Asymmetric Synthesis

International Edition: DOI: 10.1002/anie.201510910
German Edition: DOI: 10.1002/ange.201510910

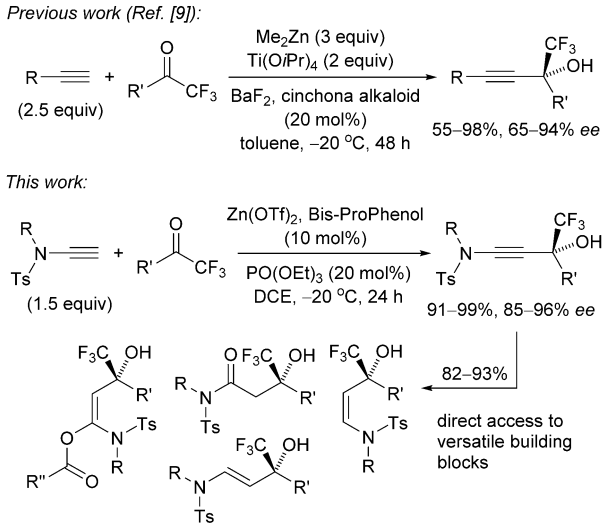
Efficient Access to Multifunctional Trifluoromethyl Alcohols through Base-Free Catalytic Asymmetric C–C Bond Formation with Terminal Ynamides

*Andrea M. Cook and Christian Wolf**

Abstract: *The asymmetric addition of terminal ynamides to trifluoromethyl ketones with a readily available chiral zinc catalyst gives CF_3-substituted tertiary propargylic alcohols in up to 99% yield and 96% ee. The exclusion of organozinc additives and base as well as the general synthetic utility of the products are key features of this reaction. The value of the β-hydroxy-β-trifluoromethyl ynamides is exemplified by selective transformations to chiral Z- and E-enamides, an amide, and N,O-ketene acetals. The highly regioselective hydration, stereoselective reduction, and hydroacyloxylation reactions proceed with high yields and without erosion of the ee value of the parent β-hydroxy ynamides.*

The significance of the trifluoromethyl-substituted propargylic alcohol moiety, for example, in the anti-HIV drug Efavirenz, has stimulated the development of several methods that furnish this motif in racemic form.[1] In contrast to the general advance with asymmetric alkynylations of aldehydes,[2] ketones,[3] and imines,[4] trifluoromethyl ketones have remained challenging substrates,[5] and initially required the use of stoichiometric amounts of lithium or zinc aminoalkoxides.[6] Shibasaki and co-workers first demonstrated the feasibility of asymmetric catalysis, and generated CF_3-substituted propargylic alcohols in up to 52% *ee*.[7] Significant progress in this field emerged in 2011, when Carreira and co-workers reported an intriguing autocatalytic procedure that is tailored to the production of an Efavirenz precursor.[8] At the same time, Ma and co-workers introduced an alkynylation method that gives 55–98% yield and 65–94% *ee* with non-enolizable trifluoromethyl ketones when 2.5 equivalents of the alkyne, 3 equivalents of Me_2Zn, and 2 equivalents of $Ti(OiPr)_4$ are used in addition to catalytic amounts of a cinchona alkaloid and BaF_2.[9]

In recent years, terminal ynamides have become readily available surrogates of the highly reactive and less practical parent ynamines, and have been applied in a variety of cycloadditions[10] and several other reactions.[11] By contrast, the usefulness of terminal ynamides in nucleophilic addition reactions has rarely been explored,[12] and the reaction with trifluoromethyl ketones has not been reported to date. We hypothesized that a catalytic asymmetric method that allows addition of terminal ynamides to trifluoroacetophenone and derivatives thereof has potential to overcome the remaining drawbacks of the reaction with alkynes, in particular the use of excess pyrophoric dimethylzinc. At the same time, the enantioselective synthesis of ynamide-derived, CF_3-substituted propargylic alcohols would provide unprecedented access to a variety of highly functionalized chiral building blocks if one could exploit the unique reactivity of the polarized N-substituted triple bond (Scheme 1).[13] The recent introduction of a very practical two-step synthesis of terminal ynamides from tosylamides and trichloroethylene by Anderson and co-workers provided an excellent starting point for our study.[14]



Scheme 1. Catalytic asymmetric addition of ynamides to trifluoromethyl ketones provides practical access to chiral enamides, amides, and N,O-ketene acetals with a tertiary CF_3-substituted alcohol group.

