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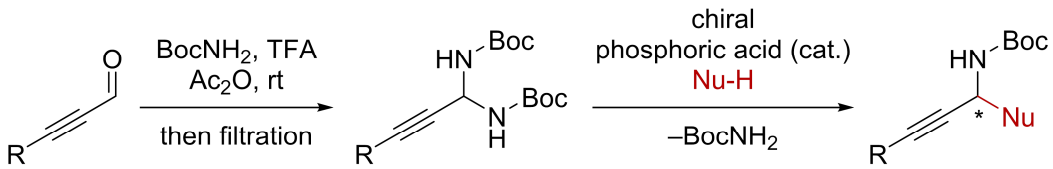

up to 92% yield

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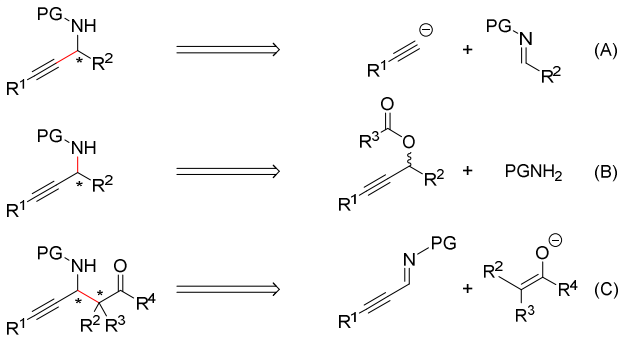
ABSTRACT

We developed a facile and practical synthesis of *N*-Boc-aminals, which can be used as precursors for less accessible *N*-Boc-imines. Aminals were obtained via simple dehydration condensation reactions of *t*-butyl carbamate ($BocNH_2$) and various aldehydes in acetic anhydride, followed by filtration and washing with hexane. The obtained *N*-Boc-alkynylaminals could be successfully applied in enantioselective Mannich-type reactions, catalyzed by chiral phosphoric acids, to afford optically active propargylamine derivatives.

1. Introduction

As optically active propargylamines are attractive building blocks for the construction of highly functionalized amines,[1,2] efficient synthetic pathways to such propargylamines have been pursued for several decades. So far, the most prevalent synthetic route is the enantioselective addition of nucleophilic terminal alkynes to imines or *in situ*-generated iminium intermediates (Scheme 1A). In this context, chiral transition metal catalysts, based on Cu(I), Ag(I), and Zn(II), which can form the corresponding metal acetylides, have also been intensively investigated.[3–6] Enantioselective propargylic aminations represent a powerful alternative approach, since stable and easily attainable racemic propargyl esters can be used as substrates (Scheme 1B).[7] In these methods, asymmetry is introduced only at the propargylic position. In contrast, the enantioselective nucleophilic addition to alkynylimines allows the simultaneous generation of two adjacent stereocenters with several prochiral nucleophiles (Scheme 1C).[8,9] These imines contain both amino and alkynyl groups, and structurally diverse propargylamines can be easily prepared by using various nucleophiles. A few examples have been reported to use isolable *N*-aryl-protected alkynylimines in such reactions.[8,9] These imines are especially appealing substrates due to their high reactivity and ease of deprotection. However, despite their synthetic utility, simple routes to *N*-Boc-alkynylimines still remain unprecedented. [1]



Scheme 1. Retrosynthetic approach to optically active propargylamines: (A) enantioselective addition of terminal alkynes to imines, (B) propargylic amination of racemic propargyl esters, and (C) enantioselective addition of a nucleophile to alkynylimines.

N-Boc-alkynylimines are most effective when they are generated *in situ* and consumed rapidly. Efficient and easily accessible precursors for such imines are accordingly attractive research targets. Unfortunately, amidosulfones,[10] which are widely used imine precursors, are not suitable for this purpose, as those containing alkynyl groups are nontrivial to synthesize. Hence, we focused on *N*-Boc-protected aminals as potential precursors for such imines;[11] *N*-Boc-aminals exhibit an N-C-N substructure, which can be converted into highly reactive

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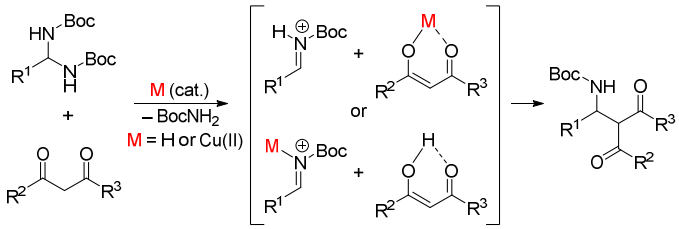
iminium cations under acidic conditions by releasing one of the two carbamoyl groups on the central carbon atom. Recently, we successfully demonstrated that *N*-Boc-imines can be generated *in situ* from *N*-Boc-aminals, and that a subsequent acid-catalyzed Mannich-type reaction generates *N*-Boc-amines (Scheme 2).[12,13] Herein, we summarize the chemical properties of these *N*-Boc-aminals and describe their synthetic utility, especially with respect to the enantioselective synthesis of *N*-Boc-propargylamines. For the reactions involved, we also propose reaction mechanisms.



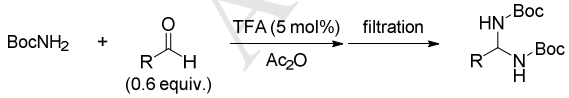
Scheme 2. Acid-catalyzed Mannich-type reaction of *N*-Boc-iminium intermediates, generated *in situ* from *N*-Boc-aminals.

