

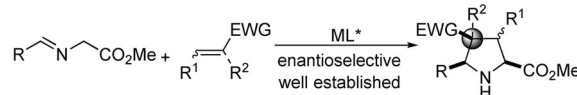
Cycloadditions

Deutsche Ausgabe: DOI: 10.1002/ange.201602542
Internationale Ausgabe: DOI: 10.1002/anie.201602542Diastereo- and Enantioselective Copper(I)-Catalyzed Intermolecular [3+2] Cycloaddition of Azomethine Ylides with β -Trifluoromethyl β,β -Disubstituted EnonesZhan-Ming Zhang⁺, Bing Xu⁺, Shan Xu, Hai-Hong Wu, and Junliang Zhang*

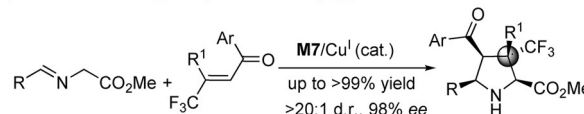
Abstract: Reported herein is an asymmetric [3+2] cycloaddition reaction of azomethine ylides with β -trifluoromethyl β,β -disubstituted enones, a reaction which is enabled by a Ming-Phos-derived copper(I) catalyst (Ming-Phos = chiral sulfinamide monophosphines, Figure 2). This method provides scalable and efficient access to the highly substituted pyrrolidines with a trifluoromethylated, all-carbon quaternary stereocenter in good yields with up to greater than 20:1 d.r. and 98% ee. The reaction has a broad substrate scope and tolerates a wide range of functional groups.

Five-membered nitrogen heterocycles, especially highly substituted pyrrolidines, are frequently found in pharmaceuticals, natural alkaloids, and as fascinating building blocks in organic synthesis, as well as outstanding catalysts in asymmetric catalysis.^[1] The transition metal catalyzed asymmetric 1,3-dipolar [3+2] cycloaddition of azomethine ylides with electron-deficient alkenes is one of the most powerful and widely used methods for the construction of these compounds.^[2] Despite great progress in this field,^[3] the synthesis of chiral pyrrolidines with four contiguous stereocenters, including at least one all-carbon quaternary stereocenter^[4] at either the 3- or 4-position, still poses a considerable challenge because of the requisite use of sterically encumbered and less reactive β,β - or α,β -disubstituted unsaturated compounds. Recently, the latter cycloaddition was successfully achieved by the groups of Waldmann, Wang, and Arai,^[5] and provides facile access to chiral pyrrolidines with one all-carbon quaternary stereocenter at the 4-position (Scheme 1a). However, to the best of our knowledge, a metal-catalyzed diastereo- and enantioselective intermolecular [3+2] cycloaddition reaction of azomethine ylides with β,β -disubstituted unsaturated compounds, such as enones, has not been reported thus far. Therefore, the development of novel transition-metal catalysts to enable this asymmetric [3+2] cycloaddition is highly desirable.

a) Previous work: reacting with α,β -disubstituted unsaturated compounds by Waldmann, Wang, Arai



b) This work: reacting with β -trifluoromethyl β,β -disubstituted enones



- Novel P,O ligand
- High stereoselectivity
- Broad substrate scope
- β -CF₃- β,β -disubstituted enones
- contiguous 4 chiral stereocenters including one quaternary

Scheme 1. [3+2] cycloaddition of azomethine ylides with disubstituted α,β -unsaturated compounds. EWG = electron-withdrawing group.