At the onset of this investigation, we employed *N*-ethynyl-*N*-butylbenzenesulfonamide (**1**) and other ynamides in several literature procedures previously developed for catalytic enantioselective alkynylations of carbonyl electrophiles. While these screening efforts were mostly unsuccessful, we were excited to find that asymmetric addition of an ynamide to trifluoroactophenone occurs in the presence of catalytic amounts of zinc triflate, *N*-methylephedrine, and excess Et_3N or iPr_2NEt. Further investigation then revealed that the yield and *ee* value varied substantially depending on the source of the tertiary amine employed.[15] Careful purification of the amines used as well as investigation of possible effects of

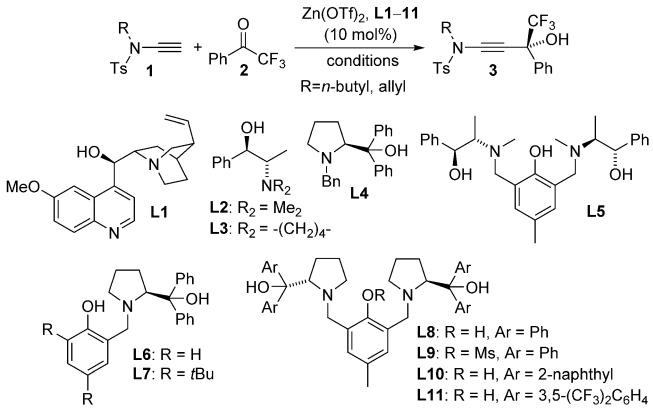
[*] A. M. Cook, Dr. C. Wolf
Department of Chemistry, Georgetown University
37th and O Streets, Washington, DC 20057 (USA)
E-mail: cw27@georgetown.edu
Homepage: http://www.thewolfgrouponline.com/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201510910.

impurities and amine degradation products that may be present in small amounts but could possibly affect the ynamide addition did not resolve this problem. We therefore decided to develop a practical catalytic method that avoids both organozinc reagents and amine additives. Comprehensive screening of zinc and copper complexes, a large variety of chiral ligands in several solvents, and analysis of the effect of $(MeO)_3PO$, $(EtO)_3PO$, Ph_3PO, Ph_3PS, tBu_3P, HMPA, and other additives on the asymmetric induction and turnover gave mixed results. Initially, moderate *ee* values were obtained with 10 mol% zinc triflate and **L1**–**L4**. However, we were delighted to find that the reaction between the readily available ynamide **1** and **2** occurs with these catalysts even in the absence of triethylamine or Hünig's base, thereby providing **3** in up to 95% yield at 25°C (Table 1, entries 1–4).

Although encouraging results were obtained with quinine,[16] we turned our attention to Trost's Bis-ProPhenols, which can be more easily modified if ligand fine-tuning becomes necessary.[17] The employment of **L5**–**L7**, with either *N*-methylephedrine or diphenylprolinol units attached to a phenol core, did not show improvement (entries 5–7). However, the introduction of C_2-symmetric **L8** gave **3** in 87% yield and 89% *ee* within 16 h and essentially the same results were obtained with the *N*-allyl analogue of **1**, thereby indicating that this method tolerates different ynamides (compare entries 8 and 12). The presence of the free phenol group appears to be essential to the catalytic activity of **L8** and very low yields were obtained with **L9**. The use of the naphthyl analogue **L10** further improved the yield, but at the expense of the enantioselectivity, while to our surprise **L11** gave poor results (entries 10 and 11). We therefore continued to evaluate different solvents and the effect of temperature on this reaction using 10 mol% $Zn(OTf)_2$ and **L8** (entries 13–20). Chlorinated solvents proved superior and gave consistently high yields and *ee* values. When using dichloroethane as the solvent, we observed that *ee* values improve above 90% when the temperature was decreased to at least 0°C, but the reaction time increased to approximately 2 days. This was addressed through the addition of catalytic amounts of triethyl phosphate to affect catalytic turnover and we obtained **3** in 96% yield and 96% *ee* at −20°C in 24 h (entry 21).

