Asymmetric Catalysis

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Efficient Synthesis of Chiral Trisubstituted 1,2-Allenyl Ketones by Catalytic Asymmetric Conjugate Addition of Malonic Esters to Enynes

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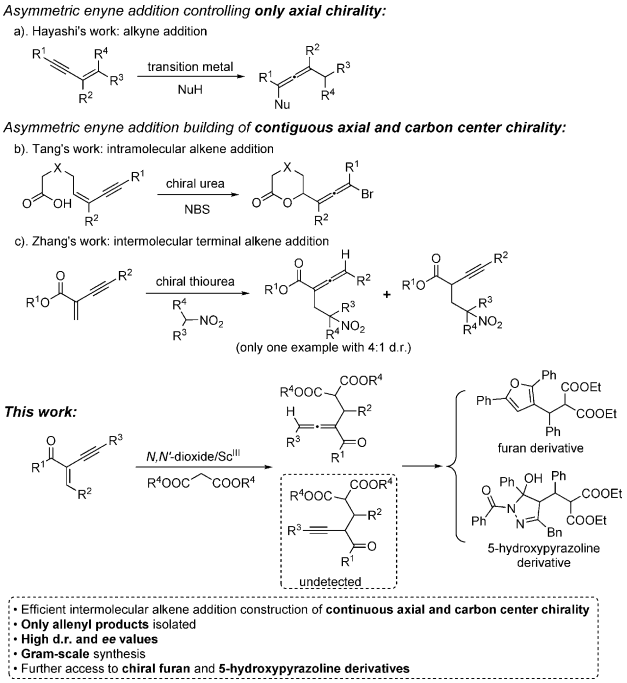
Abstract: *An N,N′-dioxide/scandium(III) complex catalyzed, highly efficient conjugate addition of malonic esters to enynes is described. A range of trisubstituted 1,2-allenyl ketones were obtained in high yields (up to 99%) with good d.r. (up to 95/5) and excellent ee values (97%–99%). Moreover, the products could be easily transformed into chiral furan and 5-hydroxypyrazoline derivatives, both of which are important skeletons of many biologically active compounds and pharmacologicals.*

Chiral allenes are valuable compounds for their importance in organic synthesis and pharmaceuticals.[1,2] Over the past two decades, substantial efforts have been devoted to their asymmetric synthesis.[3] Early successful examples were limited to the use of stoichiometric amounts of chiral auxiliaries/promoters or enantioenriched substrates.[4] Until now, some ingenious methods for catalytic asymmetric synthesis of chiral allenes have been reported. They include the isomerization of 3-alkynes,[5] kinetic resolution of racemic allenes,[6] β-hydride elimination of enol triflates,[7] desymmetrization of *meso*-allenes[8] or alkyenes,[9] rearrangements of alkynes,[10] C–H insertion of α-diazoesters into 1-alkynes,[11] functionalization of racemic allenes,[12] and addition to enynes.[13] Among them, addition to enynes is a simple but very efficient route to obtain chiral allenes. For instance, Hayashi has pioneered a metal-catalyzed enyne addition for synthesis of chiral allenes (Scheme 1a).[13a–c] Subsequently, Tang has provided an intramolecular enyne addition for the highly diastereo- and enantioselective synthesis of bromoallenes in the presence of chiral ureas (Scheme 1b).[13d] Zhang has developed an intermolecular enyne addition in the assistance of chiral thioureas (Scheme 1c).[13e] Although a series of 2,3-allenoates were obtained with up to 98% *ee* value, there was only one example containing the axial and carbon center chirality with 4:1 d.r. Furthermore, the reaction also gave the byproduct alkynoate as a result of direct conjugate addition (Scheme 1c). Zhang has also reported two racemic enyne addtion to construct contiguous axial and carbon center,[14] but the catalytic asymmetric manner is still unrealized. In short, the highly diastereoselective and enantioselective construction of continuous axial and carbon center chirality by intermolecular enyne addition is a challenge. Stimulated by the successful application of our unique catalysts in conjugate addition,[15] herein, we report a highly efficient conjugate addition of malonic esters to enynes catalyzed by an *N,N′*-dioxide/scandium(III) complex, affording a range of trisubstituted 1,2-allenyl ketones. It should be mentioned that the direct conjugate addition product alkynones **4** were not detected during the reaction course (Scheme 1).