2. Results and discussion

2.1. Preparation of N-Boc-aminals as imine precursors

Initially, we investigated a general and highly effective synthetic protocol for the preparation of *N*-Boc-aminals from readily available aldehydes. We expected to obtain the desired *N*-Boc-aminals from a simple dehydration condensation using *t*-butyl carbamate ($BocNH_2$) and aldehydes, and we speculated that acetic anhydride (Ac_2O) should be an effective solvent for this reaction. When phenylpropargyl aldehyde was stirred with $BocNH_2$ (1.67 equiv) in the presence of a catalytic amount of trifluoroacetic acid (TFA) in Ac_2O for 30 minutes at room temperature, the desired dehydration proceeded smoothly. Fortunately, the resulting aminal precipitated from the reaction mixture, and filtration, followed by washing with hexane afforded the pure aminal as an air-, moisture- and light-stable white powder. A wide variety of aldehydes containing alkynyl, alkenyl, alkyl, and aryl groups were also applicable to this synthetic method, furnishing the corresponding aminals in high yield (Table 1). In contrast, ketones such as benzophenone were inert under otherwise identical conditions (Scheme 3). All *N*-Boc-aminals were isolated as white powders, which were stable under ambient conditions, while the corresponding *N*-Boc-imines are sensitive towards atmospheric moisture.

Table 1. Preparation of *N*-Boc-aminals from a dehydration condensation of $BocNH_2$ and aldehydes.[a]



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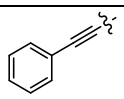
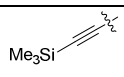
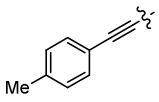
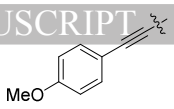
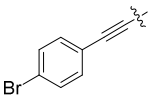
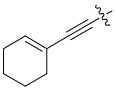
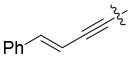
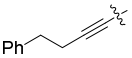
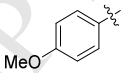
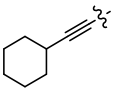
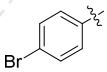
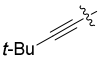
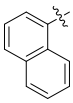
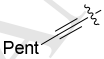
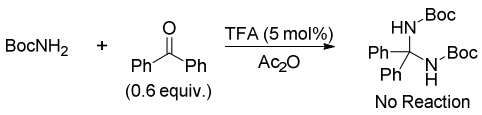
1		92	12		90
2		80	13		54
3		89	14		71
4		81	15		91
5		69	16		85
6		42	17		77
7		50	18		64
8		84	19		66
9		70	20		62
10		61	21		81
11		73	22		57

[a] Reaction conditions: aldehyde (3.3 mmol), $BocNH_2$ (5.5 mmol), Ac_2O (750 µL), and TFA (0.028 mmol, 5 mol% with respect to $BocNH_2$). The precipitated aminal was isolated by filtration and washed with hexane; [b] Isolated yield.

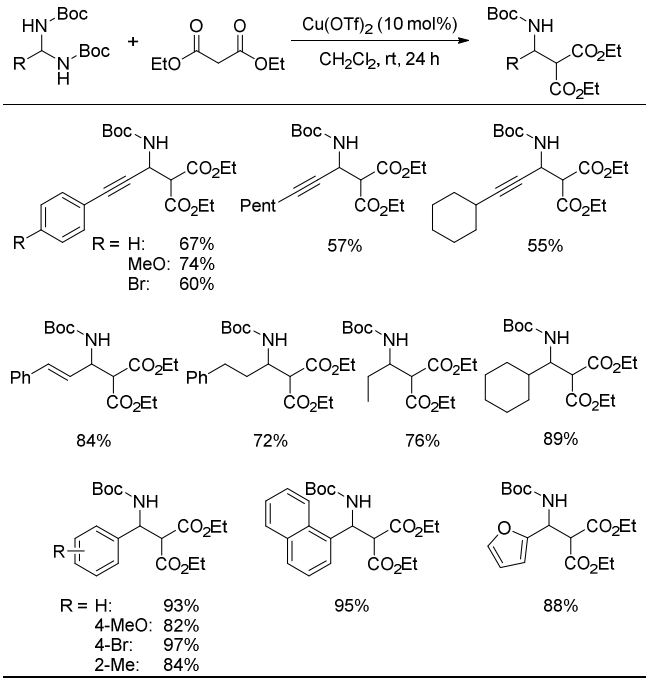


Scheme 3. Attempted formation of the corresponding *N*-Boc-aminal from benzophenone.

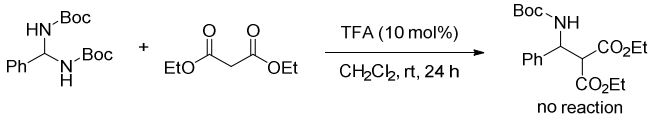
2.2. Reactivity of N-Boc-aminals under acidic conditions

With a wide variety of the *N*-Boc-aminals in hand, we then evaluated their potential as the corresponding imine precursors under acidic conditions. For the Lewis acid-catalyzed Mannich-type reaction of these aminals, diethyl malonate was used as nucleophile of choice. In the presence of 10 mol% $Cu(OTf)_2$, the desired nucleophilic addition to the *in situ*-generated *N*-Boc-imines from the corresponding aminals proceeded smoothly to afford the β-amino acid derivatives (Table 2). Most notably, this is the first practical example for the synthesis of *N*-Boc-propargylamines via a Mannich-type reaction of *in situ*-generated *N*-Boc-alkynylimines. Conversely, Brønsted acid catalysts, such as e.g. TFA, were found to be inefficient for the present transformation (Scheme 4).

Table 2. Lewis acid-catalyzed Mannich-type reactions of various *N*-Boc-aminals with diethyl malonate.[a,b]



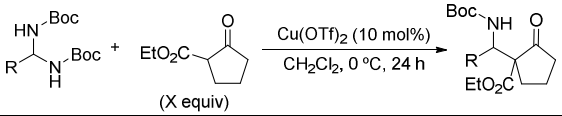
[a] Detailed reaction conditions are described in the experimental section; [b] isolated yield.



Scheme 4. Attempted TFA-catalyzed Mannich-type reaction of the *N*-Boc-aminal with diethyl malonate.