Table 1: Optimization of the zinc triflate catalyzed asymmetric addition of ynamides to trifluoroacetophenone.



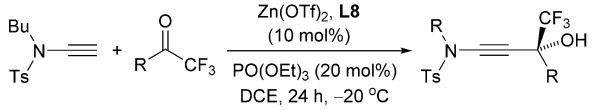
Entry	Ligand	R	Conditions	Yield [%]	*ee* [%]
1	**L1**	*n*Bu	DCE, 25°C, 20 h	75	48
2	**L2**	*n*Bu	DCE, 25°C, 20 h	95	44
3	**L3**	*n*Bu	DCE, 25°C, 20 h	89	33
4	**L4**	*n*Bu	DCE, 25°C, 16 h	27	3
5	**L5**	*n*Bu	DCE, 25°C, 20 h	15	22
6	**L6**	*n*Bu	DCE, 25°C, 16 h	25	14
7	**L7**	*n*Bu	DCE, 25°C, 16 h	72	45
8	**L8**	*n*Bu	DCE, 25°C, 16 h	87	89
9	**L9**	*n*Bu	DCE, 25°C, 20 h	15	0
10	**L10**	*n*Bu	DCE, 25°C, 16 h	93	80
11	**L11**	*n*Bu	DCE, 25°C, 16 h	22	9
12	**L8**	allyl	DCE, 25°C, 16 h	88	86
13	**L8**	*n*Bu	CH_2Cl_2, 25°C, 20 h	95	87
14	**L8**	*n*Bu	$CHCl_3$, 25°C, 20 h	95	86
15	**L8**	*n*Bu	toluene, 25°C, 16 h	70	78
16	**L8**	*n*Bu	THF, 25°C, 16 h	55	66
17	**L8**	*n*Bu	ACN, 25°C, 20 h	90	31
18	**L8**	*n*Bu	EtOH, 25°C, 20 h	5	n.d.
19	**L8**	*n*Bu	DCE, 0°C, 45 h	78	93
20	**L8**	*n*Bu	DCE, −10°C, 51 h	73	91
21[a]	**L8**	*n*Bu	DCE, −20°C, 24 h	96	96

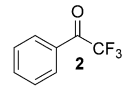
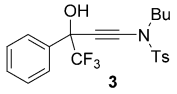
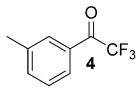
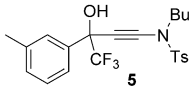
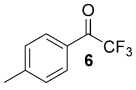
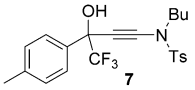
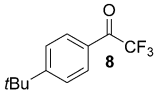
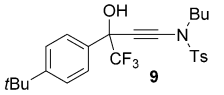
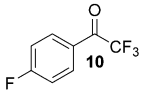
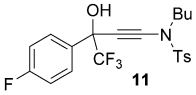
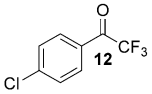
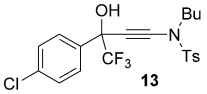
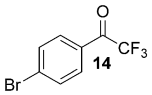
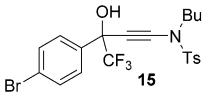
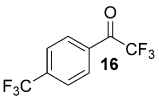
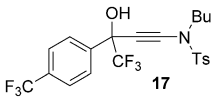
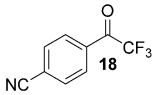
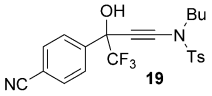
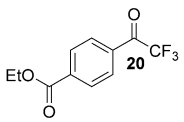
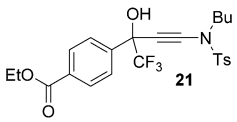
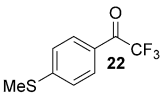
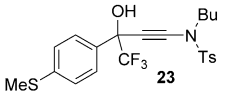
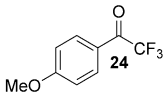
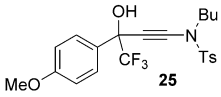
[a] $(EtO)_3PO$ (20 mol%). DCE = 1,2-dichloroethane.

