Organic LETTERS

Letter

pubs.acs.org/OrgLett

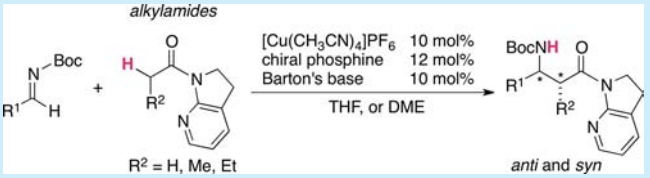
Direct Catalytic Asymmetric Mannich-Type Reaction of Alkylamides

Fernando Arteaga Arteaga, Zijian Liu, Lennart Brewitz, Jianyang Chen, Bo Sun, Naoya Kumagai,* and Masakatsu Shibasaki*

Institute of Microbial Chemistry (Bikaken), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

Supporting Information

ABSTRACT: Direct enolate formation coupled with subsequent enantioselective C−C bond formation remains a topic of intense interest in asymmetric catalysis. This methodology is achieved even with low acidic amides without an electron-withdrawing group at the α-position in the context of a Mannich-type reaction. Acetate-, propionate-, and butyrate-type 7-azaindoline amides served as enolate precursors to afford the desired Mannich adducts with high stereoselectivity, and ligand-enabled diastereo-divergency provided access to both *anti*/*syn* diastereomers. The facile transformation of the amide moiety ensures the synthetic utility of the Mannich adducts.



Enolates, commonly used active carbon nucleophiles in organic synthesis, have contributed to a rich chemistry with productive development in several fields. In the field of asymmetric catalysis, in particular, methodologies for in situ, catalytic, and direct enolization that eliminate the coproduction of unwanted reagent-derived waste required for the preformation of enolates have become highly popular.[1] Unfavorable enolization kinetics are a major obstacle in direct enolization, however, due to their dependence on the intrinsic acidity of the enolate precursors used; ketones and aldehydes having a fairly acidic α-proton can be catalytically deprotonated, while less acidic esters and amides are almost intractable for catalytic enolization.[2] The synthetic utility of enantioenriched products derived from enolates generated from carboxylic acid derivatives led us to focus on the direct enolization of thioamides and their use for enantioselective C−C bond forming reactions.[2g,3] As a more easily accessible alternative, we reported that 7-azaindoline amides bearing electron-withdrawing groups (−SMe, $-N_3$, $-R_F$) at the α-position readily generated the corresponding enolates, which could be coupled with electrophiles in the designed cooperative catalytic system.[4,5] In our continuing studies of direct enolization chemistry, we explored the direct enolization of 7-azaindoline alkylamides for enantioselective Mannich-type reactions.[6] Due to the large number of natural products bearing propionate and acetate units with β-stereogenic centers,[7] this class of enolates allows for enantioselective access to useful chiral building blocks, including β-amino acid derivatives.[8] Kobayashi et al. reported examples of successful direct Mannich-type reactions of simple alkylamides and *N*-Ts imines by a binary catalytic system of silyl triflate/Et_3N.[9] The enantioselective variant of the direct catalytic Mannich-type reactions of simple alkylamides, however, was only partially successful, demonstrated in a sole substrate set with moderate yield and enantioselectivity.

The 7-azaindoline propionamide **1a** was synthesized and submitted to NMR studies to examine its coordination properties with a Cu(I) complex. Previously used 7-azaindoline amides bearing electron-withdrawing groups were activated via bidentate coordination with flipping of the amide moiety from an *E* to *Z* conformation.[4] Upon the addition of *E*-**1a** to a Cu(I)/(*R*)-xyl-BINAP (**L1**) complex in THF, a 1:1 complex was rapidly formed and the activation mode was likely identical (Figures 1a, S4).[10] This observation prompted us to conduct an initial trial of a catalytic asymmetric Mannich-type reaction to *N*-Boc imine **2a** with a soft Lewis acid/Brønsted base cooperative catalyst composed of (*R*)-**L1**/Cu(I) and Barton's base (Table 1). The catalytic enolization and subsequent addition to imine **2a** proceeded at 25 °C with promising enantioselectivity (entry 1). Brief ligand screening revealed that alkylphosphine (*R*,*R*)-Ph-BPE (**L2**) performed well in terms of enantioselectivity, albeit with only marginal dominance of the *anti*-diastereomer (entry 2). Among chiral biarylphosphines