Meanwhile, it is well established that the strategic introduction a trifluoromethyl (CF₃) group into heterocycles can substantially modify their metabolic stability, lipophilicity, and bioavailability.^[6] Consequently, the development of reliable synthetic approaches to CF₃-bearing heterocycles has attracted much attention from synthetic chemists in recent years.^[7] However, the enantioselective construction of a trifluoromethylated all-carbon quaternary stereocenter has been less-often reported and remains extremely challenging, especially for construction of an all-carbon quaternary stereocenter bearing both CF₃ and CH₃.^[8] With the importance of pyrrolidines with one trifluoromethylated all-carbon quaternary stereocenter in mind (Figure 1),^[9] we decided to develop an efficient method to construct this skeleton. Recently, we developed a new chiral sulfinamide phosphine ligand, Ming-Phos, which can be easily made from inexpensive commercially available starting materials (i.e., *tert*-butanesulfinamide 2200 CNY kg⁻¹). This Ming-Phos showed good performance in the asymmetric gold-catalyzed dipolar

[*] Z.-M. Zhang,^[†] B. Xu,^[†] S. Xu, Prof. Dr. H.-H. Wu, Prof. Dr. J. Zhang
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering
East China Normal University
3663 N. Zhongshan Road, Shanghai 200062 (China)
E-mail: jlzhang@chem.ecnu.edu.cn
Homepage: <http://faculty.ecnu.edu.cn/s/1811/t/20975/main.jsp>

Prof. Dr. J. Zhang

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, Shanghai 200032 (China)

[†] These authors contributed equally to this work.

Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201602542>.

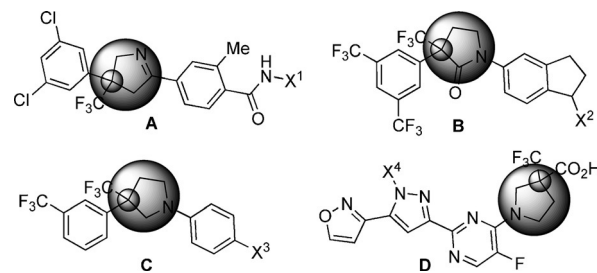


Figure 1. Pharmaceuticals and agrochemicals featuring ring-fused CF₃-bearing pyrrolidines.

[3+3] cycloaddition reaction of 2-(1-alkynyl)-alk-2-en-1-ones with nitrones.^[10] To extend the utility of this ligand to other dipolar cycloaddition reactions, we examined the asymmetric intermolecular [3+2] cycloaddition reaction of azomethine ylides with β -trifluoromethyl β,β -disubstituted enones. Herein, we present a highly diastereo- and enantioselective copper(I)/Ming-Phos-catalyzed intermolecular [3+2] cycloaddition reaction of azomethine ylides with β -trifluoromethyl β,β -disubstituted enones (Scheme 1b), a reaction, which to the best of our knowledge, is the first of its kind.

With a series of Ming-Phos ligands (**M1**–**M5**; Figure 2) in hand and inspired by the high catalytic activity of copper in [3+2] asymmetric cycloaddition reactions of azomethine ylides, we started to examine the performance of copper/Ming-Phos in the asymmetric [3+2] cycloaddition of the enone **1a** and azomethine ylide **2a** (for structures see Table 1;

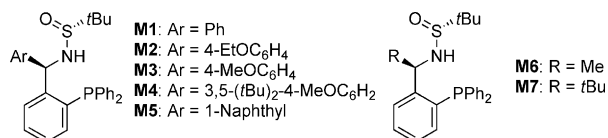


Figure 2. Screened ligands.