Ynamide addition is ligand-accelerated and does not occur in the absence of a zinc catalyst (see the Supporting Information).[18] When we employed phenylacetylene in our optimized base-free procedure we observed sluggish conversion, with the propargylic alcohol produced in low yields. ^{1}H NMR spectroscopic analysis of a stoichiometric mixture of zinc triflate, the Bis-ProPhenol ligand, and **1** showed formation of a Zn-**L8** complex in deuterated chloroform, but no sign of coordination and activation of the ynamide (see the Supporting Information). The reaction presumably involves an intermediate side-on or end-on zinc-ynamide species which does not form in the absence of the trifluoromethyl ketone. In accordance with a study by Cozzi et al.,[19] the substrate may, therefore, play a pivotal role in promoting the ynamide activation and its own consumption. Altogether, these observations reveal the strikingly different reactivity of terminal ynamides compared to simple alkynes and the distinct behavior of trifluoromethyl ketones. Having developed a base-free catalytic method for the asymmetric addition of readily available ynamides to **2** and excluding the use of pyrophoric dialkylzinc reagents as well as other stoichiometric additives, we began with the evaluation of the substrate scope. The introduction of simple trifluoroacetophenone analogues to our procedure gave the β-hydroxy ynamides **5**, **7**, and **9** in 96–97% yield and in 94–96% *ee* (Table 2, entries 2–4). Similar results were obtained with a series of functionalized analogues (entries 5–12).

The intrinsic synthetic value of the β-hydroxy ynamides shown above stems from the high density of functional groups that are combined into a relatively small chiral building block. The trifluoromethylated tertiary chiral alcohol moiety is an increasingly attractive motif with potential use in medicinal applications,[20] and the adjacent ynamide unit provides unique synthetic versatility that is orthogonal to the chemistry of C-substituted propargylic alcohols. With this in mind, we set out to investigate selective transformations that would generate unprecedented access to new or generally challeng-

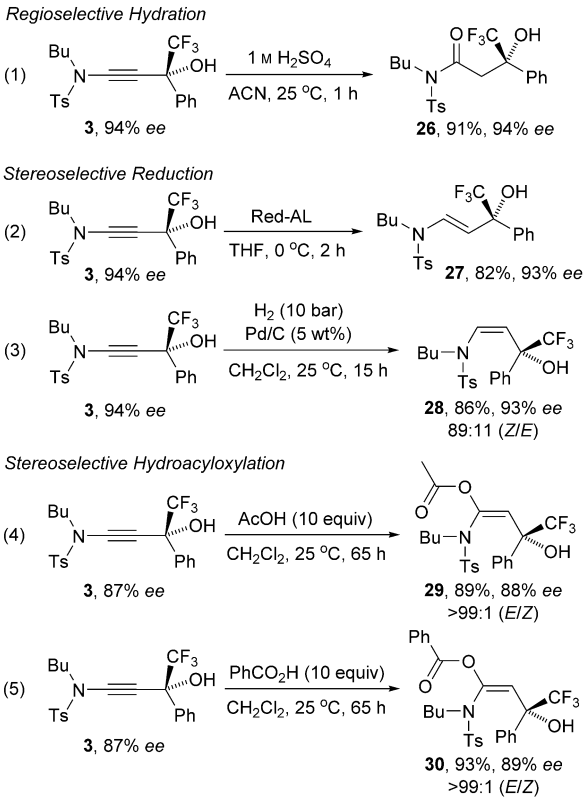
Table 2: Asymmetric catalytic addition of ynamides to trifluoromethyl ketones.