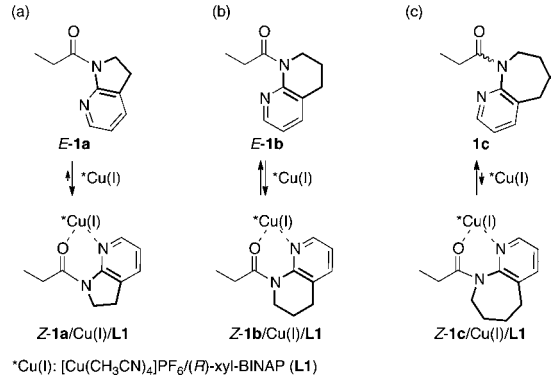
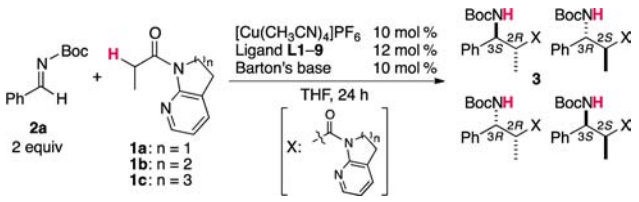


Figure 1. Coordination preference of pyrrolidine, piperidine, and azepane amide **1a**−**c** fused with a pyridine ring in the presence of a Cu(I)/(*R*)-xyl-BINAP (**L1**) complex.

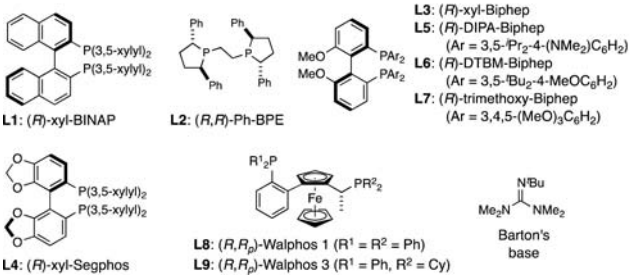
Received: March 26, 2016
Published: May 12, 2016

DOI: 10.1021/acs.orglett.6b00879
Org. Lett. 2016, 18, 2391−2394

Table 1. Initial Trials of Direct Catalytic Asymmetric Mannich-Type Reaction of 7-Azaindoline Propionamide 1a[a]



entry	ligand	amide 1 n =		temp (°C)	pdt	yield[b] (%)	anti/syn[c]	ee (%)[d] anti	ee (%)[d] syn	config.[e] anti	config.[e] syn
1	L1	1	1a	25	3a	99	2.4/1	86	34	2*R*,3*S*	2*R*,3*R*
2	L2	1	1a	25	3a	97	1.7/1	−94	−91	2*S*,3*R*	2*S*,3*S*
3	L3	1	1a	25	3a	97	3.2/1	77	0	2*R*,3*S*	—
4	L4	1	1a	25	3a	92	3.2/1	74	4	2*R*,3*S*	2*R*,3*R*
5	L5	1	1a	25	3a	60	2.0/1	25	0	2*R*,3*S*	—
6	L6	1	1a	25	3a	32	3.1/1	61	−42	2*R*,3*S*	2*S*,3*S*
7	L7	1	1a	25	3a	95	5.3/1	86	64	2*R*,3*S*	2*R*,3*R*
8	L7	1	1a	0	3a	70	8.3/1	95	88	2*R*,3*S*	2*R*,3*R*
9[f]	L7	1	1a	−10	3a	94	10/1	96	92	2*R*,3*S*	2*R*,3*R*
10	L8	1	1a	25	3a	58	1/1	63	62	2*R*,3*S*	2*R*,3*R*
11	L9	1	1a	25	3a	87	1/2.8	90	78	2*R*,3*S*	2*R*,3*R*
12[f]	L7	2	1b	−10	3ba	0	—	—	—	—	—
13[f]	L7	3	1c	−10	3ca	0	—	—	—	—	—