Scheme 1. Comparison of previous catalytic asymmetric enyne addition for synthesis of chiral allenes with current work.

Our investigation began with the addition of diethyl malonate (**2b**) to enyne (**1a**) as the model reaction to optimize the reaction conditions. Initially, chiral ligands were evaluated (Table 1, entries 1–3). The results showed that by complexing with $Sc(OTf)_3$, L-proline-derived L-$PrEt_2Me$, L-ramipril-derived L-$RaEt_2Me$, and L-pipecolic acid-derived L-$PiEt_2Me$, all of the complexes could promote the reaction

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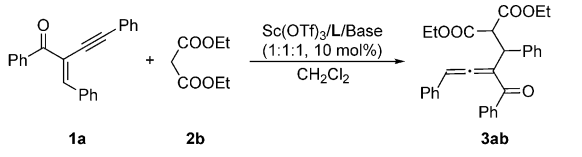
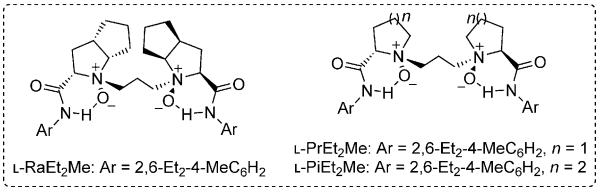
Table 1: Optimization of the reaction conditions.[a]





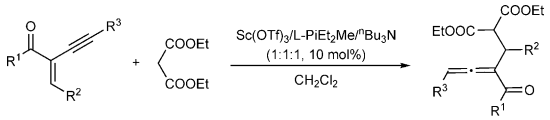
Entry	L	Base	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	L-PrEt$_2$Me	DMAP	98	76:76	67:33
2	L-RaEt$_2$Me	DMAP	98	99:99	64:36
3	L-PiEt$_2$Me	DMAP	98	99:99	68:32
4	L-PiEt$_2$Me	Na_2CO_3	93	98:99	84:16
5	L-PiEt$_2$Me	^{i}Pr$_2$EtN	89	95:95	86:14
6	L-PiEt$_2$Me	*n*Bu$_3$N	88	98:98	88:12
7[e]	L-PiEt$_2$Me	*n*Bu$_3$N	85	99:99	92:8
8[f]	L-PiEt$_2$Me	*n*Bu$_3$N	66	99:99	93:7

[a] Unless otherwise noted, reactions were carried out with **L** (10 mol%), $Sc(OTf)_3$ (10 mol%), base (10 mol%), **1a** (0.2 mmol), **2b** (0.8 mmol) in CH_2Cl_2 (0.8 mL) at 30°C for 24 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR analysis. [e] Reactions were carried out at 0°C. [f] Reactions were carried out at −5°C.

smoothly in the presence of 4-dimethylaminopyridine (DMAP) at 30°C. However, the diastereoselectivity was low even though the enantioselectivity was moderate to excellent. To improve the diastereoselectivity, other bases were investigated (Table 1, entries 4–6). To our delight, *n*Bu$_3$N gave the highest 88:12 d.r. (Table 1, entry 6). Gratifyingly, when the reaction temperature was decreased to 0°C, the diastereoselectivity could be further enhanced to 92:8 (Table 1, entry 7). Unfortunately, the d.r. value could not be improved significantly (93:7) by continuing to decrease the reaction temperature to −5°C (Table 1, entry 8). Thus, the optimized reaction conditions were established as $Sc(OTf)_3$/L-PiEt$_2$Me (10 mol%), *n*Bu$_3$N (10 mol%), **1a**:**2b** = 1:4 in CH_2Cl_2 at 0°C.