Entry	CF_3 ketone	β-Hydroxy ynamide	Yield[a] [%]	*ee* [%]
1	 **2**	 **3**	96	96
2	 **4**	 **5**	97	95
3	 **6**	 **7**	97	94
4	 **8**	 **9**	95	96
5	 **10**	 **11**	97	94
6	 **12**	 **13**	95	93
7	 **14**	 **15**	97	90
8	 **16**	 **17**	99	92
9	 **18**	 **19**	91	90
10	 **20**	 **21**	99	89
11	 **22**	 **23**	99	90
12[b]	 **24**	 **25**	91	85

[a] Yields of isolated product. [b] 0 °C, 50 h. The absolute configuration of **3** was determined by crystallographic analysis of the partial reduction and hydroacyloxylation derivatives **28** and **30** (see the Supporting Information).

ing structures. In contrast to alkynes, the ynamide unit can be considered a masked amide bond and we, therefore, decided to develop a catalytic method that exploits regioselective hydration. After screening of several acids and solvents, we found that smooth conversion of **3** into **26** occurs in the presence of dilute sulfuric acid at room temperature. By using this procedure, we obtained the corresponding β-hydroxy sulfonamide **26** in 91 % yield and without compromising the *ee* value of the starting material [Equation (1) in Scheme 2].



Scheme 2. Selective transformations of β-hydroxy ynamides.

Next, we turned our attention to *N*-tosyl β-hydroxy enamines, which are viable substrates for the synthesis of a variety of compounds, including aminocyclopropyl carbinols and 1,3-amino alcohols.[21] Urabe and co-workers originally developed a diastereoselective method that utilizes a chiral sulfonamide auxiliary to afford *N*-tosyl (*E*)-β-hydroxy enamines through Ti-mediated ynamide addition to aldehydes.[22] Walsh and co-workers introduced an asymmetric route toward a series of *E* isomers that is based on sequential hydroboration of internal *N*-tosyl ynamides, boron-to-zinc transmetalation, and catalytic nucleophilic addition to aldehydes in one pot.[21a] We now complement these methods, which afford *E*-enamines with a secondary alcohol moiety, by providing stereoselective access to both (*Z*)- and (*E*)-*N*-tosyl β-hydroxy enamines with a tertiary chiral carbinol group. Selective reduction of **3** with either Red-Al or by Pd-catalyzed hydrogenation gave **27** and **28** in one step in 82 and 86 % yield and 93 % *ee* [Equations (2) and (3) in Scheme 2].

Finally, we explored the possibility of a mild diastereoselective addition of carboxylic acids to ynamide **3**. To the best of our knowledge, few achiral α-acyloxyenamides have been prepared to date. The Lam research group were the first to prepare α-acyloxyenamides by palladium-catalyzed hydro-

acyloxylation of ynamides at 70 °C and demonstrated the synthetic utility of these N,O-ketene acetals in rearrangement reactions.[23] Recently, a metal-free procedure that gives moderate to high yields although at even higher temperatures (100 °C) was reported.[24] We found that the hydroacyloxylation of **3** with acetic and benzoic acid can be accomplished in dichloromethane at room temperature without loss of the enantiomeric purity. In both cases, the *E* isomers were produced with high diastereoselectivity ($E/Z > 99{:}1$) and we obtained **29** and **30** in yields of 89 % and 93 %, respectively [Equations (4) and (5) in Scheme 2].[25]

Slow evaporation of concentrated solutions of **28** and **30** in chloroform and dichloromethane, respectively, gave single crystals suitable for X-ray determination of the absolute and relative configurations (Figure 1).[26] These enamides have relatively short C=C bonds (1.319–1.325 Å) and significantly longer C–N bonds (1.421–1.437 Å) compared to typical enamines, which explains the increased thermal stability and ease of isolation.

