

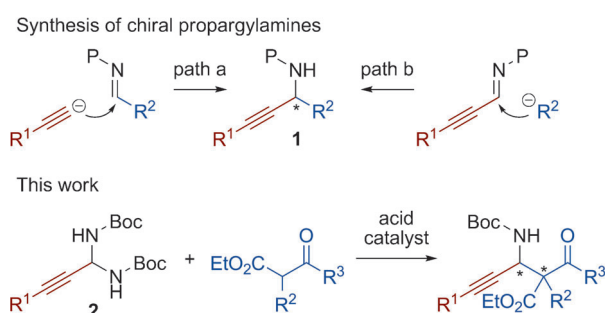
Organocatalytic Asymmetric Synthesis of Propargylamines with Two Adjacent Stereocenters: Mannich-Type Reactions of In Situ Generated C-Alkynyl Imines with β -Keto Esters**

Taichi Kano, Taiga Yurino, and Keiji Maruoka*

Propargylamines are important synthetic intermediates for the preparation of polyfunctional amine derivatives as well as biologically active compounds.^[1] The standard method of preparing chiral propargylamines (**1**; Scheme 1) involves the asymmetric alkylation of imines, thereby creating one new

prepared by the frequently employed alkylation of imines. Herein we report our results on this subject.

Our initial investigation began by evaluating the effect of the acid catalyst and solvent in the tandem in situ generation of C-alkynyl imines/Mannich-type reaction of β -keto esters (Table 1). In the presence of trifluoroacetic acid (TFA) as



Scheme 1. Approaches to chiral propargylamines through the C–C bond formation.

stereogenic center in the bond-forming reaction,^[2] and a number of the catalytic variants of this transformation have also been reported (Scheme 1, path a).^[3] In contrast, there are only a few cases of the catalytic asymmetric addition of carbon nucleophiles (R^2) to C-alkynyl imines, thus giving chiral propargylamines (Scheme 1, path b),^[4] and the reactions with prochiral nucleophiles to create two adjacent stereogenic centers are scarce, despite the high synthetic utility.^[4c] Accordingly, we were interested in the chiral phosphoric acid catalyzed reaction of in situ generated C-alkynyl imines,^[5,6] from the amins **2**, with β -keto esters as nucleophiles.^[7] The reaction between C-alkynyl imines and α -substituted β -keto esters would give polyfunctional chiral propargylamines having an alkynyl group and adjacent quaternary and tertiary stereocenters,^[8,9] which cannot be

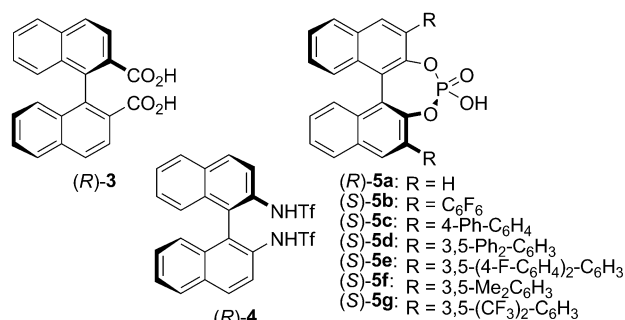


Table 1. Asymmetric Mannich reaction of the amins **2a** with the β -keto ester **6**.^[a]

Entry	Catalyst	Solvent	Yield [%] ^[b]	anti/syn ^[c]	ee [%] ^[d]
1 ^[e]	TFA	CH ₂ Cl ₂	78	1.0:1	–
2	(<i>R</i>)- 3	CH ₂ Cl ₂	15	–	–
3	(<i>R</i>)- 4	CH ₂ Cl ₂	12	–	–
4	(<i>R</i>)- 5a	CH ₂ Cl ₂	94	2.3:1	–5
5	(<i>S</i>)- 5b	CH ₂ Cl ₂	62	1.0:1	13
6	(<i>S</i>)- 5c	CH ₂ Cl ₂	50	2.1:1	59
7	(<i>S</i>)- 5d	CH ₂ Cl ₂	68	2.8:1	76
8	(<i>S</i>)- 5e	CH ₂ Cl ₂	97	9.1:1	94
9	(<i>S</i>)- 5f	CH ₂ Cl ₂	44	2.5:1	91
10	(<i>S</i>)- 5g	CH ₂ Cl ₂	94	2.1:1	81
11	(<i>S</i>)- 5e	CHCl ₃	99	7.7:1	93
12	(<i>S</i>)- 5e	PhCl	69	3.4:1	92
13	(<i>S</i>)- 5e	PhCF ₃	44	4.3:1	90
14	(<i>S</i>)- 5e	toluene	82	6.0:1	91
15	(<i>S</i>)- 5e	CH ₃ CN	0	–	–

