Asymmetric Catalysis

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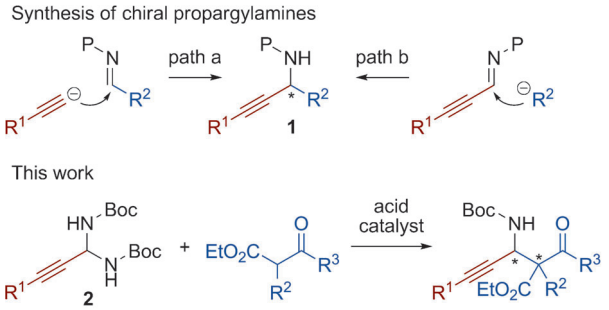
Organocatalytic Asymmetric Synthesis of Propargylamines with Two Adjacent Stereocenters: Mannich-Type Reactions of In Situ Generated C-Alkynyl Imines with β-Keto Esters**

*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 alkynylation of imines, thereby creating one new 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 aminals **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 prepared by the frequently employed alkynylation of imines. Herein we report our results on this subject.



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

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

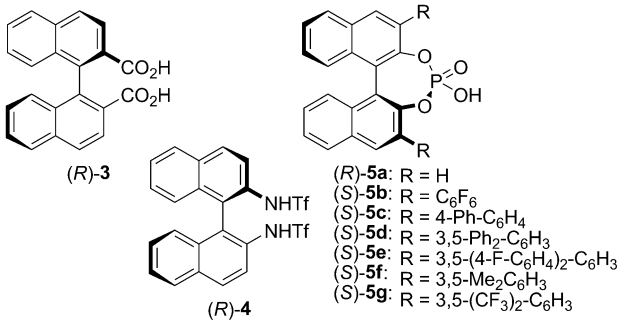
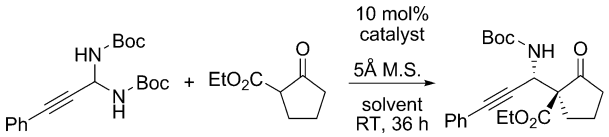


Table 1: Asymmetric Mannich reaction of the aminal **2a** with the β-keto ester **6**.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1[e]	TFA	CH_2Cl_2	78	1.0:1	–
2	(*R*)-**3**	CH_2Cl_2	15	–	–
3	(*R*)-**4**	CH_2Cl_2	12	–	–
4	(*R*)-**5a**	CH_2Cl_2	94	2.3:1	−5
5	(*S*)-**5b**	CH_2Cl_2	62	1.0:1	13
6	(*S*)-**5c**	CH_2Cl_2	50	2.1:1	59
7	(*S*)-**5d**	CH_2Cl_2	68	2.8:1	76
8	(*S*)-**5e**	CH_2Cl_2	97	9.1:1	94
9	(*S*)-**5f**	CH_2Cl_2	44	2.5:1	91
10	(*S*)-**5g**	CH_2Cl_2	94	2.1:1	81
11	(*S*)-**5e**	$CHCl_3$	99	7.7:1	93
12	(*S*)-**5e**	PhCl	69	3.4:1	92
13	(*S*)-**5e**	$PhCF_3$	44	4.3:1	90
14	(*S*)-**5e**	toluene	82	6.0:1	91
15	(*S*)-**5e**	CH_3CN	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 ^{1}H 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.

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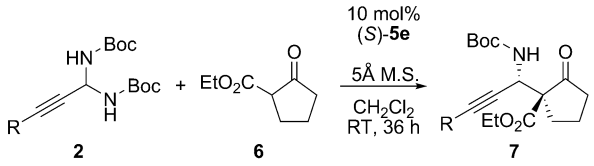
(Table 1). In the presence of trifluoroacetic acid (TFA) as a Brønsted acid catalyst, the reaction between the N-Boc-aminal **2a** and β-keto ester **6** in CH_2Cl_2 proceeded to give the Mannich-type product **7a** in good yield, albeit without diastereoselectivity (entry 1).[10] In contrast, the chiral 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

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



Entry	R	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	Ph	94	9.1:1	94
2	4-BrC_6H_4	86	9.1:1	94
3[e]	4-MeC_6H_4	93	5.9:1	93
4[f]	1-cyclohexenyl	95	6.1:1	94
5	(*E*)-styryl	93	10:1	90
6[e]	pentyl	98	6.3:1	92
7	$PhCH_2CH_2$	95	7.7:1	91
8	Cy	89	6.3:1	95
9	cyclopropyl	97	6.7:1	93
10	*t*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.