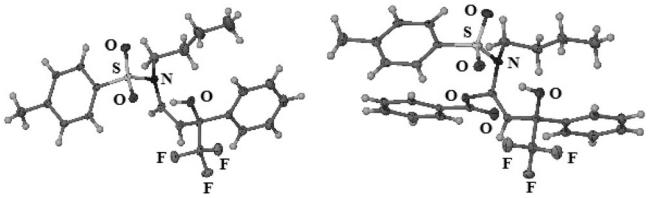


Figure 1. X-ray structures of (*S*,*Z*)-**28** (left) and (*S*,*E*)-**30** (right). Selected bond lengths for **28** [Å]: C=C: 1.325, N-C(sp^2): 1.437; **30**: C=C: 1.319, N-C(sp^2): 1.421, O-C(sp^2): 1.411.

In summary, we have introduced the first catalytic enantioselective addition of terminal ynamides to trifluoromethyl ketones. The reaction occurs in the presence of catalytic amounts of $Zn(OTf)_2$, a bis(prolinol)phenol ligand, and triethyl phosphate, and it provides practical access to synthetically versatile CF_3-substituted tertiary propargylic alcohols that are obtained in high yields and enantiomeric excess. The utility of the tertiary β-hydroxy-β-trifluoromethyl ynamides was demonstrated with highly regioselective hydration, stereoselective reductions, and hydroacyloxylations, which afforded trifluoromethylated chiral alcohols with adjacent *Z*- and *E*-enamide, amide and N,O-ketene acetal functionalities.

Experimental Section

3: Zinc triflate (7.4 mg, 0.02 mmol), (*R*,*R*)-(−)-**L8** (14.8 mg, 0.022 mmol), **1** (75.0 mg, 0.30 mmol), **2** (35 mg, 0.20 mmol), and triethyl phosphate (7.3 mg, 0.04 mmol) were dissolved in 1,2-dichloroethane (0.2 mL) under a nitrogen atmosphere. The mixture was stirred at −20 °C for 24 h. Purification of the crude mixture by flash chromatography on silica gel using 1 % Et_3N in CH_2Cl_2 as the mobile phase gave **3** as a colorless oil (82.0 mg, 0.19 mmol, 96 %, 96 % *ee*). ^{1}H NMR (400 MHz): $\delta = 7.76$ (d, $J = 8.1$ Hz, 2H), 7.69 (m, 2H), 7.43–7.36 (m, 3H), 7.32 (d, $J = 8.1$ Hz, 2H), 3.44–3.32 (m, 2H), 3.05 (s, 1H), 3.05 (s, 3H), 1.67–1.58 (m, 2H), 1.40–1.29 (m, 2H), 0.90 ppm (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta = 145.0$, 135.4, 134.3, 129.9, 129.4, 128.2, 127.7, 127.2, 123.4 (q, $J = 285.6$ Hz), 81.7, 73.4 (q, $J = 32.5$ Hz), 67.4, 50.9, 29.8, 21.7, 19.4, 13.5 ppm. The *ee* value was determined by HPLC on Phenomenex Cellulose-3. Elemental analysis calcd for $C_{21}H_{22}F_3NO_3S$ (%): C 59.28, H 5.21, N 3.29; found: C 59.02, H 5.12, N 3.29.

Acknowledgments

We thank the National Institutes of Health (GM106260) for financial support.

Keywords: enamides · homogeneous catalysis · organofluorine compounds · synthetic methods · ynamides

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2929–2933
Angew. Chem. **2016**, *128*, 2982–2986

[1] a) V. R. Chintareddy, K. Wadhwa, J. G. Verkade, *J. Org. Chem.* **2011**, *76*, 4482; b) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945; *Angew. Chem.* **2015**, *127*, 5028; c) L. Wang, N. Liu, B. Dai, X. Ma, L. Shi, *RSC Adv.* **2015**, *5*, 10089.

[2] a) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687; b) X. Li, G. Lu, W. H. Kwok, A. S. C. Chan, *J. Am. Chem. Soc.* **2002**, *124*, 12636; c) G. Gao, R.-G. Xie, L. Pu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5417; d) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760; e) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie, L. Pu, *Angew. Chem. Int. Ed.* **2006**, *45*, 122; *Angew. Chem.* **2006**, *118*, 128; f) C. Wolf, S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 10996.