Other *C*-nucleophiles than malonate, e.g. a β-ketoester and a silyl enol ether, also afforded the target adducts. Using these *C*-nucleophiles, we investigated Lewis acid-catalyzed reactions with *N*-Boc-aminals, bearing phenyl, phenylethynyl, (*E*)-phenylethenyl, and phenylethyl groups (Table 3 and 4). It should be noted that, depending on their substituents, the aminals exhibited different reactivity. While Mannich-type reactions with the β-ketoester converted *N*-Boc-aminals carrying phenyl and phenylethynyl groups effectively into the corresponding adducts, those carrying (*E*)-phenylethenyl and phenylethyl substituents required an excess of nucleophile (Table 3). In Mukaiyama-Mannich-type reactions, *N*-Boc-(*E*)-phenylethenylaminal proved to be exceptionally reactive: this reaction reached complete conversion within 3 h, while other aminals required at least 24 h for completion under otherwise identical reaction conditions (Table 4). For both reactions, *N*-Boc-phenylethylaminal proved to be a relatively inactive reagent, probably on account of its intrinsic stability.

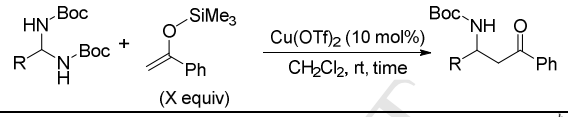
Table 3. Lewis acid-catalyzed Mannich-type reactions of *N*-Boc-aminals with ethyl-2-oxocyclopentanecarboxylate.[a]



R	X equiv.	Yield (%)[b]	dr[c]
Ph–	1.1	99	6.0/1
PhC≡C–	1.1	97	1.3/1
(*E*)-PhCH=CH–	3.3	82	1.5/1
$PhCH_2CH_2$–	3.3	75	1.4/1

[a] Detailed reaction conditions are described in the experimental section; [b] isolated yield; [c] determined by ^{1}H-NMR spectroscopy.

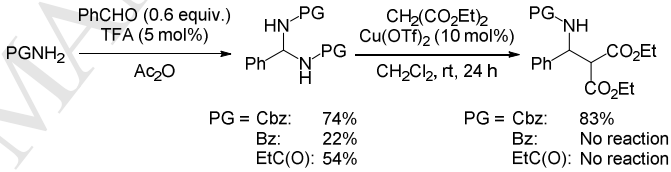
Table 4. Lewis acid-catalyzed Mannich-type reactions of *N*-Boc-aminals with a silyl enol ether.[a]



R	X equiv.	Time (h)	Yield (%)[b]
Ph–	1.1	24	77
PhC≡C–[c]	3.3	48	73
(*E*)-PhCH=CH–	1.1	3	90
$PhCH_2CH_2$–	3.3	120	30

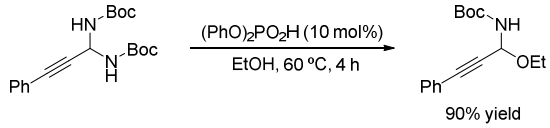
[a] Detailed reaction conditions are described in the experimental section; [b] isolated yield; [c] $[Cu(OTf)]_2(tol)$ (tol = toluene) was used instead of $Cu(OTf)_2$.

The benzyloxycarbonyl (Cbz) group could also be used as a protecting group for the present method. The corresponding aminal was isolated in high yield using the same synthetic procedure as for the *N*-Boc-aminals, and it could also be applied to the Mannich-type reaction. In contrast, aminals bearing acyl groups, such as benzoyl and propionyl substituents were inert under acidic conditions (Scheme 5).



Scheme 5. Preparation of aminals with various *N*-protecting groups and their application in Mannich-type reactions.

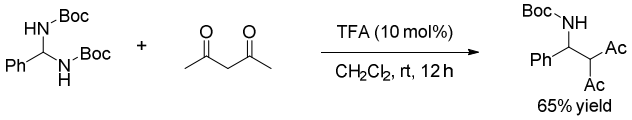
Finally, we examined reactions between heteroatom nucleophiles and *N*-Boc-aminals in the presence of an acid catalyst (Scheme 6). When *N*-Boc-phenylethynylaminal was treated with ethanol, diphenyl phosphate proved to be the most effective Brønsted acid catalyst to form the corresponding hemiaminal ether. Most notably, a recent report by Shao and coworkers described that this hemiaminal ether could be used as a precursor for the formation of the corresponding *N*-Boc-alkynylimine under basic conditions.[14] Moreover the report disseminated that this synthetic method required 36 h to prepare the hemiaminal ether from the substrate aldehyde. Even though our method requires two steps from the corresponding aldehyde, the same precursor could be prepared significantly faster via the alcoholysis of the aminal.



Scheme 6. Preparation of a hemiaminal ether from an *N*-Boc-aminal.

2.3. Enantioselective synthesis of propargylamine derivatives by Mannich-type reactions of N-Boc-alkynylaminals

Subsequently, we evaluated the utility of a Brønsted acid catalyst for the addition of *C*-nucleophiles to the *in situ*-generated *N*-Boc-imines from *N*-Boc-aminals. For the Mannich-type reaction between *N*-Boc-phenylaminal and acetylacetone, we found that TFA is a highly effective Brønsted acid catalyst, while diethyl malonate was inert under identical reaction conditions (Scheme 7 vs. Scheme 4). This result prompted us to investigate enantioselective Mannich-type reactions using chiral Brønsted acid catalysts such as C_2-symmetric chiral phosphoric acids (Fig. 1).[15]



Scheme 7. TFA-catalyzed Mannich-type reaction of *N*-Boc-phenylaminal with acetylacetone.