for results see Table S1 in the Supporting Information). Gratifyingly, the reaction proceeded to give **3aa** in 95 % yield as a single diastereomer (d.r. > 20:1) in 63 % *ee*, when the Ming-Phos **M1**, having a phenyl ring, was used as the chiral ligand. The modified ligands **M2**–**M5**, having different aryl rings, failed to improve the enantioselectivity (Table S1, entries 2–5). We then studied the performance of **M6**, bearing an alkyl group (R = Me), but the enantioselectivity was still moderate (Table S1, entry 6). Gratifyingly, **M7**, with a bulky *tert*-butyl group, led to a much higher *ee* value (Table S1, entry 7). Inspired by this result, other copper(I) salts such as [Cu(CH₃CN)₄]ClO₄ and [Cu(CH₃CN)₄]NTf₂ were then examined as precatalysts for the reaction under identical reaction conditions (Table S2, entries 8 and 9), and [Cu(CH₃CN)₄]ClO₄ exhibited better enantioselectivity (Table S1, entry 9; 95 % yield, > 20:1 d.r., 89 % *ee*). Meanwhile, a series of commercially available chiral ligands such as (*S*)-TF-Biphosphos, (*S*)-BINAP, (*R*)-SEGPPOS, (*R*)-DM-SEGPPOS, (*R,S*)-O-PINAP, (*R*)-MOP, Binol-derived phosphoramidite, P,N ligands, and chiral bis(oxazoline)s were screened (see Table S2). Among them, the ferrocenyl P,N ligand (*R*)-1-[(*S*)-2-diphenylphosphino]ferrocenylethylamine was the most promising, and delivered **3aa** in 83 % yield with 88 % *ee* and 6:1 diastereoselectivity. Then, we studied the solvent effect with the use of **M7** as the chiral ligand. By changing the solvent to either xylene or MTBE (methyl tertiary butyl ether) increased the *ee* value to 90 % (Table S1, entries 10 and 11). When the temperature was lowered to –50 °C in THF, the *ee* value of the desired product **3aa** was increased from 89 to 91 % (Table S1, entries 8 and 12), whereas, only trace amounts of product were detected at –50 °C in MTBE (Table S1, entry 13). Finally, the optimal reaction conditions were found to be: a mixed solvent system (THF and MTBE) at –50 °C with the use of [Cu(CH₃CN)₄]ClO₄ as the precat-

alyst and **M7** as the ligand (Table S1, entry 14; 98 % yield, > 20:1 d.r., 95 % *ee*).

With the optimal reaction conditions in hand, we turned to examine the reaction scope by variation of the enone component **1** (Table 1). Both electron-donating and electron-withdrawing substituents on the aryl ring (R¹) were tolerated (entries 1–8) and the reaction afforded the desired products

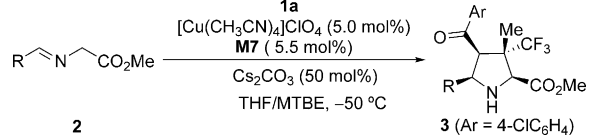
Table 1: Exploration of enone scope.^[a]

Entry	R ¹ /R ²	(–)- 3	Yield [%] ^[b]	<i>ee</i> [%]
1	4-ClC ₆ H ₄ /Me (1a)	(–)- 3aa	98	95
2	4-FC ₆ H ₄ /Me (1b)	(–)- 3ba	98	90
3	4-BrC ₆ H ₄ /Me (1c)	(–)- 3ca	92	94
4	4-CNC ₆ H ₄ /Me (1d)	(–)- 3da	94	95
5	4-NO ₂ C ₆ H ₄ /Me (1e)	(–)- 3ea	88	90
6	4-CF ₃ C ₆ H ₄ /Me (1f)	(–)- 3fa	99	95
7	4-CH ₃ C ₆ H ₄ /Me (1g)	(–)- 3ga	> 99	93
8	4-CH ₃ OC ₆ H ₄ /Me (1h)	(–)- 3ha	94	90
9 ^[c]	3,4-Cl ₂ C ₆ H ₃ /Me (1i)	(–)- 3ia	96	84
10 ^[c]	Ph/Me (1j)	(–)- 3ja	98	96
11	4-ClC ₆ H ₄ /Et (1k)	(–)- 3ka	97	94
12	4-ClC ₆ H ₄ /Ph (1l)	(–)- 3la	> 99	98
13	4-ClC ₆ H ₄ /2-naphthyl (1m)	(–)- 3ma	94	96
14	4-ClC ₆ H ₄ /3,5-(CH ₃) ₂ C ₆ H ₃ (1n)	(–)- 3na	94	90
15	Me/Ph (1o)	3oj	0	0
16 ^[d]	1j	(–)- 3jj	93	94

[a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.4 mmol of **2a**, 5 mol % of catalyst ([Cu]/**M7** = 1:1.1) in 4.0 mL MTBE/THF (*V*_{MTBE}/*V*_{THF} = 3:1) at –50 °C for 2–12 h and the diastereomeric ratios are > 20:1. [b] Yield of the isolated product. [c] –70 °C. [d] **2j** was used.