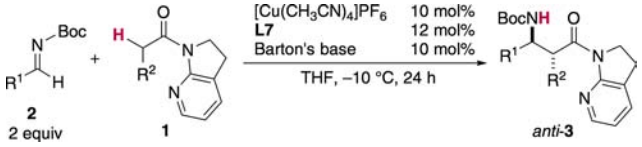


[a]**1**: 0.1 mmol. **2a**: 0.2 mmol. [b]Determined by ^{1}H NMR of the crude mixture with 3,4,5-trichloropyridine as internal standard. [c]Determined by ^{1}H NMR of the crude product. [d]Determined by HPLC analysis. Values are provided based on enantiomeric excess of 2*R*,3*S*-**3** for the *anti* product and 2*R*,3*R*-**3** for the *syn* product. Negative sign denotes that the opposite enantiomer was obtained predominantly. [e]Con°guration of the major enantiomer. [f]0.5 M in **1**.

(**L1**, **L3**, **L4**) with *P*-3,5-xylyl substituents, Biphep-type ligand **L3** and Segphos-type ligand **L4** afforded encouraging *anti*-selectivity (entry 1 vs 3, 4). Based on the Biphep-type ligand architecture, we examined ligands **L5**−**7** with larger *P*-substituents (entries 5−7). Lower conversion and stereoselectivity were observed with highly sterically demanding ligands **L5** and **L6** (entries 5, 6), whereas high catalytic efficiency and high *anti*- and enantioselectivity were observed when using **L7** with a 3,4,5-trimethoxyphenyl groups as the *P*-substituents (entry 7). Unexpectedly, **L6** preferentially afforded the opposite *syn*-enantiomer (2*S*,3*S*), suggesting that the stereochemical course of the present catalytic system was fairly sensitive to the structure of the ligand.[11] In the case of **L7**, major enantiomers of both *anti* and *syn* products have identical configurations at the α-position, and the observed *anti*-selectivity was thought to be due to the prochiral face selection of imine **2a** by the **L7**/Cu(I)/enolate complex. Stereoselectivity was further improved with high yield by performing the reaction at lower temperature and higher concentration (entries 8, 9). The use of ferrocene-embedded ligand **L9** switched the diastereoselectivity from *anti* to *syn*, albeit with moderate diastereoselectivity (entry 11). Intriguingly, **L9** having dialkyl and diarylphosphino groups outperformed **L8**, which has two diphenylphosphino groups (entries 10, 11). In contrast to 7-azaindoline amide **1a**, six- and seven-membered analogs **1b** and **1c** failed in the reaction under the optimized conditions for an *anti*-selective reaction (entries 12, 13). NMR studies of the Cu(I)/**L1** complex revealed that ca. 50% of **1b** formed the Cu(I)/amide complex and **1c** remained uncomplexed (Figure 1b,c). The difference in reactivity was partly attributed to the ability of the amides to coordinate to the Cu(I) complex, which triggers deprotonation by Barton's base to generate the active Cu(I) enolate.

The *anti*-selective protocol using **L7** was applicable to various *N*-Boc imines **2**, as shown in Table 2. Imines **2b**−**d** bearing

Table 2. *anti*-Selective Direct Catalytic Asymmetric Mannich-Type Reaction of 7-Azaindoline Propionamide 1a and Butyramide 1d[a]



entry	imine 2 R1 =		amide 1 R2 =		pdt	yield[b] (%)	anti/syn[c]	ee[d] (%)
1	Ph	2a	Me	1a	3a	94	10/1	96
2	4-MeOC6H4	2b	Me	1a	3b	89	16/1[d]	98
3	3-MeOC6H4	2c	Me	1a	3c	97	12/1	98
4[e]	2-MeOC6H4	2d	Me	1a	3d	82	>20/1	97
5	4-FC6H4	2e	Me	1a	3e	95	14/1[d]	95
6	2-FC6H4	2f	Me	1a	3f	95	10/1	97
7[f]	3-FC6H4	2g	Me	1a	3g	93	12/1	95
8	4-O2NC6H4	2h	Me	1a	3h	66	6.8/1	92
9	3-BrC6H4	2i	Me	1a	3i	95	10/1[d]	95
10	4-TfOC6H4	2j	Me	1a	3j	90	13/1[d]	96
11	3-(pin)BC6H4	2k	Me	1a	3k	45	9.5/1[d]	91
12	2-furyl	2l	Me	1a	3l	78	9.3/1[d]	94
13	2-thienyl	2m	Me	1a	3m	90	12/1	98
14[g]	(E)-2-(4-FC6H4)CH=CH	2n	Me	1a	3n	85	3.1/1[d]	92
15[e,h]	3-FC6H4	2g	Et	1d	3dg	68	8/1[d]	90