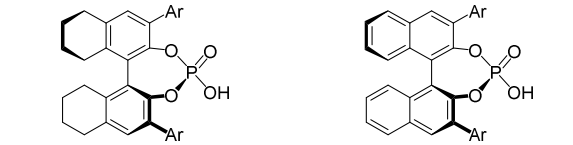
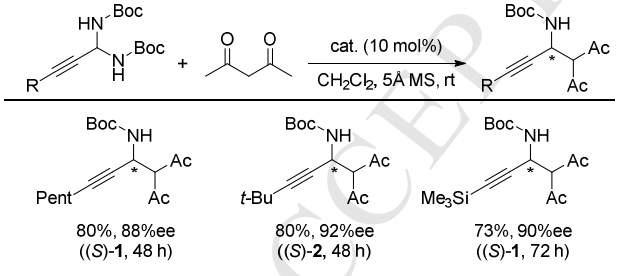


Fig. 1. C_2-symmetric chiral phosphoric acid catalysts for enantioselective Mannich-type reactions of *N*-Boc-aminals.

To our delight, the chiral phosphoric acids (*S*)-**1** and (*S*)-**2** (Figure 1), which are based on a 3,3'-disubstituted octahydrobinaphthyl scaffold, turned out to be efficient catalysts for the enantioselective addition of acetylacetone to the *N*-Boc-alkynylimines generated *in situ* from the corresponding aminals. In competition to the formation of the desired product, an acid-catalyzed hydrolysis of the imines occurred. Upon addition of molecular sieves, this decomposition pathway could be suppressed effectively and the Mannich adducts were obtained in good yield (Table 5).

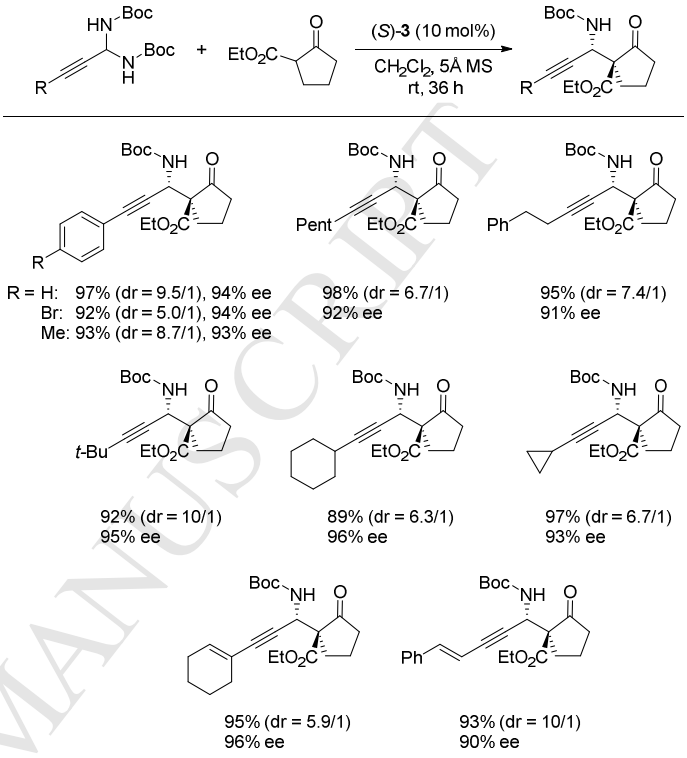
Table 5. Enantioselective Mannich-type reactions of *N*-Boc-alkynylaminals with acetylacetone.[a,b]



[a] Isolated yield; [b] ee determined by chiral HPLC analysis.

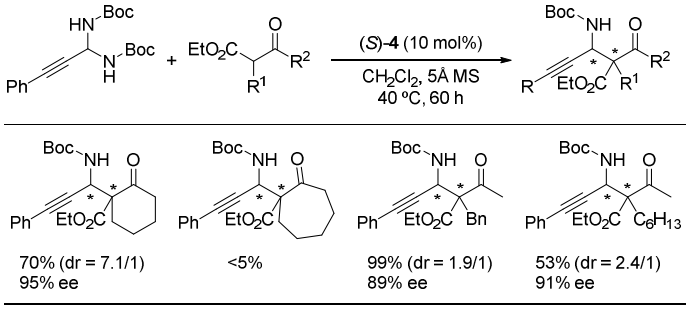
We then investigated the enantioselective addition of α-substituted β-ketoesters to generate adjacent quaternary-tertiary stereocenters (Table 6). In the case of the enantioselective addition of ethyl 2-oxocyclopentanecarboxylate, (*S*)-**3** exhibited the best catalytic performance towards the desired adducts in high diastereo- and enantioselectivity. Applying optimal reaction conditions smoothly converted a wide variety of *N*-Boc-alkynylaminals into the corresponding *N*-Boc-propargylamines. Subsequently, we also examined reactions with other β-ketoesters (Table 7), and observed that cyclic β-ketoesters, bearing larger cycloalkanone moieties than cyclopentanone, exhibited lower reactivity. As the Mannich-type reaction with ethyl 2-oxocyclohexanecarboxylate did not proceed at room temperature, we conducted the reaction at 40 ºC. However, even at elevated temperatures, 2-oxocycloheptanecarboxylate was inert. The Mannich-type reactions of *N*-Boc-phenylalkynylaminal with α-substituted acyclic β-ketoesters were also carried out at 40 ºC, which afforded the corresponding optically active products with moderate diastereoselectivity.

Table 6. Enantioselective Mannich-type reaction between *N*-Boc-aminals and ethyl-2-oxocyclopentanecarboxylate.[a,b,c]



[a] Isolated yield; [b] ee determined by chiral HPLC analysis; [c] dr determined by ^{1}H-NMR spectroscopy.