With the optimized conditions in hand, the reaction scope was next examined. As shown in Table 2, enynes tethering aryl or alkyl substituents (R^1) on the carbonyl group are suitable substrates, providing the desired trisubstituted 1,2-allenyl ketones in high yields with high d.r. and excellent *ee* values (Table 2, entries 1–4). Regardless of the electron-withdrawing or electron-donating groups on the 4-position of aromatic rings on the double bond (R^2), there was little influence on the reaction. The corresponding products were obtained in high yields (88–94%) with excellent d.r. (92:8–95:5) and *ee* values (99%) (Table 2, entries 6–9). When the R^2 group was changed to 2-chlorophenyl, it just gave a moderate yield (77%) and d.r. (78:22; Table 2, entries 5). Various substituents (R^3) on the triple bond were also examined. The aryl groups bearing an electron-donating substituent furnished higher diastereoselectivities than electron-withdrawing groups (Table 2, entries 15–17 vs. entries 10–14). The

Table 2: Substrate scope for enynes.[a,b]



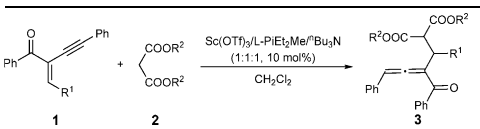
Entry	$R^1/R^2/R^3$	Yield [%][c]	*ee* [%][d]	d.r.[e]
1	Ph/Ph/Ph	85 (**3ab**)	99	92:8
2	3-MeC_6H_4/Ph/Ph	84 (**3bb**)	99	91:9
3[f]	3-ClC_6H_4/Ph/Ph	98 (**3cb**)	99	91:9
4	CH_3/Ph/Ph	92 (**3db**)	98	89:11
5	Ph/2-ClC_6H_4/Ph	77 (**3eb**)	97	78:22
6[f]	Ph/4-ClC_6H_4/Ph	90 (**3fb**)	99	92:8
7[f]	Ph/4-BrC_6H_4/Ph	94 (**3gb**)	99	93:7
8[f]	Ph/4-MeC_6H_4/Ph	90 (**3hb**)	99	94:6
9	Ph/4-MeOC_6H_4/Ph	88 (**3ib**)	99	95:5
10[f]	Ph/Ph/2-FC_6H_4	94 (**3jb**)	99	91:9
11[f]	Ph/Ph/3-FC_6H_4	91 (**3kb**)	99	92:8
12	Ph/Ph/4-FC_6H_4	90 (**3lb**)	99	88:12
13	Ph/Ph/2-ClC_6H_4	93 (**3mb**)	99	89:11
14[f]	Ph/Ph/4-ClC_6H_4	96 (**3nb**)	99	89:11
15[f]	Ph/Ph/3-MeC_6H_4	75 (**3ob**)	99	94:6
16	Ph/Ph/4-MeC_6H_4	91 (**3pb**)	99	93:7
17	Ph/Ph/4-MeOC_6H_4	59 (**3qb**)	99	93:7
18[f]	Ph/Ph/3-Thienyl	90 (**3rb**)	97	94:6
19	Ph/Ph/*n*Bu	73 (**3sb**)	99	89:11

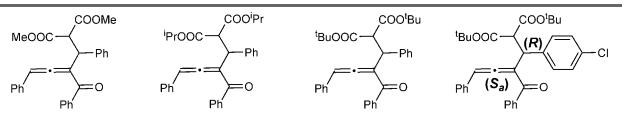
[a] Unless otherwise noted, reactions were carried out with L-PiEt$_2$Me (10 mol%), $Sc(OTf)_3$ (10 mol%), *n*Bu$_3$N (10 mol%), **1** (0.2 mmol), **2b** (0.8 mmol) in CH_2Cl_2 (0.8 mL) at 0°C for 24 h. [b] Enyne **1t** (R^1 = OEt, R^2 = H, and R^3 = Ph) was also examined. For results, see the Supporting Information. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis. [e] Determined by ^{1}H NMR analysis. [f] Reactions were carried out at −5°C.

enyne **1r** containing a 3-thienyl group afforded the desired product **3rb** in 90% yield with 97% *ee* and 94:6 d.r. by decreasing the reaction temperature to −5°C (Table 2, entry 18). The n-butyl-substituted **1s** was also a competent substrate, providing the allene **3sb** with good results (Table 2, entry 19).