investigated for the generality of this reaction. All of these 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

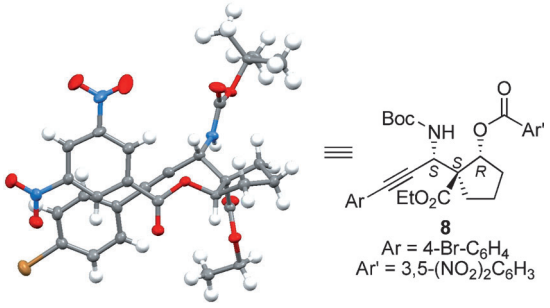
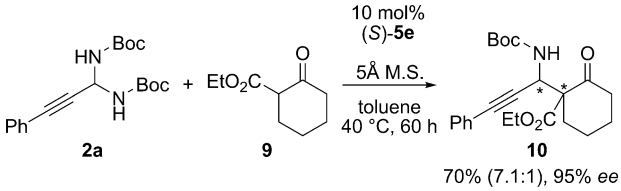
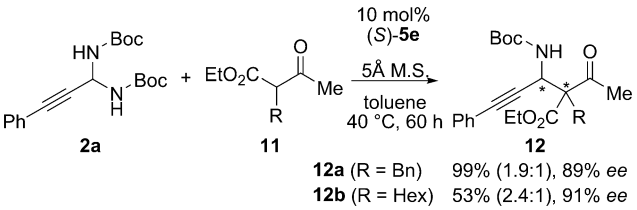


Figure 1. X-ray crystal structure of **8** with ellipsoids set at 50% probability.[11]

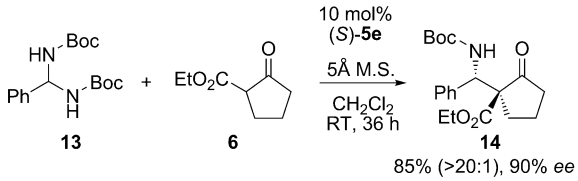


Scheme 2. Asymmetric Mannich reaction of the aminal **2a** with the keto ester **9**. Boc = *tert*-butoxycarbonyl.

reaction of the acyclic β-keto esters **11a**,**b** was also carried out 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]

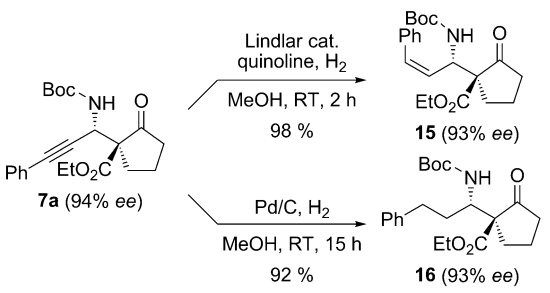


Scheme 3. Asymmetric Mannich reaction of the aminal **2a** with the keto ester **11**.



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

The alkynyl substituent on the obtained Mannich adduct was readily converted into the corresponding *Z*-alkenyl and alkyl groups by hydrogenation (Scheme 5). Treatment of the Mannich adduct **7a** (*anti*/*syn* = 9.1:1) with the Lindlar catalyst under a hydrogen atmosphere for 2 hours led cleanly to the *Z*-



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.

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[10] Under identical reaction conditions, copper (II) trifluoromethanesulfonate ($Cu(OTf)_2$) 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.

Communications

Asymmetric Catalysis

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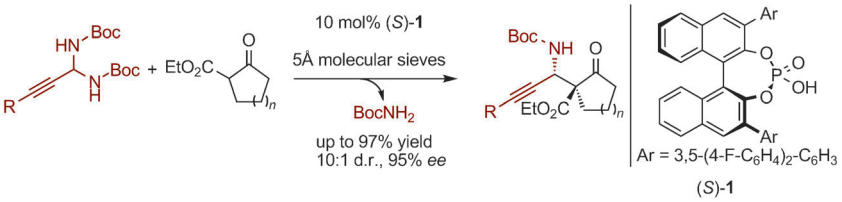
Organocatalytic Asymmetric Synthesis of Propargylamines with Two Adjacent Stereocenters: Mannich-Type Reactions of In Situ Generated C-Alkynyl Imines with β-Keto Esters



Side by side: The title reaction is catalyzed by the chiral Brønsted acid (*S*)-**1**, and affords hitherto less accessible chiral propargylamines, having two adjacent stereocenters, in good to excellent diastereo- and enantioselectivities. Boc = *tert*-butoxycarbonyl.