3aa–ha in yields ranging from 88 to greater than 99 % with *ee* values of 90–95 %. For the 3,4-dichlorophenyl-substituted enone **1i** and phenyl-substituted enone **1j**, the reactions required a lower temperature (–70 °C) to achieve high enantioselectivities of **3ia** and **3ja**, respectively, as single diastereomers in 96–98 % yields (entries 9 and 10). Meanwhile, the β -trifluoromethyl β -ethyl enone **1k** delivered the corresponding product **3ka** in 97 % yield and 94 % *ee*. Gratifyingly, the reaction could be also successfully extended to β -trifluoromethyl β -aryl enones and excellent enantioselectivities of **3la–na** were generally obtained (entries 12–14). Unfortunately, the less reactive methyl enone **1o** could not be used in the present dipolar [3+2] cycloaddition and even the racemic reaction did not occur (entry 15). It is noteworthy that the phenyl-substituted product **3jj** was obtained with excellent diastereo- and enantioselectivity (> 20:1 d.r., 94 % *ee*) with a lower reaction temperature of –70 °C (entry 16).

Next, we examined the scope with respect to the azomethine ylide component **2** by reaction with **1a** (Table 2). Both the electron-rich and electron-deficient aryl-aldehyde-derived **2b–m** delivered the corresponding products **3ab–am** in high yields with excellent diastereo- and enantioselectivities (92–> 99 % yields, > 20:1 d.r., 91–97 % *ee*;

Table 2: Exploration of azomethine ylide scope.^[a]


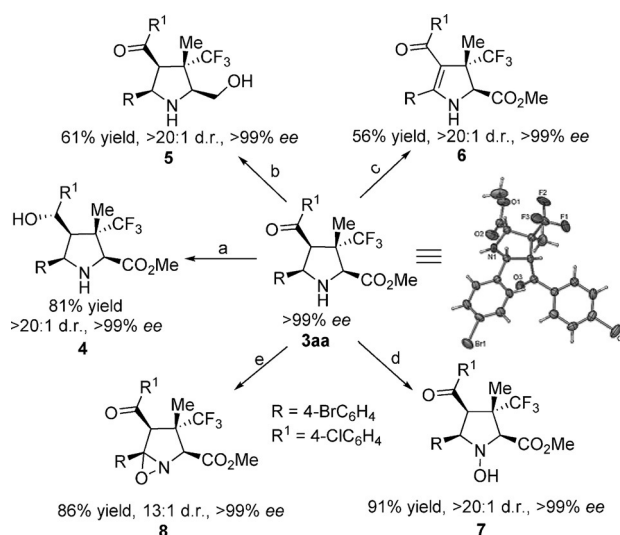
Entry	R	(-)-3	Yield [%] ^[b]	ee [%]
1	3-BrC ₆ H ₄ (2b)	(-)- 3ab	99	92
2	2-BrC ₆ H ₄ (2c)	(-)- 3ac	98	93
3	4-ClC ₆ H ₄ (2d)	(-)- 3ad	92	95
4	3-ClC ₆ H ₄ (2e)	(-)- 3ae	98	91
5	4-FC ₆ H ₄ (2f)	(-)- 3af	95	95
6	4-CF ₃ C ₆ H ₄ (2g)	(-)- 3ag	98	94
7	4-CNC ₆ H ₄ (2h)	(-)- 3ah	> 99	92
8	Ph (2i)	(-)- 3ai	> 99	91
9	4-PhC ₆ H ₄ (2j)	(-)- 3aj	> 99	97
10	4-CH ₃ C ₆ H ₄ (2k)	(-)- 3ak	> 99	95
11	4-CH ₃ OC ₆ H ₄ (2l)	(-)- 3al	> 99	93
12	3-CH ₃ C ₆ H ₄ (2m)	(-)- 3am	99	91
13	2-naphthyl (2n)	(-)- 3an	98	95
14 ^[c]	2-thienyl (2o)	(-)- 3ao	97	85
15 ^[d]	styryl (2p)	(-)- 3ap	70	80
16 ^[e]	cyclohexyl (2q)	(-)- 3aq	94	86