Several malonic esters **2** were also tested (Table 3). Although the reactivity and diastereoselectivity markedly

Table 3: Substrate scope for malonic esters.[a]



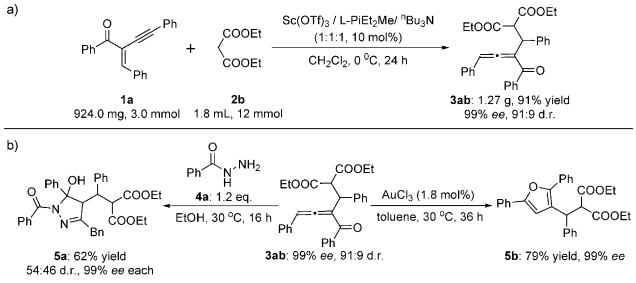


3aa: 88% yield[b] 89:11 d.r.,[c] 99% *ee*[d].
3ac: 82% yield[b] 86:14 d.r.,[c] 98% *ee*[d].
3ad: 61% yield[b] 69:31 d.r.,[c] 99% *ee*[d].
3cd: 78% yield[b] 64:36 d.r.,[c] 98% *ee*[d]. (>99:1 d.r.,[c] >99% *ee*[d])[e]

[a] Reactions were carried out with L-PiEt$_2$Me (10 mol%), $Sc(OTf)_3$ (10 mol%), *n*Bu$_3$N (10 mol%), **1** (0.2 mmol), **2** (0.8 mmol) in CH_2Cl_2 (0.8 mL) at 0°C (for **3aa**) or 30°C (for **3ac**, **3ad**, and **3cd**) for 24 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis. [e] After recrystallization from CH_2Cl_2, the absolute configuration of **3cd** was determined by X-ray crystallography.

decreased with the increased steric hindrance of ester alkyl group (R_2), the *ee* values were maintained. To determine the absolute configuration of products, **3cd** was synthesized (Table 3). After recrystallized from CH_2Cl_2, **3cd** with > 99:1 d.r. and > 99% *ee* could be obtained. The absolute configuration of **3cd** was determined by X-ray crystallography to be (R,S_a).[16]

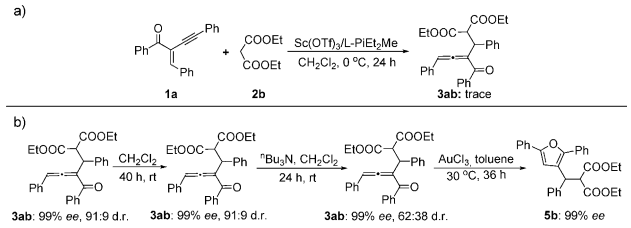
To show the synthetic potential of this strategy, a gram scale synthesis of **3ab** was carried out (Scheme 2a). Under the optimized condition, 3 mmol of **1a** reacted smoothly with 4 equivalents of **2b** to provide 1.27 g **3ab** (91% yield) with



Scheme 2. a) Gram-scale version of the reaction. b) Transformation of 1,2-allenyl ketone **3ab**.

91:9 d.r. and 99% *ee*. Furthermore, when treated with 1.2 equiv of **4a** at 30 °C, **3ab** could be transformed to the tetrasustituted 5-hydroxypyrazoline **5a** in 62% yield with 54:46 d.r. (99% *ee* each).[17] Importantly, the family of **5a** has been reported to possess antimicrobial,[18] *anti*-PDE_3,[19] *anti*-inflammatory,[20] antimalarial,[21] hypolipidemic,[22] and analgesic[23] activities (Scheme 2b). Additionally, **3ab** could be transformed to trisustituted furan **5b** under treatment by $AuCl_3$ in 79% yield with 99% *ee*,[24,25] which are important skeletons for many biologically active compounds and pharmacologicals (Scheme 2b).

To gain insight into the function of nBu$_3$N in our system, some control experiments were carried out (Scheme 3). First, when the reaction of **1a** and **2b** was performed in the absence of nBu$_3$N (Scheme 3a), it gave a trace amount of **3ab**. This suggested that nBu$_3$N served as an effective promoter for the formation of enolate from **2**. Second, when **3ab** (91:9 d.r. and 99% *ee*) was dissolved in CH_2Cl_2 and stirred at room temperature for 40 h, there was no influence on its d.r. and *ee* values. In contrast, when nBu$_3$N was added to the mixture, the d.r. value rapidly decreased to 62:38 (Scheme 3b). Clearly, nBu$_3$N was the cause of the



Scheme 3. Control experiments.

reducion in the d.r. value of **3ab**. An additional derivation of the recovered **3ab** (62:38 d.r.) was undertaken, and the produced furan was obtained with 99% *ee*. This demonstrated that the low d.r. was attributed to the partial racemization of axial chirality of the allene (Scheme 3b). In other words, nBu$_3$N might not participate in the allenes production, but instead serves as an effective promoter for the formation of enolates from **2** in the catalytic system.

