also removed under the base hydrolysis conditions. The GABA could be easily synthesized from optically enriched **8a** according to a literature procedure.<sup>[17]</sup>

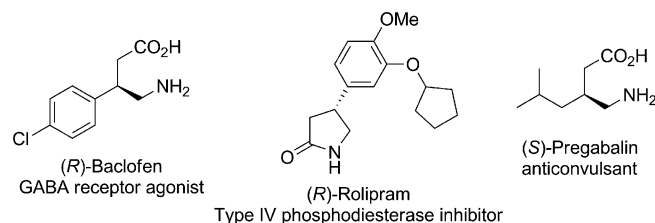
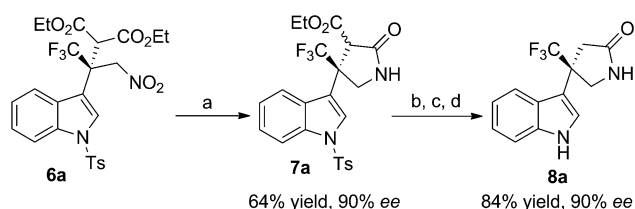


Figure 3. Biologically active pyrrolidinone and GABA analogues.



Scheme 2. Synthetic transformation of the Michael addition products. Reagents and conditions: (a)  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{NaBH}_4/\text{MeOH}$ , 0 °C to room temp., 20 h; (b) 6 N  $\text{NaOH}/\text{EtOH}$ , 45 °C, 24 h; (c) 6 N  $\text{HCl}$ , pH < 1; (d) xylene, 150 °C, 12 h.

## Conclusions

We have developed an enantioselective Michael addition reaction between malonates and  $\beta$ - $\text{CF}_3$ - $\beta$ -(3-indolyl)nitroalkenes that affords  $\gamma$ -nitrobutyric acid esters bearing an all-carbon quaternary stereogenic centre in moderate to high yields and with good to excellent enantioselectivities. The Michael products can also be conveniently transformed into the optically enriched  $\gamma$ -butyrolactams and  $\gamma$ -amino-butyric acids.

## Experimental Section

**General Procedure for the Asymmetric Michael Addition Reactions:** A thiourea catalyst (20 mol-%), malonate (1 mmol), and  $\text{AcONa}$  (80 mol-%) were added to a solution of  $\beta$ - $\text{CF}_3$ - $\beta$ -(3-indolyl)nitroalkene (0.05 mmol) in toluene (0.5 mL) at room temperature. The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC) and then purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 50:1 to 10:1) to yield  $\gamma$ -nitrobutyric acid esters **6a–6p**.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures,  $^1\text{H}$ ,  $^{19}\text{F}$ , and  $^{13}\text{C}$  NMR spectra, HPLC data of **6–8**, and crystal data of **6k**.

## Acknowledgments

This work was supported by the National Natural Science Foundation of China (NSFC) (21102116) and the Innovative Research Team in the College of Sichuan Province (Grant no. 14TD0016).

- [1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; b) I. Ojima (Ed.), *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley, Chichester, **2009**.
- [2] a) H. Hasegawa, M. Muraoka, K. Matsui, A. Kojima, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3471–3475; b) P. R. Daga, R. J. Doerksen, *J. Comput. Chem.* **2008**, *29*, 1945–1954; c) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; d) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777–791; e) H. Xie, Y. Zhang, S. Zhang, X. Chen, W. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 11773–11776; *Angew. Chem.* **2011**, *123*, 11977–11980.
- [3] F. Diederich in *Fluorine in Pharmaceutical and Medicinal Chemistry* (Eds.: V. Gouverneur, K. Müller), Imperial College Press, London, **2012**, pp. v–x.
- [4] For recent reviews, see: a) R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 9322–9324; *Angew. Chem.* **2010**, *122*, 9510; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) F.-L. Qing, F. Zheng, *Synlett* **2011**, 1052–1072; d) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161–2195; e) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; f) T. Besset, C. Schneider, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 5048–5050; *Angew. Chem.* **2012**, *124*, 5134.
- [5] a) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; *Angew. Chem.* **1998**, *110*, 2092; b) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; e) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295–7306.
- [6] For selected reviews, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) J. Aleman, A. Milelli, S. Cabrera, E. Reys, K. A. Jorgensen, *Chem. Eur. J.* **2008**, *14*, 10958–10966; c) A. J. M. Barrett, *Chem. Soc. Rev.* **1991**, *20*, 95–127; d) D. A. Evans, S. Mito, D. Seidel, *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592; e) A. J. M. Barrett, G. G. Graboski, *Chem. Rev.* **1986**, *86*, 751–762; f) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; g) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; *Angew. Chem.* **2004**, *116*, 5248.
- [7] For selected examples, see: a) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han, Y.-X. Jia, *J. Am. Chem. Soc.* **2013**, *135*, 2983–2986; b) J. Wu, D. M. Mampreian, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585; c) F.-L. Liu, J. R. Chen, B. Feng, X.-Q. Fu, L.-H. Ye, L.-Q. Lu, W.-J. Xiao, *Org. Biomol. Chem.* **2014**, *12*, 1057–1060; d) Y.-L. Liu, T.-D. Shi, F. Zhou, X.-L. Zhou, X. Wang, J. Zhou, *Org. Lett.* **2011**, *13*, 3826–3829; e) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; *Angew. Chem.* **2008**, *120*, 6232.
- [8] For selected reviews on chiral thiourea catalysis, see: a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; b) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; *Angew. Chem.* **2006**, *118*, 1550; e) X. H. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516–532; f) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; g) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol.*