[3] a) P. G. Cozzi, *Angew. Chem. Int. Ed.* **2003**, *42*, 2895; *Angew. Chem.* **2003**, *115*, 3001; b) G. Lu, X. Li, X. Jia, W. L. Chan, A. S. C. Chan, *Angew. Chem. Int. Ed.* **2003**, *42*, 5057; *Angew. Chem.* **2003**, *115*, 5211; c) T. Ohshima, T. Kawabata, Y. Takeuchi, T. Kakinuma, T. Iwasaki, T. Yonezawa, H. Murakami, H. Nishiyama, K. Mashima, *Angew. Chem. Int. Ed.* **2011**, *50*, 6296; *Angew. Chem.* **2011**, *123*, 6420.

[4] a) C. Wie, C. J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638; b) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; *Angew. Chem.* **2003**, *115*, 5941; c) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; *Angew. Chem.* **2004**, *116*, 6097; d) J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196; e) P. de Armas, D. Tejedor, F. Garcia-Tellado, *Angew. Chem. Int. Ed.* **2010**, *49*, 1013; *Angew. Chem.* **2010**, *122*, 1029.

[5] For excellent reviews, see a) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963; b) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455; c) S. Li, J.-A. Ma, *Chem. Soc. Rev.* **2015**, *44*, 7439.

[6] a) A. S. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 8937; b) L. Tan, C.-Y. Chen, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Angew. Chem. Int. Ed.* **1999**, *38*, 711; *Angew. Chem.* **1999**, *111*, 724.

[7] R. Motoki, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 2997.

[8] N. Chinkov, A. Warm, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 2957; *Angew. Chem.* **2011**, *123*, 3014.

[9] G.-W. Zhang, W. Meng, H. Ma, J. Nie, W.-Q. Zhang, J.-A. Ma, *Angew. Chem. Int. Ed.* **2011**, *50*, 3538; *Angew. Chem.* **2011**, *123*, 3600.

[10] a) H. Li, R. P. Hsung, *Org. Lett.* **2009**, *11*, 4462; b) X. Zhang, R. P. Hsung, H. Li, Y. Zhang, W. L. Johnson, R. Figueroa, *Org. Lett.* **2008**, *10*, 3477; c) M. F. Martínez-Esperón, D. Rodriguez, L. Castedo, C. Saá, *Org. Lett.* **2005**, *7*, 2213; d) B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1999**, *38*, 2426; *Angew. Chem.* **1999**, *111*, 2521; e) B. Witulski, C. Alayrac, *Angew. Chem. Int.*

Ed. **2002**, *41*, 3281; *Angew. Chem.* **2002**, *114*, 3415; f) R. B. Dateer, B. S. Shaibu, R.-S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 113; *Angew. Chem.* **2012**, *124*, 117.

[11] a) R. Tanaka, A. Yuza, Y. Watai, D. Suzuki, Y. Takayama, F. Sato, M. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7774; b) D. Tanaka, Y. Sato, M. Mori, *J. Am. Chem. Soc.* **2007**, *129*, 7730; c) M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder, R. P. Hsung, *Org. Lett.* **2004**, *6*, 2209; d) S. Couty, B. Liegault, C. Meyer, J. Cossy, *Org. Lett.* **2004**, *6*, 2511; e) Z. F. Al-Rashid, R. P. Hsung, *Org. Lett.* **2008**, *10*, 661; f) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* **2003**, *125*, 2368.

[12] a) M. Egi, Y. Yamaguchi, N. Fujiwara, S. Akai, *Org. Lett.* **2008**, *10*, 1867; b) X.-N. Wang, G. N. Winston-McPherson, M. Walton, Y. Zhang, R. P. Hsung, K. A. DeKorver, *J. Org. Chem.* **2013**, *78*, 6233; c) X.-N. Wang, R. P. Hsung, Q. Rui, S. K. Fox, M.-C. Lv, *Org. Lett.* **2013**, *15*, 2514; d) A. M. Cook, C. Wolf, *Chem. Commun.* **2014**, *50*, 3151; e) P. Zhang, A. M. Cook, Y. Liu, C. Wolf, *J. Org. Chem.* **2014**, *79*, 4167; f) A. M. Cook, C. Wolf, *Tetrahedron Lett.* **2015**, *56*, 2377.