Table 7. Enantioselective Mannich-type reactions of *N*-Boc-phenylalkynylaminal with other cyclic or α-substituted acyclic β-ketoesters.[a,b,c]

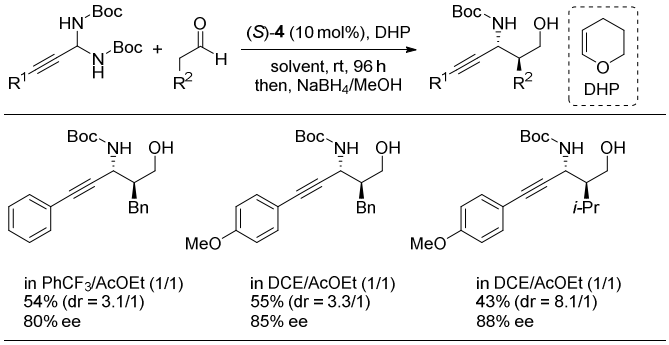


[a] Isolated yield; [b] ee determined by chiral HPLC analysis; [c] dr determined by ^{1}H-NMR spectroscopy.

These Brønsted acid-catalyzed Mannich-type reactions proceeded effectively, when the enol concentration of the carbonyl compound was sufficiently high. Using optimal reaction conditions, acetylacetone and β-ketoesters afforded the corresponding products, while diethylmalonate was inert.[16,17] To our surprise, we found that aldehydes could also be used for this Mannich-type reaction, even though their enol form is far less favorable than that of β-ketoesters.[18] The reactions were promoted by catalyst (*S*)-**4**, and the optically active aminoalcohols were obtained via a Mannich-type reaction, followed by a reduction (Table 8). In this reaction, 3,4-dihydro-

2*H*-pyran (DHP) acted as an efficient $BocNH_2$ scavenger, and the yield slightly decreased in the absence of DHP.

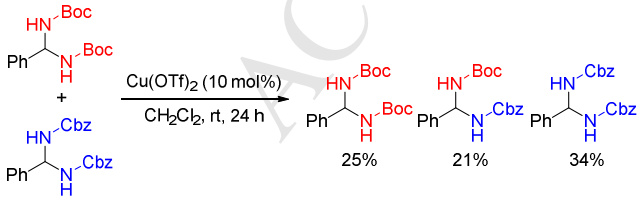
Table 8. Enantioselective Mannich-type reactions of *N*-Boc-alkynylaminals with aldehydes.[a,b,c]



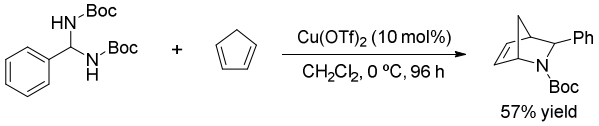
[a] Isolated yield; [b] ee determined by chiral HPLC analysis; [c] dr determined by ^{1}H-NMR spectroscopy.

2.4. Mechanistic aspects of the Mannich-type reactions of aminals

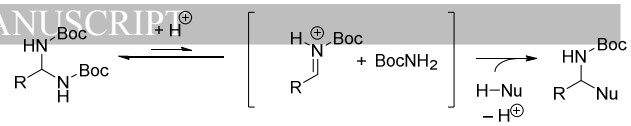
We speculated that the present Mannich-type reactions should proceed via a two–step mechanism. Initially, *N*-Boc-imines (or *N*-Boc-iminium cations) should be generated from the corresponding aminals by acid-mediated catalysis, before the C—C bond would be formed by nucleophilic addition to the imines. To obtain evidence for the generation of an imine, we attempted to detect this intermediate by ^{1}H-NMR spectroscopy. Unfortunately, we were unable to directly observe any imine or corresponding iminium species under the conditions applied. However, when a mixture of exclusively *N*-Boc- or *N*-Cbz-substituted aminals was stirred in the presence of $Cu(OTf)_2$, the corresponding aminal containing both an *N*-Boc and an *N*-Cbz substituent was obtained in 21% yield (Scheme 8). Moreover, under acidic conditions, an aza-Diels-Alder reaction of the *in situ*-generated iminium intermediate with cyclopentadiene proceeded to afford the expected product in moderate yield (Scheme 9). These results suggested the following reaction mechanism (Scheme 10): under acidic conditions, the iminium intermediate should be generated reversibly from the corresponding aminal under simultaneous release of the carbamoyl group. As the concentration of the iminium intermediate should be very low in this equilibrium, it seems plausible that it could not be observed directly in the ^{1}H-NMR spectrum. However, in the presence of the nucleophile, a small amount of the *in situ*-generated iminium intermediate should be smoothly consumed to afford the desired product.



Scheme 8. Carbamoyl group scrambling between *N*-Boc- and *N*-Cbz-aminals under acidic conditions.

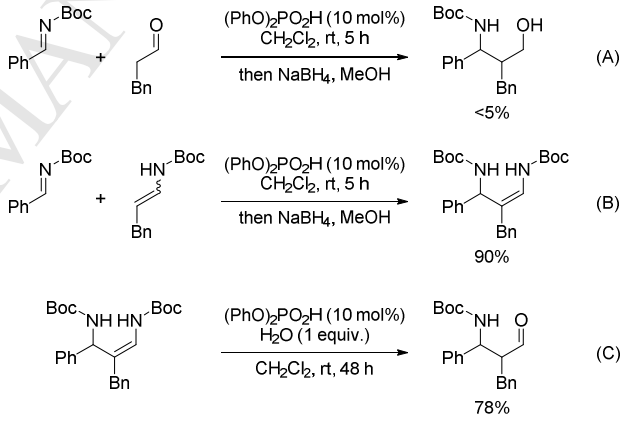


Scheme 9. Aza-Diels-Alder reaction between *N*-Boc-phenylaminal and cyclopentadiene.



Scheme 10. A plausible reaction mechanism for the acid-catalyzed Mannich-type reactions of *N*-Boc-aminals.