Based on the determination of the absolute configuration of product **3cd**,[16] control experiments, and our previous study,[26] a possible catalytic cycle with a transition-state model was proposed (Figure 1). First, the *N*-oxides and amide oxygen atoms of L-PiEt$_2$Me coordinate to Sc^{3+} in a tetradentate manner to form two six-membered chelate rings. Then, enynes **1** attach to Sc^{3+} at the favorable equatorial position to give intermediate **T1**. Additionally, the enolates are generated from malonates **2** assisted by nBu$_3$N. The *Re* face of enynes **1** are strongly shielded by the nearby benzyl ring. Therefore, the incoming enolates prefers to attack enynes **1** from the *Si* face (**T2**). Finally, the desired products **3** dissociat after a protonation of the favored intermediate **T3**, and the catalyst is regenerated to accomplish one catalytic cycle.

In summary, we have developed an efficient *N*,*N*′-dioxide/scandium complex catalyst for the intermolecular addition of

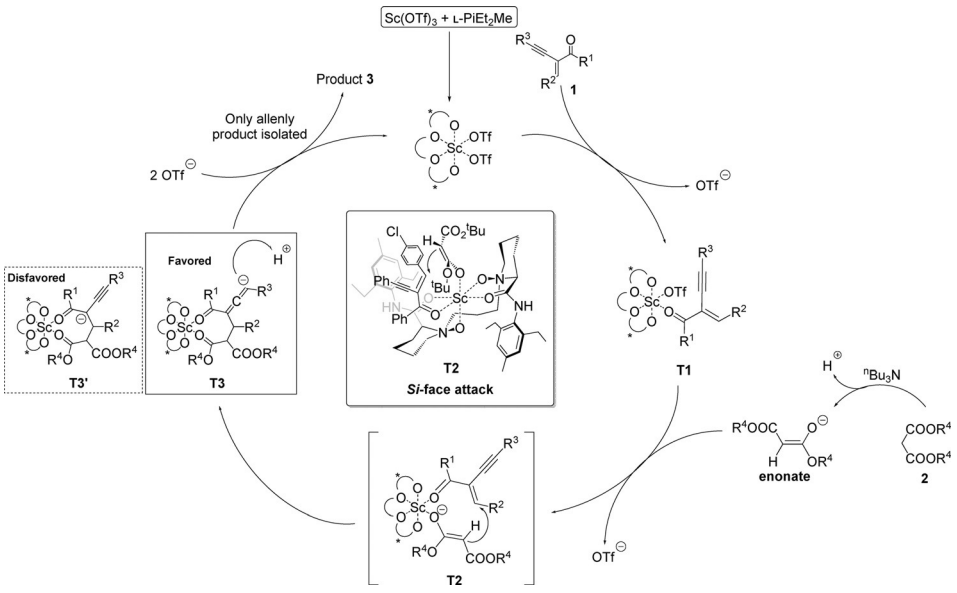


Figure 1. Proposed catalytic cycle.

malonic esters to enynes. A range of trisubstituted 1,2-allenyl ketones were obtained in good to excellent yields (up to 99%) with high d.r. (up to 95:5) and excellent *ee* values (up to 99%). The products could be easily transformed into furan and 5-hydroxypyrazoline derivatives, which are important skeletons in many biologically active compound and pharmacologicals. Moreover, based on the experiments and our previous work, a possible catalytic cycle was proposed.

Experimental Section

A dry reaction tube was charged with L-$PiEt_2Me$ (0.02 mmol) and $Sc(OTf)_3$ (0.02 mmol), enyne **1a** (0.2 mmol) under an N_2 atmosphere, malonic ester **2b** (0.8 mmol), and CH_2Cl_2 (0.8 mL) were added and the mixture was stirred at 0 °C for 15 min. Then nBu_3N (0.02 mmol) was added and the mixture was stirred at 0 °C for 24 h. The reaction mixture was purified by column chromatography on silica gel (ethyl acetate/petroleum ether 1:50-1:4) to afford the desired product **3ab** (85% yield, 99% *ee*, 92:8 d.r.).