[a]**1**: 0.1 mmol. **2**: 0.2 mmol. [b]Isolated yield of mixture of diastereomers. [c]Determined by ^{1}H NMR of the crude product. [d]Determined by HPLC analysis. [e]20 mol % of Barton's base was used. [f]1 g of **1a** was used. [g]Reaction was run at 10 °C. [h]Reaction was run at 0 °C.

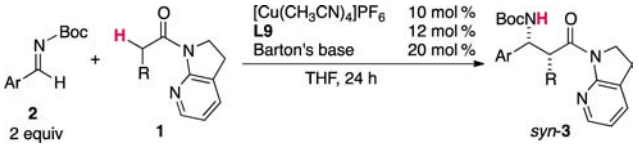
electron-donating Me and MeO substituents provided the corresponding product with high stereoselectivity (entries 2−4). The *o*-, *m*-, and *p*-substitution patterns were examined with a fluorine substituent, and the reactions produced a similarly high yield and stereoselectivity (entries 5−7), and no detrimental effect was observed in a gram-scale reaction (entry 7). Imines **2i**−**k** having *m*-Br, *p*-TfO, or *m*-(pin)B, whose reaction products can be applied to cross-coupling reactions, afforded the desired product with high stereoselectivity, albeit with only moderate yield for **3k** (entries 9−11). Heteroaromatic imines **2l** and **2m** were tolerated (entries 12, 13). α,β-Unsaturated imine **2n** reacted exclusively in a 1,2-

DOI: 10.1021/acs.orglett.6b00879
Org. Lett. 2016, 18, 2391−2394

fashion to afford **3n** with moderate *anti*-selectivity and high enantioselectivity (entry 14). 7-Azaindoline butyramide **1d** also afforded the Mannich adduct **3da** in an *anti*-selective manner (entry 15).

The use of Walphos-type ligand **L9** instead of **L7** preferentially gave the *syn*-diastereomer with high enantioselectivity, although the diastereoselectivity was only moderate and the scope was limited to electron-deficient imines (Table 3). Switching the diastereoselectivity was also valid for butyramide **1d**, affording *syn*-**3dg** with a high yield and stereoselectvity (entry 4).

Table 3. *syn*-Selective Direct Catalytic Asymmetric Mannich-Type Reaction of 7-Azaindoline Propionamide 1a and Butyramide 1d[a]



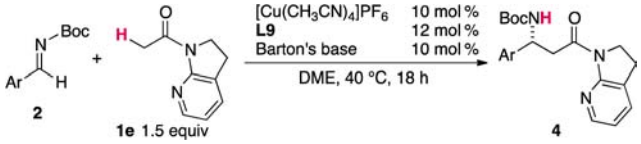
entry	imine **2** Ar =	amide **1** R =	product	temp (°C)	yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	 **2g**	Me **1a**	**3g**	10	85	1/2.9	90
2	 **2j**	Me **1a**	**3j**	10	70	1/2.2	83
3	 **2o**	Me **1a**	**3o**	10	79	1/3.4	83
4	 **2g**	Et **1d**	**3dg**	rt	72	1/3.0	95

[a]**1**: 0.1 mmol. **2**: 0.2 mmol. [b]Isolated yield of mixture of diastereomers. [c]Determined by HPLC analysis.