[a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.4 mmol of **2a**, 5 mol% of catalyst ([Cu]/**M7** = 1:1.1) in 4.0 mL MTBE/THF ($V_{\text{MTBE}}/V_{\text{THF}}$ = 3:1) at -50 °C for 2–12 h and the diastereomeric ratios are > 20:1. [b] Yield of the isolated product. [c] -70 °C. [d] d.r. = 4:1. [e] 10 mol% of catalyst was used.

entries 1–12). The 2-naphthyl-substituted **2n** afforded **3an** in 98% yield with 95% ee (entry 13). Additionally, the thiophene-2-carbaldehyde-derived imino ester **2o** worked well, thus leading to 97% yield of **3ao** with 85% ee (entry 14). The styryl-substituted **2p** delivered the corresponding compound **3ap** in 70% yield with 4:1 d.r. and 80% ee (entry 15). Notably, the less reactive **2q**, derived from an aliphatic aldehyde, is also applicable to this reaction, thereby giving the corresponding product **3aq** in 94% yield with high diastereo- and enantioselectivity (entry 16). Unfortunately, the reaction of an α -methyl iminoester with **1a** is messy, thus indicating that the construction of pyrrolidine with two contiguous quaternary stereocenters still pose a considerable challenge.

The absolute configuration of **3aa** was determined by single-crystal X-ray diffraction analysis (Scheme 2).^[11] Fortunately, the single-crystal of [(**M7**)Cu(CH₃CN)]ClO₄ was also obtained (Figure 3a).^[11] X-ray diffraction analysis revealed that the copper binds to both the phosphine and oxygen atom, thus indicating that **M7** serves as a P,O ligand here, and is different to the case of the gold complex (only binding to the phosphine).^[10] With the assistance of the X-ray structure of the copper(I) complex, a possible model for asymmetric induction is also proposed (Figure 3b).

A gram-scale reaction delivered 1.43 grams of **3aa** in 94% yield with excellent diastereo- and enantioselectivity (> 20:1 d.r., 94% ee), thus indicating the present asymmetric cycloaddition is easy to scale-up. Gratifyingly, the enantiopure **3aa** (> 99% ee) can be easily obtained by simple recrystallization of the crude reaction mixture from *n*-hexanes. To demonstrate the synthetic utility, several transformations of **3aa** were carried out. Firstly, the ketone and ester group of **3aa** could be



Scheme 2. The synthetic transformations of **3aa**.^[a] [a] Reaction conditions: a) NaBH₄ (2.0 equiv), MeOH, RT, 30 min. b) DIBAL-H (5.0 equiv), THF, -78 to -30 °C, 4 h. c) DDQ (1.2 equiv), toluene, 40 °C, 36 h. d) MCPBA (1.1 equiv), DCM, RT, 5 h. e) MCPBA (2.1 equiv), DCM, RT, 12 h. DCM = dichloromethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, MCPBA = *m*-chloroperbenzoic acid, THF = tetrahydrofuran.

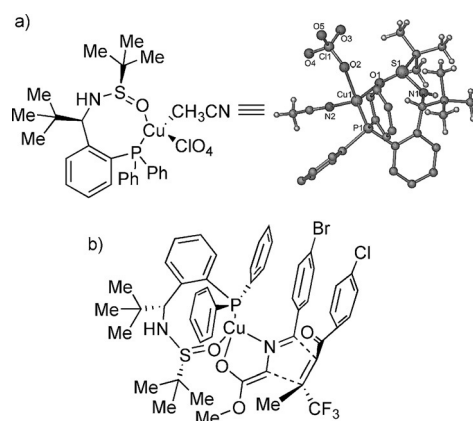


Figure 3. a) X-ray crystal structure of [(**M7**)Cu(CH₃CN)]ClO₄. b) Proposed model for asymmetric induction.

selectively reduced by different reducing reagents, thus leading to the corresponding alcohols **4** and **5** in 81 and 61% yields, respectively (Scheme 2). The absolute configuration of **4** was established by single-crystal X-ray diffraction analysis.^[11] Treatment of **3aa** with DDQ delivered the highly substituted 2-pyrroline **6** in 56% yield. It is very interesting to find that the oxidation of **3aa** with different equivalents of *m*-CPBA could produce the *N*-hydroxyl pyrrolidine **7** and bicyclic compound **8**, respectively, in high yields.