When a Brønsted acid was used as a catalyst for the Mannich-type reactions, the concentration of the enol tautomer of the nucleophile in the equilibrium played a crucial role. However, the corresponding Mannich adducts were also obtained from *N*-Boc-aminals and aldehydes, even though the equilibrium enol concentration for aldehydes is lower than that of β-ketoesters. To gain further insight into this phenomenon, we carried out a Brønsted acid-catalyzed Mannich reaction between the isolable *N*-Boc-phenylimine and 3-phenylpropanal (Scheme 11A). When an achiral phosphoric acid catalyst was used, only trace amounts of the product were formed, suggesting that the enol concentration was insufficient under acidic conditions. Conversely, when the corresponding *N*-Boc-enecarbamate was used, the desired adduct was obtained in high yield (Scheme 11B). In the presence of water, this enecarbamate product was smoothly hydrolyzed to furnish the corresponding aldehyde (Scheme 11C). These results prompted us to consider that the enecarbamate generated *in situ* from aldehyde and $BocNH_2$ was the actual nucleophile in this Brønsted acid-catalyzed Mannich-type reaction.



Scheme 11. (A) Mannich reaction between *N*-Boc-phenylimine and 3-phenylpropanal, (B) Mannich reaction with the corresponding enecarbamate, and (C) hydrolysis of the resulting adduct obtained through the reaction described in Scheme 11B.

Considering all these results in their entirety, we would like to propose the following plausible mechanism (Fig. 2): under acidic conditions, only a very small amount of iminium cation should be gradually generated from the corresponding aminal through the aminal/iminium equilibrium. In the presence of several nucleophiles, this cationic intermediate may then be rapidly consumed to form the corresponding adducts. Especially in the case of Brønsted acid-catalyzed Mannich-type reactions with carbonyl compounds (except aldehydes), it is the amount of enol present at the equilibrium that promotes the title reaction. In contrast, the reaction did not proceed when the concentration of the carbonyl-derived enol was too low. When aldehydes were employed, the desired Mannich-type reaction proceeded effectively. In these cases and under acidic conditions, the corresponding enecarbamates were generated *in situ* from $BocNH_2$, which had been released from the *N*-Boc-aminal, and these species acted as potent nucleophiles instead of aldehydes.

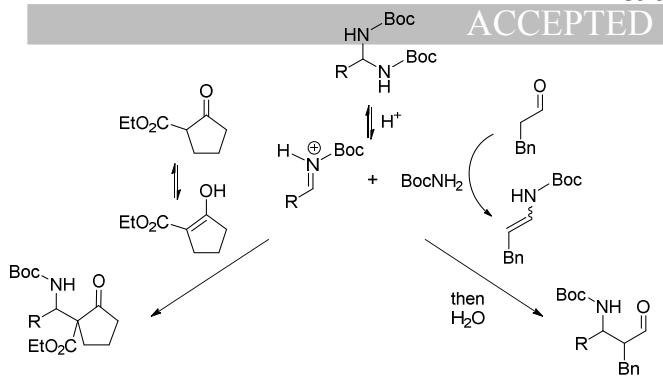


Fig. 2. Plausible reaction mechanisms for acid-catalyzed Mannich-type reactions of *N*-Boc-aminals.

3. Conclusion

In conclusion, we demonstrated that the *in situ* generation of imines from readily accessible and stable *N*-Boc-aminals, followed by nucleophilic addition, afforded the corresponding *N*-Boc-amines. Most interestingly, these aminals are also available as efficient precursors for unprecedented *N*-Boc-alkynylimines; from these aminals, we successfully obtained a wide variety of the corresponding optically active *N*-Boc-propargylamines, including examples with two adjacent stereocenters. In addition, we proposed a plausible reaction mechanism for these reactions. Under acidic conditions, only a small amount of the reactive iminium intermediate was generated *in situ* from the aminals, and subsequently consumed by several nucleophiles. These *N*-Boc-aminals should represent new efficient precursors for the synthesis of highly functionalized amines, and may thus be important for natural product synthesis and/or drug discovery.

4. Experimental Section

4.1. General

Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer or on a Thermo SCIENTIFIC NICOLET iS5. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer or on a JEOL JNM-ECA500 (500 MHz) spectrometer. Data are reported as follows: chemical shifts in ppm relative to tetramethylsilane or the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, dd = double-doublet, td = triple-doublet, qd = quadruple-doublet, ddd = double-double-doublet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C{^{1}H} NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) spectrometer or on a JEOL JNM-ECA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent (internal standard). ^{19}F{^{1}H} NMR spectra were measured on a JEOL JNM-ECA500 (500 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm relative to $CFCl_3$ (0 ppm; external standard). ^{31}P{^{1}H} NMR spectra were measured on JEOL JNM-ECA500 (200 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm relative to H_3PO_4 (0 ppm; external standard). High performance liquid chromatography (HPLC) was performed on a Shimadzu 10A instrument using a Daicel CHIRALPAK AD-H, AD-3, AS-H, IB, IC, IE, IF, 4.6 mm × 25 cm column and Daicel CHIRALCEL OZ-H, 4.6 mm × 25 cm column. High-resolution mass spectra (HRMS) were performed on a Brucker microTOF or Thermo SCIENTIFIC Exactive Plus. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Precoated TLC plates (silica gel 60 GF254, 0.25 mm; Merck) were used throughout this study for thin layer chromatography (TLC). Products were purified by flash column chromatography on neutral silica gel 60N (Kanto Chemical Co. Inc., 40-50μm). Acetic anhydride, dichloromethane, chloroform, 1,2-dichloroethane (DCE), ethyl acetate (AcOEt), methanol, and toluene were purchased from Wako Pure Chemical Industries Co. Inc. Molecular sieves (4A and 5A) and α,α,α-trifluorotoluene ($PhCF_3$) were purchased from Sigma-Aldrich Co. LLC.