Acetate-type enolates generally display lower stereoselectivity, presumably because a smaller steric bias at the α-position of the enolate makes stereocontrol less tractable.[12] Given the ubiquitous nature of the chiral β-aminoacetate unit in natural products and biologically active compounds, direct enolization of acetamides coupled with the subsequent Mannich-type reaction is an important objective.[7] We hypothesized that the chelate-driven enolization of 7-azaindoline amide would be operative for 7-azaindoline acetamide **1e** in the present catalytic system. The initial trials, however, revealed that **1e** was less reactive than **1a** in the reaction with imine **2a**, suggesting that the enolate formation from **1e** was more reluctant, or the enolate of **1e** was quickly reprotonated likely due to lower thermodynamic stability. A slight modification of the reaction conditions with **L9** (DME as solvent at 40 °C) proved best for **1e**, and desired Mannich adduct **4a** was produced in 53% yield with 88% ee (Table 4, entry 1). Because **4** was prone to enolization and further reacted with imine **2** to afford double-Mannich adducts as an inseparable mixture of diastereomers, amide **1e** was used in slight excess to suppress this undesired reaction pathway. While the yields presented in Table 4 are moderate, these results are an important step toward the direct catalytic asymmetric Mannich-type reaction of acetamides.

The 7-azaindoline amide moiety of Mannich product **3g** could be transformed into various functional groups (Scheme 1). β-Amino acid **5** was obtained by simple acidic treatment of **3g**. The chelated tetrahedral intermediate generated upon the addition of metal hydride or organometallic reagents was sufficiently stable, enabling the formation of aldehyde **6** and ketone **7** with $LiAlH_4$ and PhMgBr, respectively. Myers' reduction protocol allowed for direct access to primary alcohol **8** in a single step.[13]

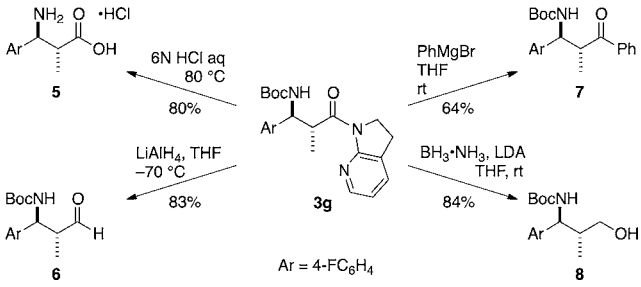
Table 4. Direct Catalytic Asymmetric Mannich-Type Reaction of 7-Azaindoline Acetamide 1e[a]



entry	imine **2** Ar =	product	yield[b] (%)	ee[c] (%)
1	 **2a**	**4a**	53	88
2	 **2b**	**4b**	55	81
3	 **2g**	**4g**	50	92
4	 **2p**	**4p**	42	88

[a]**1e**: 0.3 mmol. **2**: 0.2 mmol. [b]Isolated yield. [c]Determined by HPLC analysis.

Scheme 1. Transformation of the Product



In conclusion, we developed a direct catalytic asymmetric Mannich-type reaction of alkylamides without an electron-withdrawing group at the α-position. Active enolates were catalytically generated from the acetamide, propionamide, and butyramide of 7-azaindoline to afford enantioenriched β-amino actetate, propionate, and butyrate units. Both *anti*- and *syn*-isomers of the propionate and butyrate units were accessible using the ligand of choice. The facile transformation of the 7-azaindoline amide moiety into various functional groups demonstrates the potential synthetic utility of these reaction products as chiral building blocks. Further improvements of stereoselectivity as well as the application to the enantioselective synthesis of biologically active compounds are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00879.

X-ray crystallographic data for compound **1a** (CIF)
X-ray crystallographic data for compound **1c** (CIF)
X-ray crystallographic data for compound **1e** (CIF)
X-ray crystallographic data for compound *syn*-**3a** (CIF)
X-ray crystallographic data for compound *anti*-**3g** (CIF)
X-ray crystallographic data for compound **1e**/Cu(I)/**L1** complex (CIF)

DOI: 10.1021/acs.orglett.6b00879
Org. Lett. 2016, 18, 2391−2394

Experimental procedures and characterization of new compounds (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: nkumagai@bikaken.or.jp.
*E-mail: mshibasa@bikaken.or.jp.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by JST, ACT-C (for M.S.), and KAKENHI (No. 25713002) from JSPS (for N.K.). N.K. thanks The Naito Foundation for financial support. Dr. Ryuichi Sawa, Ms. Yumiko Kubota, and Dr. Kiyoko Iijima at the Institute of Microbial Chemistry are gratefully acknowledged for their assistance with the NMR analysis. We thank Dr. Tomoyuki Kimura at the Institute of Microbial Chemistry for assistance with the X-ray crystallography.