In summary, we developed the first highly enantioselective copper-catalyzed [3+2] cycloaddition reaction of azomethine ylides with β -trifluoromethyl β,β -disubstituted enones by the employing a cheap copper catalyst and a readily available chiral ligand, in which the Ming-Phos serves as a P,O ligand. This method provides a reliable strategy for the excellent enantioselective construction of highly substituted

pyrrolidines with a trifluoromethylated all-carbon quaternary stereocenter. The salient features of this cycloaddition include high efficiency, high diastereo- and enantioselectivity, a novel ligand, an inexpensive copper catalyst, outstanding functional-group tolerance, and diverse transformations. Further studies, including synthetic application and the employment of the chiral catalyst to other reactions, are currently underway and will be reported in due course.

Acknowledgments

We gratefully acknowledge the funding support of NSFC (21425205), 973 Program (2015CB856600), and the Program of Eastern Scholar at Shanghai Institutions of Higher Learning.

Keywords: azomethine ylides · cycloaddition · copper · heterocycles · P,O ligand

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6324–6328
Angew. Chem. **2016**, *128*, 6432–6436

- [1] For recent reviews and selected examples about the application of pyrrolidines in the natural products and biologically molecules, see: a) L. M. Harwood, R. J. Vickers, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. Pearson), Wiley, New York, **2002**; b) S. G. Pyne, A. S. Davis, N. J. Gates, K. B. Lindsay, T. Machan, M. Tang, *Synlett* **2004**, 2670; c) Y. Cheng, Z.-T. Huang, M.-X. Wang, *Curr. Org. Chem.* **2004**, *4*, 325; d) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139; e) D. Enders, C. Thiebes, *Pure Appl. Chem.* **2011**, *73*, 573. For the application of organic catalysts: f) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* (Eds.: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim, **2004**; g) *Privileged Chiral Ligands and Catalysts* (Ed.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**.
- [2] For recent reviews about 1,3-dipolar cycloaddition reactions of azomethine ylides, see: a) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247; b) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887; c) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174; d) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132; e) B. Engels, M. Christl, *Angew. Chem. Int. Ed.* **2009**, *48*, 7968; *Angew. Chem.* **2009**, *121*, 8110; f) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784; g) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703; h) L. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492; *Angew. Chem.* **2011**, *123*, 8642; i) E. E. Maroto, M. Izquierdo, S. Reboredo, J. Marco-Martínez, S. Filippone, N. Martín, *Acc. Chem. Res.* **2014**, *47*, 2660.
- [3] For selected leading examples of asymmetric [3+2] cycloaddition reactions of azomethines, for metal-catalytic ones without formation of all-carbon quaternary stereocenter, see: a) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400; b) C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174; c) T. F. Knöpfel, P. Aschwarden, T. Ichikawa, T. Watanabe, M. E. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; *Angew. Chem.* **2004**, *116*, 6097; d) S. Cabrera, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394; e) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou, Y.-D. Wu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1979; *Angew. Chem.* **2006**, *118*, 2013; f) W. Zeng, G.-W. Chen, Y.-G. Zhou, Y.-X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750; g) S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364; h) C. Nájera, M. D. G. Retamosa, J. M. Sansano, *Angew. Chem. Int. Ed.* **2008**, *47*, 6055; *Angew. Chem.