Acknowledgements

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Keywords: 1,2-allenyl ketones · 5-hydroxypyrazoline · asymmetric catalysis · enyne addition · furans

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Angew. Chem. **2016**, *128*, 1891–1895

[1] For recent reviews on allenes in organic synthesis, see: a) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; c) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; d) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954; e) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; *Angew. Chem.* **2012**, *124*, 3128; f) J. Ye, S. Ma, *Acc. Chem. Res.* **2014**, *47*, 989.

[2] A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; *Angew. Chem.* **2004**, *116*, 1216.

[3] For recent reviews on asymmetric synthesis of allenes, see: a) M. Ogasawara, *Tetrahedron: Asymmetry* **2009**, *20*, 259; b) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519.

[4] For selected early examples of asymmetric synthesis of allenes using stoichiometric amounts of chiral auxiliaries/promoters or enantioenriched substrates, see: a) Y. Nishibayashi, J. D. Singh, S.-i. Fukuzawa, S. Uemura, *J. Org. Chem.* **1995**, *60*, 4114; b) J. A. Marshall, M. A. Wolf, *J. Org. Chem.* **1996**, *61*, 3238; c) Y. Naruse, H. Watanabe, Y. Ishiyama, T. Yoshida, *J. Org. Chem.* **1997**, *62*, 3862; d) K. Mikami, A. Yoshida, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 858; *Angew. Chem.* **1997**, *109*, 892.

[5] H. Liu, D. Leow, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 7212.

[6] J. Yu, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 4050.

[7] I. T. Crouch, R. K. Neff, D. E. Frantz, *J. Am. Chem. Soc.* **2013**, *135*, 4970.

[8] C. Manzuna Sapu, J. E. Bäckvall, J. Deska, *Angew. Chem. Int. Ed.* **2011**, *50*, 9731; *Angew. Chem.* **2011**, *123*, 9905.

[9] H. Li, D. Müller, L. Guénée, A. Alexakis, *Org. Lett.* **2012**, *14*, 5880.

[10] a) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. Musaev, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 15497; b) Y. Wang, W. Zhang, S. Ma, *J. Am. Chem. Soc.* **2013**, *135*, 11517; c) Y. B. Liu, H. P. Hu, H. F. Zheng, Y. Xia, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem. Int. Ed.* **2014**, *53*, 11579; *Angew. Chem.* **2014**, *126*, 11763.

[11] Y. Tang, Q. G. Chen, X. H. Liu, G. Wang, L. L. Lin, X. M. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 9512; *Angew. Chem.* **2015**, *127*, 9648.

[12] a) Y. Imada, M. Nishida, K. Kutsuwa, S.-I. Murahashi, T. Naota, *Org. Lett.* **2005**, *7*, 5837; b) A. Boutier, C. Kammerer-Pentier, N. Krause, G. Prestat, G. Poli, *Chem. Eur. J.* **2012**, *18*, 3840; c) T. Hashimoto, K. Sakata, F. Tamakuni, M. J. Dutton, K. Maruoka, *Nat. Chem.* **2013**, *5*, 240; d) B. Wan, S. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 441; *Angew. Chem.* **2013**, *125*, 459; e) C. T. Mbofana, S. J. Miller, *J. Am. Chem. Soc.* **2014**, *136*, 3285.

[13] a) J. W. Han, N. Tokunaga, T. Hayashi, *J. Am. Chem. Soc.* **2001**, *123*, 12915; b) T. Hayashi, N. Tokunaga, K. Inoue, *Org. Lett.* **2004**, *6*, 305; c) T. Nishimura, H. Makino, M. Nagaosa, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 12865; d) W. Zhang, S. Q. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. P. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664; e) H. Qian, X. Yu, J. Zhang, J. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 18020.

[14] a) X. Yu, H. Ren, Y. Xiao, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 8481; b) X. Yu, J. Zhang, *Adv. Synth. Catal.* **2011**, *353*, 1265.