[a] The reaction of **2a** (0.10 mmol) with **6** (0.30 mmol) was carried out in the presence of a catalyst (0.010 mmol) and 5 Å molecular sieves (50 mg) in a solvent (1.0 mL) at room temperature for 36 h. [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] The reaction was performed for 24 h. M.S. = molecular sieves, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl.

[*] Dr. T. Kano, Dr. T. Yurino, Prof. K. Maruoka
Department of Chemistry, Graduate School of Science
Kyoto University
Sakyo, Kyoto 606-8502 (Japan)
E-mail: maruoka@kuchem.kyoto-u.ac.jp

[**] This work was supported by a Grant-in-Aid for Scientific Research from MEXT (Japan). T.Y. thanks the Japan Society for the Promotion of Science for Young Scientists for Research Fellowships.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201304963>.

a Brønsted acid catalyst, the reaction between the N-Boc-aminal **2a** and β -keto ester **6** in CH_2Cl_2 proceeded to give the Mannich-type product **7a** in good yield, albeit without diastereoselectivity (entry 1).^[10] In contrast, the chiral Brønsted acids (*R*)-**3** and (*R*)-**4** gave only trace amounts of product (entries 2 and 3). Since the chiral phosphoric acid catalyst (*R*)-**5a** was also effective for this reaction (entry 4), we then investigated various chiral phosphoric acid catalysts (entries 5–10).^[7] Aromatic substituents on the 3,3'-positions of the catalyst significantly affected both diastereo- and enantioselectivity, and the catalyst (*S*)-**5e** having sterically demanding terphenyls was found to be the optimal catalyst in terms of both reactivity and stereoselectivity (entry 8). Among the solvents tested, CH_2Cl_2 gave the best result with respect to yield and selectivity (entry 8 versus entries 11–15).

With the optimized reaction conditions in hand, we turned our attention to the effect of substitution on the aminal substrate (Table 2). A variety of C-alkynyl aminals were investigated for the generality of this reaction. All of these

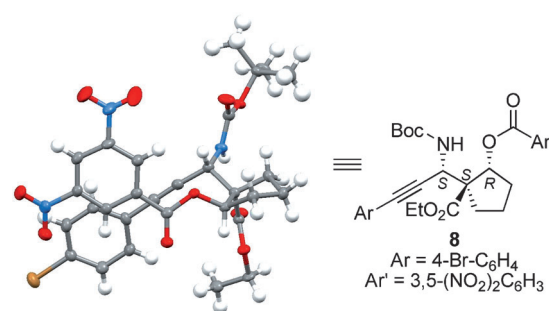
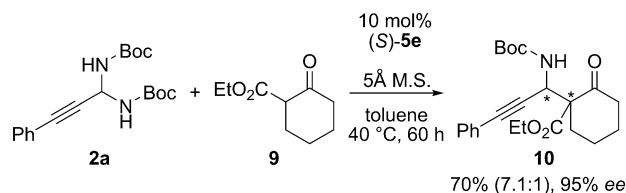
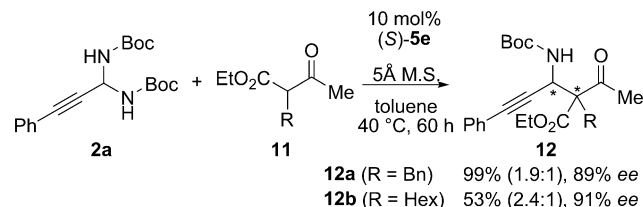