REFERENCES

(1) Direct enolization is well-discussed in the context of direct aldol reactions. For reviews, see: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (e) Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541.

(2) For attempts toward direct catalytic enolization (carbanion formation) using pronucleophiles in the carboxylic acid oxidation state without electron-withdrawing α-substituents, see: Use of alkylnitrile: (a) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (b) Sureshkumar, D.; Ganesh, V.; Kumagai, N.; Shibasaki, M. *Chem. - Eur. J.* **2014**, *20*, 15723. (c) Kawato, Y.; Kumagai, N.; Shibasaki, M. *Chem. Commun.* **2013**, *49*, 11227. (d) Yamashita, Y.; Sato, I.; Suzuki, H.; Kobayashi, S. *Chem. - Asian J.* **2015**, *10*, 2143. Use of β,γ-unsaturated ester: (e) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 10842. Use of 5*H*-oxazol-4-ones: (f) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286. Use of thioamides: (g) Iwata, M.; Yazaki, R.; Suzuki, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 18244. Use of α-hydroxyacylpyrroles: (h) Trost, B. M.; Seganish, W. M.; Chung, C. K.; Amans, D. *Chem. - Eur. J.* **2012**, *18*, 2948. Use of amide: (i) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704. (j) Saito, S.; Tsubogo, T.; Kobayashi, S. *Chem. Commun.* **2007**, 1236. (k) Suzuki, H.; Sato, I.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 4336. Direct catalytic asymmetric aldol reaction of thiazolidinethiones for which the use of stoichiometric amounts of silylating reagent was essential: (l) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.

(3) (a) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5026. (b) Iwata, M.; Yazaki, R.; Suzuki, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 18244. (c) Iwata, M.; Yazaki, R.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554. (d) Bao, Y.; Kumagai, N.; Shibasaki, M. *Chem. Sci.* **2015**, *6*, 6124.

(4) (a) Weidner, K.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 6150. (b) Yin, L.; Brewitz, L.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2014**, *136*, 17958. (c) Weidner, K.; Sun, Z.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 6236. (d) Sun, Z.; Weidner, K.; Kumagai, N.; Shibasaki, M. *Chem. - Eur. J.* **2015**, *21*, 17574. (e) Brewitz, L.; Arteaga, F. A.; Yin, L.; Alagiri, K.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2015**, *137*, 15929.

(5) Reviews on cooperative catalysis. Lewis acid/Brønsted base: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760. Lewis acid/Lewis base: (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (d) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655. Lewis acid/Brønsted acid and Lewis acid/Lewis acid: (e) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (f) Yamamoto, H.; Futatsugi, K. Recent Advance of 'Combined Acid' Strategy for Asymmetric Catalysis. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008; Vol *1*, pp 1−34. For a general review: (g) *Cooperative Catalysis*; Peters, R., Ed.; Wiley-VCH: Weinheim, 2015.

(6) For general reviews on catalytic asymmetric Mannich-type reactions: (a) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Chapter 29.5, p 143. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

(7) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380.

(8) For reviews of β-amino acids and β-peptides, see: (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111. (c) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley: NJ, 2004. (d) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366. (e) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056.

(9) (a) Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708. (b) See also ref 2j.

(10) NMR and X-ray crystallographic analyses of amides and amide/Cu(I) complexes are summarized in the Supporting Information.

(11) No epimerization occurred under the reaction conditions.

(12) Romea, P.; Urpí, F. Stereoselective Acetate Aldol Reactions. In *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2013; pp 1−81.

(13) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

DOI: 10.1021/acs.orglett.6b00879
Org. Lett. 2016, 18, 2391−2394