[15] For reviews on chiral *N*-oxides in asymmetric catalysis, see: a) A. V. Malkov, P. Kočovsky, *Curr. Org. Chem.* **2003**, *7*, 1737; b) G. Chelucci, G. Murineddu, G. A. Pinna, *Tetrahedron: Asymmetry* **2004**, *15*, 1373; c) A. V. Malkov, P. Kočovsky, *Eur. J. Org. Chem.* **2007**, 29; d) X. M. Feng, X. H. Liu, in *Scandium: Compounds, Productions and Applicatons* (Ed: V. A. Greene), Nova Science, New York, **2011**, pp. 1–48; e) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574; f) K. Shen, X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Sci.* **2012**, *3*, 327; g) X. H. Liu, L. L. Lin, X. M. Feng, *Org. Chem. Front.* **2014**, *1*, 298; For recent examples on asymmetric conjugate addition, see: h) Z. Wang, Z. L. Zhang, Q. Yao, X. H. Liu, Y. F. Cai, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2013**, *19*, 8591; i) Z. Wang, Q. Yao, T. F. Kang, J. H. Feng, X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Commun.* **2014**, *50*, 4918; j) Q. Yao, Z. Wang, Y. H. Zhang, X. H. Liu, L. L. Lin, X. M. Feng, *J. Org. Chem.* **2015**, *80*, 5704.

[16] CCDC 1044535 (**3cd**).

[17] S. Guo, J. Wang, D. Guo, X. Zhang, X. Fan, *Tetrahedron* **2012**, *68*, 7768.

[18] a) Y. Zhao, A. Bacher, B. Illarionov, M. Fischer, G. Georg, Q.-Z. Ye, P. E. Fanwick, S. G. Franzblau, B. Wan, M. Cushman, *J. Org. Chem.* **2009**, *74*, 5297; b) M. S. Karthikeyan, B. S. Holla, N. S. Kumari, *Eur. J. Med. Chem.* **2007**, *42*, 30; c) H. G. Bonacorso, A. P. Wentz, R. V. Lourega, C. A. Cechinel, T. S. Moraes, H. S. Coelho, N. Zanatta, M. A. P. Martins, M. Höerner, S. H. Alves, *J. Fluorine Chem.* **2006**, *127*, 1066.

[19] K. Y. Kim, H. Lee, S.-E. Yoo, S. H. Kim, N. S. Kang, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1617.

[20] a) P. D. Sauzem, P. Machado, M. A. Rubin, G. S. Sant′Anna, H. B. Faber, A. H. de Souza, C. F. Mello, P. Beck, R. A. Burrow, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, *Eur. J. Med. Chem.* **2008**, *43*, 1237; b) F. R. de Souza, M. R. Fighera, T. T. F. Lima, J. de Bastiani, I. B. Barcellos, C. E. Almeida, M. R. Oliveira, H. G. Bonacorso, A. E. Flores, *Pharmacol. Biochem. Behav.* **2001**, *68*, 525.

[21] W. Cunico, C. A. Cechinel, H. G. Bonacorso, M. A. P. Martins, N. Zanatta, M. V. N. de Souza, I. O. Freitas, R. P. P. Soares, A. U. Krettli, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 649.

[22] G. A. Idrees, O. M. Aly, G. E.-D. A. A. Abuo-Rahma, M. F. Radwan, *Eur. J. Med. Chem.* **2009**, *44*, 3973.

[23] a) P. Machado, F. A. Rosa, M. Rossatto, G. S. Sant'Anna, P. D. Sauzem, R. M. Siqueira da Silva, M. A. Rubin, J. Ferreira, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, *ARKIVOC* **2007**, 281; b) P. Machado, P. T. Campos, G. R. Lima, F. A. Rosa, A. F. C.

Flores, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, *J. Mol. Struct.* **2009**, *917*, 176.
[24] a) A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'in, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 1440; b) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; *Angew. Chem.* **2000**, *112*, 2382.
[25] a) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**; b) A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, in *Heterocycles in Life and Society*, Wiley, Chichester, **1997**; c) H.-K. Lee, K.-F. Chan, C.-W. Hui, H.-K. Yim, X.-W. Wu, H. N. C. Wong, *Pure Appl. Chem.* **2005**, *77*, 139; d) M. Ash, I. Ash, in *Handbook of Flavors and Fragrances*, Synapse Information Resources, New York, **2006**.
[26] Z. Wang, D. H. Chen, Z. Y. Yang, S. Bai, X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 10130.

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