Figure 1. X-ray crystal structure of **8** with ellipsoids set at 50% probability.^[11]

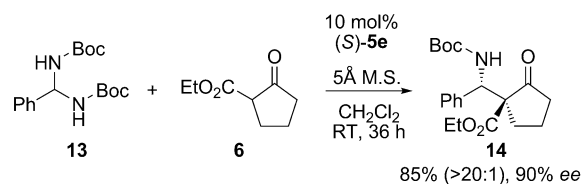


Scheme 2. Asymmetric Mannich reaction of the aminal **2a** with the keto ester **9**. Boc = *tert*-butoxycarbonyl.

at 40 °C, thus giving the Mannich adducts **12a,b** with a quaternary carbon center in good enantioselectivity, albeit with low diastereoselectivity (Scheme 3). This tandem reaction methodology was also applicable to the reaction between a C-aryl imine precursor, **13**, and **6** (Scheme 4).^[9]



Scheme 3. Asymmetric Mannich reaction of the aminal **2a** with the keto ester **11**.



Scheme 4. Asymmetric Mannich reaction of the aminal **13** with the keto ester **6**.

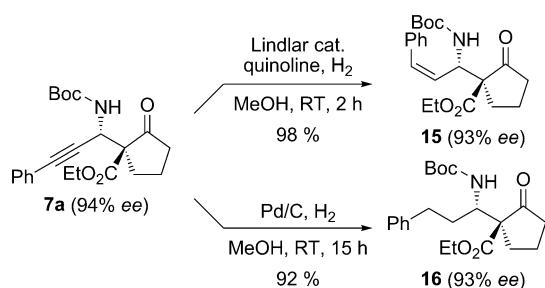
aminals **2** were found to react with **6** in the presence of the catalyst (*S*)-**5e**, thus giving the corresponding Mannich-type products **7** in satisfactory yields with good to excellent stereoselectivities. The relative and absolute configuration of the product was unambiguously confirmed by X-ray crystallographic analysis after conversion into the corresponding 3,5-dinitrobenzoate ester **8** (Figure 1).

The reactions with other β -keto esters were also investigated. We observed that the β -keto ester **9** was significantly less reactive than **6** at room temperature (Scheme 2). When the reaction of **2a** with **9** was performed in higher temperature (40 °C), the desired Mannich adduct **10** was obtained in good yield with high diastereo- and enantioselectivity. The reaction of the acyclic β -keto esters **11a,b** was also carried out

Table 2: Asymmetric Mannich reaction of **2** with **6**.^[a]

Entry	R	Yield [%] ^[b]	<i>anti</i> / <i>syn</i> ^[c]	<i>ee</i> [%] ^[d]
1	Ph	94	9.1:1	94
2	4-BrC ₆ H ₄	86	9.1:1	94
3 ^[e]	4-MeC ₆ H ₄	93	5.9:1	93
4 ^[f]	1-cyclohexenyl	95	6.1:1	94
5	(<i>E</i>)-styryl	93	10:1	90
6 ^[e]	pentyl	98	6.3:1	92
7	PhCH ₂ CH ₂	95	7.7:1	91
8	Cy	89	6.3:1	95
9	cyclopropyl	97	6.7:1	93
10	<i>t</i> Bu	92	10:1	95

[a] The reaction of **2** (0.10 mmol) with **6** (0.30 mmol) was carried out in the presence of (*S*)-**5e** (0.010 mmol) and molecular sieves 5 Å (50 mg) in CH_2Cl_2 (1.0 mL) at room temperature for 36 h. [b] Yield of the isolated product. [c] Determined by ¹H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] CHCl_3 used as the solvent. [f] Toluene used as the solvent.