- Chem.* **2013**, *11*, 7051–7071; h) J. Aleman, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774–793; i) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; j) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis* Wiley-VCH, Weinheim, **2009**.
- [9] a) “Indoles – The Monoterpenoid Indole Alkaloids” (Ed.: J. E. Saxton), *The Chemistry of Heterocyclic Compounds* (Eds.: A. Weissberger, E. C. Taylor), Wiley, New York, **1983**, vol. 25, part 4; b) “Monoterpenoid Indole Alkaloids” (Ed.: J. E. Saxton), *The Chemistry of Heterocyclic Compounds* (Ed.: E. C. Taylor), Wiley, Chichester, **1994**, supplement to vol. 25, part 4; c) R. J. Sundberg, *Indoles*, Academic Press, New York, **1996**; d) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761–793; e) S. E. O'Connor, J. J. Maresh, *Nat. Prod. Rep.* **2006**, *23*, 532–547; f) E. Marques-Lopez, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138–1167.
- [10] M. Bandini, R. Sinisi, *Org. Lett.* **2009**, *11*, 2093–2096.
- [11] a) O. V. Maltsev, A. S. Kucherenko, I. P. Beletskaya, V. A. Tartakovsky, S. G. Zilotin, *Eur. J. Org. Chem.* **2010**, 2927–2933; b) S. Vellalath, K. N. Van, D. Romo, *Angew. Chem. Int. Ed.* **2013**, *52*, 13688–13693; c) L. Wen, F. Tang, C. Ge, X. Wang, Z. Han, J. Wu, *Synth. Commun.* **2012**, *42*, 3288–3295.
- [12] a) Q.-Z. Liu, X.-L. Wang, S.-W. Luo, B.-L. Zheng, D.-B. Qin, *Tetrahedron Lett.* **2008**, *49*, 7434–7437; b) S.-S. Kan, J.-Z. Li, C.-Y. Ni, Q.-Z. Liu, T.-R. Kang, *Molecules* **2011**, *16*, 3778–3786; c) Y.-H. Deng, J.-Q. Chen, L. He, T.-R. Kang, Q.-Z. Liu, S.-W. Luo, W.-C. Yuan, *Chem. Eur. J.* **2013**, *19*, 7143–7150.
- [13] CCDC-980358 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](http://www.ccdc.cam.ac.uk/data_request/cif).
- [14] a) J. G. Hardman, L. E. Limbird, G. A. Gilman (Eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed., McGraw-Hill, New York, **2001**, Section III; b) P. L. McGeer, E. G. McGeer in *Basic Neurochemistry: Molecular Cellular and Medical Aspects*, 4th ed. (Eds.: G. J. Siegel, B. Agranoff, R. W. Albers, P. Molinoff), Raven, New York, **1989**.
- [15] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
- [16] J. Wang, W. Li, Y.-L. Liu, Y.-Y. Chu, L.-L. Li, X.-H. Liu, X.-M. Feng, *Org. Lett.* **2010**, *12*, 1280–1283.
- [17] a) M. Sobocinska, M. M. Zobacheva, V. V. Perekalin, G. Kupryszewski, *Pol. J. Chem.* **1979**, *53*, 435–446; b) R. Z. Zelle, *Synthesis* **1991**, 1023–1026; c) C. A. Martinez, S. Hu, Y. Dumond, J. Tao, P. Kelleher, L. Tully, *Org. Process Res. Dev.* **2008**, *12*, 392–398.

Received: March 11, 2014  
Published Online: May 23, 2014