4.2. General procedure for preparation of N-Boc-aminals

A substrate aldehyde (3.3 mmol) and *tert*-butyl carbamate (640 mg, 5.5 mmol) were added into acetic anhydride (750 μL). To this suspension was added trifluoroacetic acid (21 μl, 0.28 mmol), and the mixture was stirred for 15 min. The product was solidified in acetic anhydride solvent as white solid. The solid was filtered in vacuum, and obtained powder was added into hexane (10 mL) and stirred for 1 h. The *N*-Boc-protected aminal was obtained as a white powder by filtration.

4.2.1. Di-tert-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H, Ph), 7.31-7.28 (m, 3H, Ph), 5.97 (t, *J* = 8.0 Hz, 1H, $CH(NHBoc)_2$), 5.57 (br s, 2H, NHBoc), 1.47 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.1, 131.8, 128.7, 128.3, 122.0, 85.3, 82.8, 80.6, 51.4, 28.3; HRMS (ESI): calcd. for $C_{19}H_{26}N_2NaO_4^+$ $(M+Na)^+$: 369.1785, found: 369.1777; IR (neat): 3310, 2980, 1697, 1539, 1501, 1250, 1171, 1013 cm^{-1}.

4.2.2. Di-tert-butyl (3-(4-methoxyphenyl)prop-2-yne-1,1-diyl)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.8 Hz, 2H, Ar-H), 5.96 (t, *J* = 8.0 Hz, 1H, C*H*$(NHBoc)_2$), 5.50 (br s, 2H, NHBoc), 3.80 (s, 3H, MeO), 1.47 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.9, 154.1, 133.3, 114.1, 113.9, 83.9, 82.9, 80.5, 55.3, 51.5, 28.3; HRMS (ESI): calcd. for $C_{20}H_{28}N_2NaO_5^+$ $(M+Na)^+$: 399.1890, found: 399.1896; IR (neat): 3314, 2978, 1697, 1539, 1506, 1499, 1278, 1169, 1032, 1013 cm^{-1}.

4.2.3. Di-tert-butyl (3-(4-bromophenyl)prop-2-yne-1,1-diyl)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.28 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.01 (t, *J* = 7.6 Hz, 1H, C*H*$(NHBoc)_2$), 5.56 (br s, 2H, NHBoc), 1.44 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.1, 133.2, 131.6, 123.0, 121.0, 86.5, 81.7, 80.7, 51.4, 28.3; HRMS (ESI): calcd. for $C_{19}H_{25}BrN_2NaO_4^+$ $(M+Na)^+$: 447.0890, found: 447.0903; IR (neat): 3318, 2978, 1701, 1537, 1493, 1368, 1250, 1171, 1138, 1013 cm^{-1}.

4.2.4. Di-tert-butyl (2-octyne-1,1-diyl)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.72 (t, *J* = 7.6 Hz, 1H, C*H*$(NHBoc)_2$), 5.41 (br s, 2H, NHBoc), 2.17 (td, *J* = 7.2 Hz, 1.6 Hz, 2H, $CH_2C{\equiv}C$), 1.51-1.43 (m, 2H, CH_2), 1.45 (s, 18H, $C(CH_3)_3$), 1.36-1.30 (m, 4H, CH_2), 0.89 (t, *J* = 6.8 Hz, 3H, CH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.1, 83.8, 80.2, 77.3, 51.1, 30.9, 28.3, 28.0, 22.1, 18.5, 13.9; HRMS (ESI): calcd. for $C_{18}H_{32}N_2NaO_4^+$ $(M+Na)^+$: 363.2254, found: 363.2252; IR (neat): 3319, 2980, 1697, 1501, 1263, 1161, 1013 cm^{-1}.

4.2.5. Di-tert-butyl (3-cyclohexylprop-2-yne-1,1-diyl)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.73 (t, *J* = 7.6 Hz, 1H, C*H*$(NHBoc)_2$), 5.30 (br s, 2H, NHBoc), 2.37 (app t, *J* = 9.2 Hz, 1H, Cy), 1.76-1.61 (m, 5H, Cy), 1.45 (s, 18H, $C(CH_3)_3$), 1.45-

1.40 (m, 2H, Cy), 1.31-1.26 (m, 3H, Cy); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.0, 87.6, 80.2, 76.6, 51.1, 32.2, 28.7, 28.3, 25.8, 24.6; HRMS (ESI): calcd. for $C_{19}H_{32}N_2NaO_4^+$ $(M+Na)^+$: 375.2254, found: 375.2255; IR (neat): 3321, 2936, 1701, 1537, 1499, 1337, 11246, 1163, 1130, 1009 cm^{-1}.

4.2.6. Di-tert-butyl ((E)-3-phenylprop-2-ene-1,1-diyl)dicarbamate

To a suspension of *tert*-butyl carbamate (320 mg, 2.8 mmol) in (*E*)-3-phenylpropenal (350 µL) was added trifluoroacetic acid (11 µL, 0.14 mmol) at room temperature. The mixture was stirred for 6 h, and the product was solidified in the solvent aldehyde. The solid was filtered in vacuo, and obtained powder was added into hexane (10 mL) and stirred for 6 h. The *N*-Boc-protected aminal was obtained as a white powder by filtration (260 mg, 0.76 mmol, 54%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.22 (m, 5H, Ph), 6.60 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.32 (br d, *J* = 16.0 Hz, 1H, PhCH=C*H*), 5.60 (br s, 1H, CH=CHC*H*), 5.51 (br s, 2H, NHBoc), 1.46 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.7, 136.1, 131.3, 128.5, 127.9, 127.0, 126.7, 80.1, 60.4, 28.3; HRMS (ESI): calcd. for $C_{19}H_{28}N_2NaO_4^+$ $(M+Na)^+$: 371.1941, found: 371.1952; IR (neat): 3319, 2980, 1694, 1541, 1495, 1246, 1165, 1009 cm^{-1}.