Scheme 5. Hydrogenation of the Mannich adduct **7a**.

alkenyl-substituted product **15** (*anti/syn* = 9.1:1), which corresponds to the hitherto unattainable Mannich adduct derived from the unprecedented N-Boc-imine having a *Z*-alkenyl substituent. When the reduction of **7a** was carried out using palladium on carbon under a hydrogen atmosphere, the alkynyl substituent was completely reduced to give the product **16** (*anti/syn* = 9.1:1). The Mannich reaction between N-Boc-imine having the alkyl substituent and **6** also gave **16**. The present method using the C-alkynyl imine precursor **2** instead of the C-alkyl imine itself, which is readily isomerized to the corresponding enecarbamate under certain reaction conditions, is advantageous.

In summary, we have developed the stereoselective Mannich-type reactions of in situ generated C-alkynyl imines with β -keto esters catalyzed by the chiral Brønsted acid (*S*)-**5e**. In the present tandem reaction, hitherto less accessible Mannich adducts having various alkynyl substituents could be obtained in good to excellent diastereo- and enantioselectivity. We believe that the propargylamine motif and adjacent quaternary and tertiary stereocenters in the product can serve as a useful synthetic handle for further elaboration into valuable compounds.

Received: June 10, 2013

Revised: July 31, 2013

Published online: September 5, 2013

Keywords: amines · asymmetric catalysis · imines · organocatalysis · synthetic methods

- [1] a) M. A. Huffman, N. Yasuda, A. E. DeCamp, E. J. J. Grabowski, *J. Org. Chem.* **1995**, *60*, 1590; b) M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715.
- [2] For reviews, see: a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879; b) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472; c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095; d) H. J. Zhu, J. X. Jiang, J. Ren, Y. M. Yan, C. U. Pittman, Jr., *Curr. Org. Synth.* **2005**, *2*, 547; e) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263; f) M. Hatano, T. Miyamoto, K. Ishihara, *Curr. Org. Chem.* **2007**, *11*, 127; g) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963.
- [3] For representative examples on the catalytic asymmetric alkylation of imines, see: a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638; b) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; c) J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *Org. Lett.* **2003**, *5*, 3273; d) B. Jiang, Y.-G. Si, *Angew. Chem.* **2004**, *116*, 218; *Angew. Chem. Int. Ed.* **2004**, *43*, 216; e) C. Wei, J. T. Mague, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749; f) N. Gommermann, P. Knochel, *Chem. Commun.* **2004**, 2324; g) T. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 6097; *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; h) J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196; i) T. R. Wu, J. M. Chong, *Org. Lett.* **2006**, *8*, 15; j) A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143; k) A. Bisai, V. K. Singh, *Org. Lett.* **2006**, *8*, 2405; l) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437; m) A. Z. Gonzalez, E. Canales, J. A. Soderquist, *Org. Lett.* **2006**, *8*, 3331; n) F. Colombo, M. Benaglia, S. Orlandi, F. Uselli, G. Celentano, *J. Org. Chem.* **2006**, *71*, 2064; o) N. Gommermann, P. Knochel, *Chem. Eur. J.* **2006**, *12*, 4380; p) A. W. Patterson, J. A. Ellman, *J. Org. Chem.* **2006**, *71*, 7110; q) R. Dodda, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 165; r) L. Zani, T. Eichhorn, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 2587; s) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903; t) A. Labonne, L. Zani, L. Hintermann, C. Bolm, *J. Org. Chem.* **2007**, *72*, 5704; u) S. Turcaud, F. Berhal, J. Royer, *J. Org. Chem.* **2007**, *72*, 7893; v) G. Blay, L. Cardona, E. Climent, J. R. Pedro, *Angew. Chem.* **2008**, *120*, 5675; *Angew. Chem. Int. Ed.* **2008**, *47*, 5593; w) J. A. Bishop, S. Lou, S. E. Schaus, *Angew. Chem.* **2009**, *121*, 4401; *Angew. Chem. Int. Ed.* **2009**, *48*, 4337; x) S. Zhu, W. Yan, B. Mao, X. Jiang, R. Wang, *J. Org. Chem.* **2009**, *74*, 6980; y) M. J. Campbell, F. D. Toste, *Chem. Sci.* **2011**, *2*, 1369.
- [4] a) N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 3734; b) N. S. Josephsohn, E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Org. Lett.* **2005**, *7*, 2711; c) H. Mandai, K. Mandai, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 17961; d) M. Hatano, Y. Hattori, Y. Furuya, K. Ishihara, *Org. Lett.* **2009**, *11*, 2321.
- [5] Representative reactive C-alkynyl imines: a) H. Ishitani, S. Nagayama, S. Kobayashi, *J. Org. Chem.* **1996**, *61*, 1902; b) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, E. M. Carreira, *Angew. Chem.* **1999**, *111*, 3379; *Angew. Chem. Int. Ed.* **1999**, *38*, 3186; c) F. Ferreira, M. Audouin, F. Chemla, *Chem. Eur. J.* **2005**, *11*, 5269; d) C. Roe, T. M. Solá, L. Sasraku-Neequaye, H. Hobbs, I. Churcher, D. MacPherson, R. A. Stockman, *Chem. Commun.* **2011**, 47, 7491; e) J. Louvel, F. Chemla, E. Demont, F. Ferreira, A. Pérez-Luna, A. Voituriez, *Adv. Synth. Catal.* **2011**, *353*, 2137; f) K. Banert, M. Hagedorn, A. Müller, *Eur. J. Org. Chem.* **2001**, 1089; g) P. Wipf, C. R. J. Stephenson, K. Okumura, *J. Am. Chem. Soc.* **2003**, *125*, 14694.
- [6] T. Kano, T. Yurino, D. Asakawa, K. Maruoka, *Angew. Chem.* **2013**, *125*, 5642; *Angew. Chem. Int. Ed.* **2013**, *52*, 5532.
- [7] For pioneering reports and a representative review on chiral phosphoric acid catalysts, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; c) M. Terada, *Synthesis* **2010**, 1929.
- [8] For a related organocatalytic Mannich-type reaction between N-aryl-C-alkynyl imines and aldehydes, see: E. Gómez-Bengo, J. Jiménez, I. Lapuerta, A. Mielgo, M. Oiarbide, I. Otazo, I. Velilla, S. Vera, C. Palomo, *Chem. Sci.* **2012**, *3*, 2949.
- [9] For representative quaternary carbon construction through asymmetric Mannich reactions of imines with β -keto esters, see: a) M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359; b) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umehayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525; c) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896; d) C. Foltz, B. Stecker, G. Marconi, S.

- Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Commun.* **2005**, 5115; e) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191; f) A. Ting, S. Lou, S. E. Schaus, *Org. Lett.* **2006**, 8, 2003; g) Y. Yamaoka, H. Miyabe, Y. Yasui, Y. Takemoto, *Synthesis* **2007**, 2571; h) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, 13, 8338; i) S. Lou, P. Dai, S. E. Schaus, *J. Org. Chem.* **2007**, 72, 9998; j) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, 130, 2170; k) Y. Hamashima, N. Sasamoto, N. Umebayashi, M. Sodeoka, *Chem. Asian J.* **2008**, 3, 1443; l) Y. K. Kang, D. Y. Kim, *J. Org. Chem.* **2009**, 74, 5734; m) M. Hatano, T. Horibe, K. Ishihara, *J. Am. Chem. Soc.* **2010**, 132, 56; n) X. Jiang, D. Fu, G. Zhang, Y. Cao, L. Liu, J. Song, R. Wang, *Chem. Commun.* **2010**, 46, 4294; o) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, 122, 3911; *Angew. Chem. Int. Ed.* **2010**, 49, 3823; p) Z. Liu, M. Shi, *Organometallics* **2010**, 29, 2831; q) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, 123, 10613; *Angew. Chem. Int. Ed.* **2011**, 50, 10429; r) W. Yan, D. Wang, J. Feng, P. Li, D. Zhao, R. Wang, *Org. Lett.* **2012**, 14, 2512.
- [10] Under identical reaction conditions, copper (II) trifluoromethanesulfonate ($\text{Cu}(\text{OTf})_2$) as a Lewis acid catalyst also gave the adduct **7a** in good yield (97%) with low diastereoselectivity (*anti/syn* = 1:1.3).
- [11] CCDC 942074 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.