* **2008**, *120*, 6144; i) T. Arai, N. Yokoyama, H. Sato, *Angew. Chem. Int. Ed.* **2010**, *49*, 7895; *Angew. Chem.* **2010**, *122*, 8067; j) T. Arai, A. Mishiro, N. Yokoyama, K. Suzuki, H. Sato, *J. Am. Chem. Soc.* **2010**, *132*, 5338; k) Y. Yamashita, X.-X. Guo, R. Takashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 3262; l) H. Y. Kim, J.-Y. Li, S. Kim, K. Oh, *J. Am. Chem. Soc.* **2011**, *133*, 20750; m) Y. Yamashita, T. Imaizumi, S. Kobayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 4893; *Angew. Chem.* **2011**, *123*, 4995; n) M. Potowski, M. Schürmann, H. Preut, A. P. Antonchick, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 428; o) X.-F. Bai, T. Song, Z. Xu, C.-G. Xia, W.-S. Huang, L.-W. Xu, *Angew. Chem. Int. Ed.* **2015**, *54*, 5255; *Angew. Chem.* **2015**, *127*, 5344. For organo-catalytic ones, see: p) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168; *Angew. Chem.* **2007**, *119*, 5260; q) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652. For selected leading examples of asymmetric non-[3+2] cycloaddition of azomethine ylides, see: r) Z.-Y. Xue, Q.-H. Li, H.-Y. Tao, C.-J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 11757; s) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 9512; *Angew. Chem.* **2012**, *124*, 9650; t) Z.-L. He, H.-L. Teng, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2934; *Angew. Chem.* **2013**, *125*, 3006; u) M.-C. Tong, X. Chen, H.-Y. Tao, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12377; *Angew. Chem.* **2013**, *125*, 12603; v) H. Guo, H. Liu, F.-L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X.-P. Hu, M. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12641; *Angew. Chem.* **2013**, *125*, 12873; w) H.-L. Teng, L. Yao, C.-J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 4075; x) Q.-H. Li, L. Wei, *J. Am. Chem. Soc.* **2014**, *136*, 8685; y) H. Liu, Y. Wu, Y. Zhao, Z. Li, L. Zhang, W. Yang, H. Jiang, C. Jing, H. Yu, B. Wang, Y. Xiao, H. Guo, *J. Am. Chem. Soc.* **2014**, *136*, 2625.
- [4] For reviews of catalytic asymmetric construction of all-carbon quaternary stereocenters, see: a) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388; *Angew. Chem.* **1998**, *110*, 402; b) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; e) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295; f) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593; g) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247.
- [5] Synthesis of pyrrolidines with an all-carbon quaternary stereocenter by [3+2] cycloaddition with α,β -disubstituted unsaturated compounds. For metal catalysis, see: a) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735; b) H.-L. Teng, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 5494; c) T.-L. Teng, Z.-L. He, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 9600; d) T.-L. Liu, Z.-Y. Xue, H.-Y. Tao, C.-J. Wang, *Org. Biomol. Chem.* **2011**, *9*, 1980; e) T.-L. Liu, Z.-L. He, Q.-H. Li, H.-Y. Tao, C.-J. Wang, *Adv. Synth. Catal.* **2011**, *353*, 1713; f) A. Awata, T. Arai, *Chem. Eur. J.* **2012**, *18*, 8278; g) Q.-H. Li, T.-L. Liu, L. Wei, X. Zhou, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2013**, *49*, 9642; h) H.-Y. Tao, Z.-L. He, Y. Yang, C.-J. Wang, *RSC Adv.* **2014**, *4*, 16899; i) T. Arai, H. Ogawa, A. Awata, M. Sato, M. Watabe, M. Yamanaka, *Angew. Chem. Int. Ed.* **2015**, *54*, 1595; *Angew. Chem.* **2015**, *127*, 1615; for organocatalysis, see: j) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819; k) L. He, X.-H. Chen, D.-N. Wang, S.-W. Luo, W.-Q. Zhang, J. Yu, L. Ren, L.-Z. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 13504.
- [6] a) *Biomedical Aspects of Fluorine Chemistry* (Eds.: R. Filler, Y. Kobayashi), Elsevier Biomedical Press and Kodansha Ltd., Amsterdam, **1982**; b) *Fluorine in Bioorganic Chemistry* (Eds.:

- J. T. Welch, S. Eswarakrishnan), Wiley, New York, **1991**;
- c) "Organofluorine Compounds": *Medicinal Chemistry and Biomedical Applications* (Eds.: R. Filler, Y. Kobayashi, L. M. Yagupolskii), Elsevier, Amsterdam, **1993**; d) *Fluorine Containing Amino Acids: Synthesis and Properties* (Eds.: V. P. Kuhar, V. A. Soloshonok), Wiley, Chichester, **1995**; e) P. Jeschke, *ChemBioChem* **2004**, *5*, 570; f) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303; g) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; h) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359; i) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470.
- [7] *Fluorinated Heterocyclic Compounds: Synthesis Chemistry, and Applications* (Ed.: V. A. Petrov), Wiley, Hoboken, **2009**.
- [8] For organocatalysis: a) H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2012**, *51*, 4959; *Angew. Chem.* **2012**, *124*, 5043; b) H. Kawai, Z. Yuan, T. Kitayama, E. Tokunaga, N. Shibata, *Angew. Chem. Int. Ed.* **2013**, *52*, 5575; *Angew. Chem.* **2013**, *125*, 5685; c) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin, R. Wang, *Org. Lett.* **2014**, *16*, 1394; for trifluoromethylation reagents: d) Q.-H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769; for transition-metal catalysis: e) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han, Y.-X. Jia, *J. Am. Chem. Soc.* **2013**, *135*, 2983.
- [9] a) J. Mihara, M. Hatazawa, D. Yamazaki, N. Sasaki, T. Murata, E. Shimojo, T. Ichihara, M. Ataka, K. Shibuya, U. Görgens, WO 2011080211, **2011**; b) K. Köerber, F. Kaiser, W. V. Deyn, P. Deshmukh, A. Narine, J. Dickhaut, N. G. Bandur, D. L. Culbertson, D. D. Anspaugh, F.-J. Braun, WO 2012042007, **2012**;
- c) J. Y. Cassayre, P. Renold, M. E. Qacemi, T. Pitterna, J. C. Toueg, WO 2012163959, **2012**; d) J. Y. Cassayre, P. Renold, M. El Qacemi, G. Berthon, WO 2012045700, **2012**; e) R. Fischer, P. Bruechner, T. Kapferer, K. Ilg, U. Görgens, A. Voerste, M. Hatazawa, E. Shimojo, WO 22013135724, **2013**; f) M. El Qacemi, J. Y. Cassayre, WO 2014019609, **2014**; g) M. El Qacemi, J. Y. Cassayre, WO 2014029706, **2014**; h) S. M. K. Sheehan, V. A. Vaillancourt, WO 2014038489, **2014**; i) M. Follmann, J.-P. Stasch, G. Redlich, D. Lang, WO 2014131741, **2014**; j) M. Follmann, J.-P. Stasch, G. Redlich, D. Lang, A. Vakalopoulos, F. Wunder, A. Tersteegen, WO 2014131760, **2014**; k) T. Nakai, J. Moore, N. R. Perl, R. R. Iyenagar, A. Mermerian, G.-Y. J. Im, T. W.-H. Lee, C. Hudson, G. R. Rennie, J. Jia, P. A. Renhowe, T. C. Barden, X. Yu, J. E. Sheppeck, K. Iyer, J. Jung, WO 2014144100, **2014**; l) U. Görgens, J. Mihara, T. Murata, D. Yamazaki, Y. Yoneta, K. Araki, N. Sasaki, K. Domon, M. Hatazawa, E. Shimojo, T. Ichihara, M. Ataka, K. Shibuya, US 20150073139, **2015**.
- [10] Z.-M. Zhang, P. Chen, W. Li, Y. Niu, X.-L. Zhao, J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4350; *Angew. Chem.* **2014**, *126*, 4439.
- [11] CCDC 1450897 (**3aa**), 1450898 (**4**) and 11450899 ([**(M7)**Cu-(CH₃CN)]ClO₄) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: March 25, 2016

Published online: April 13, 2016