[13] Excellent reviews on ynamide chemistry: a) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840; *Angew. Chem.* **2010**, *122*, 2902; b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064; c) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560.

[14] Prime examples of terminal ynamide synthesis: a) B. Witulski, M. Goessmann, *Chem. Commun.* **1999**, 1879; b) D. Brückner, *Tetrahedron* **2006**, *62*, 3809; c) D. Rodriguez, L. Castedo, C. Saa, *Synlett* **2007**, 1963; d) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833; e) S. J. Mansfield, C. D. Campbell, M. W. Jones, E. A. Anderson, *Chem. Commun.* **2015**, *51*, 3316.

[15] For examples of asymmetric additions of alkynes to aldehydes in the presence of $Zn(OTf)_2$, amino alcohols, and amine additives, see a) D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806; b) B. Jiang, Z. Chen, W. Xiong, *Chem. Commun.* **2002**, 1524; c) E. R. Graham, R. R. Tykwinski, *J. Org. Chem.* **2011**, *76*, 6574; several groups reported inconsistent results using these methods, which have been attributed to variations in the $Zn(OTf)_2$ quality: d) J. A. Marshall, M. P. Bourbeau, *Org. Lett.* **2003**, *5*, 3197; e) J. E. D. Kirkham, T. D. L. Courtney, V. Lee, J. E. Baldwin, *Tetrahedron* **2005**, *61*, 7219; and references therein; f) M. D. B. Fenster, G. R. Dake, *Chem. Eur. J.* **2005**, *11*, 639; g) for a general review of this topic, see Ref. [5].

[16] For cinchona alkaloid catalyzed alkynylation of ketones, see Ref. [9] and L. Liu, R. Wang, Y.-F. Kang, C. Chen, Z.-Q. Xu, Y.-F. Zhou, M. Ni, H.-Q. Cai, M.-Z. Gong, *J. Org. Chem.* **2005**, *70*, 1084.

[17] For Bis-ProPhenol-catalyzed asymmetric alkynylations of aldehydes in the presence of dimethylzinc, see a) B. M. Trost, A. H. Weiss, A. Jacobi von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8; b) B. M. Trost, V. S. Chan, D. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5186; c) B. M. Trost, B. A. Quintard, *Angew. Chem. Int. Ed.* **2012**, *51*, 6704; *Angew. Chem.* **2012**, *124*, 6808; d) B. M. Trost, M. J. Bartlett, A. H. Weiss, A. Jacobi von Wangelin, V. S. Chan, *Chem. Eur. J.* **2012**, *18*, 16498.

[18] We used a slight excess of the ynamide, but essentially the same results are obtained with 1.0 equivalent of **1** and 1.5 equivalents of **2**. The reaction is sluggish in the absence of **L8** and affords **3** in only 47% yield after 26 h. The replacement of $Zn(OTf)_2$ by Et_2Zn gave racemic **3**.

[19] P. G. Cozzi, J. Rudolph, C. Bolm, P.-O. Norrby, C. Tomasini, *J. Org. Chem.* **2005**, *70*, 5733.

[20] J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.

[21] a) P. Valenta, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2010**, *132*, 14179; b) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599.

[22] S. Hirano, Y. Fukudome, R. Tanaka, F. Sato, H. Urabe, *Tetrahedron* **2006**, *62*, 3896.

[23] D. L. Smith, W. R. F. Goundry, H. W. Lam, *Chem. Commun.* **2012**, *48*, 1505.

[24] S. Xu, J. Liu, D. Hu, X. Bi, *Green Chem.* **2015**, *17*, 184.

[25] The hydroacyloxylations were carried out using batches of **3**, with slightly lower *ee* values obtained during reaction optimization studies.

[26] CCDC 1438550 [(*S*,*Z*)-**28**] und -1438551 [(*S*,*E*)-**30**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: November 24, 2015
Published online: January 25, 2016