4.2.7. Di-tert-butyl (3-phenylpropane-1,1-diyl)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H, Ph), 7.19-7.16 (m, 3H, Ph), 5.42 (br s, 2H, NHBoc), 4.81 (br s, 1H, C*H*$(NHBoc)_2$), 2.66 (t, *J* = 8.0 Hz, 2H, PhC*H*$_2$CH$_2$), 2.13 (br s, 2H, PhCH$_2$C*H*$_2$), 1.44 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 155.0, 141.0, 128.4, 128.3, 126.0, 79.7, 59.7, 35.8, 32.1, 28.3; HRMS (ESI): calcd. for $C_{19}H_{30}N_2NaO_4^+$ $(M+Na)^+$: 373.2098, found: 373.2084; IR (neat): 3352, 2978, 1692, 1535, 1493, 1366, 1242, 1169, 1049 cm^{-1}.

4.2.8. Di-tert-butyl propane-1,1-diyldicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.25 (br s, 2H, NHBoc), 4.75 (br s, 1H, C*H*$(NHBoc)_2$), 1.79 (br s, 2H, C*H*$_2$CH$_3$), 1.44 (s, 18H, $C(CH_3)_3$), 0.93 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.0, 79.7, 61.4, 28.3, 27.6, 10.1; HRMS (ESI): calcd. for $C_{13}H_{26}N_2NaO_4^+$ $(M+Na)^+$: 297.1785, found: 297.1784; IR (neat): 3327, 2972, 1695, 1547, 1512, 1364, 1250, 1177, 1148 cm^{-1}.

4.2.9. Di-tert-butyl (cyclohexylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.18 (br s, 2H, NHBoc), 4.58 (br s, 1H, C*H*$(NHBoc)_2$), 1.80-1.57 (m, 6H, Cy), 1.44 (s, 18H, $C(CH_3)_3$), 1.27-1.08 (m, 3H, Cy), 1.00-0.94 (m, 2H, Cy); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.1, 79.5, 64.3, 40.8, 29.2, 28.3, 26.2, 25.7; HRMS (ESI): calcd. for $C_{17}H_{32}N_2NaO_4^+$ $(M+Na)^+$: 351.2254, found: 351.2249; IR (neat): 3316, 2977, 2928, 1694, 1504, 1364, 1246, 1173, 1007 cm^{-1}.

4.2.10. Di-tert-butyl (phenylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5H, Ph), 6.11 (t, *J* = 8.0 Hz, 1H, C*H*$(NHBoc)_2$), 5.58 (br s, 2H, NHBoc), 1.44 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.7, 139.7, 128.6, 128.0, 125.8, 80.2, 61.7, 28.3; HRMS (ESI): calcd. for $C_{17}H_{26}N_2NaO_4^+$ $(M+Na)^+$: 345.1785, found: 345.1786; IR (neat): 3333, 2978, 2932, 1701, 1539, 1497, 1366, 1244, 1173, 1011 cm^{-1}.

4.2.11. Di-tert-butyl (4-methoxyphenylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.87 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.05 (t, *J* = 8.0 Hz, 1H, C*H*$(NHBoc)_2$), 5.44 (br s, 2H, NHBoc), 3.79 (s, 3H, CH_3O), 1.44 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.3, 154.7, 132.0, 127.0, 113.9, 80.1, 61.4, 55.3, 28.3; HRMS (ESI): calcd. for $C_{18}H_{28}N_2NaO_5^+$ $(M+Na)^+$: 375.1890, found: 375.1886; IR (neat): 3339, 2978, 2932, 1694, 1510, 1366, 1244, 1163, 1042, 1009 cm^{-1}.

4.2.12. Di-tert-butyl (4-bromophenylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.28 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.01 (t, *J* = 7.6 Hz, 1H, C*H*$(NHBoc)_2$), 5.56 (br s, NHBoc), 1.44 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.8, 138.8, 131.6, 127.6, 121.9, 80.4, 61.3, 28.3; HRMS (ESI): calcd. for $C_{17}H_{25}BrN_2NaO_4^+$ $(M+Na)^+$: 423.0890, found: 423.0884; IR (neat): 3319, 2978, 1694, 1537, 1497, 1248, 1173, 1142, 1011 cm^{-1}.

4.2.13. Di-tert-butyl (2-tolylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (m, 1H, Ar-H), 7.21-7.15 (m, 3H, Ar-H), 6.33 (t, *J* = 7.6 Hz, 1H, C*H*$(NHBoc)_2$), 5.16 (br s, 2H, NHBoc), 2.37 (s, 3H, Me), 1.43 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.3, 138.0, 135.6, 130.8, 128.1, 126.1, 124.6, 80.1, 59.4, 28.3, 18.9; HRMS (ESI): calcd. for $C_{18}H_{28}N_2NaO_4^+$ $(M+Na)^+$: 359.1941, found: 359.1929; IR (neat): 3329, 2970, 1692, 1503, 1368, 1250, 1163, 1009 cm^{-1}.

4.2.14. Di-tert-butyl (1-naphthylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.87 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.82 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.61 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.57-7.49 (m, 2H, Ar-H), 7.45 (app. t, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, C*H*$(NHBoc)_2$), 5.26 (br s, 2H, NHBoc), 1.45 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.4, 135.2, 134.0, 130.2, 129.1, 128.7, 126.6, 125.9, 125.0, 123.1, 122.9, 80.2, 59.5, 28.3; HRMS (ESI): calcd. for $C_{21}H_{28}N_2NaO_4^+$ $(M+Na)^+$: 395.1941, found: 395.1938; IR (neat): 3310, 2978, 1690, 1541, 1504, 1366, 1246, 1163, 1049 cm^{-1}.

4.2.15. Di-tert-butyl (2-furylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (br s, 1H, furyl-H), 6.34 (dd, *J* = 3.2 Hz, 1.6 H, 1H, furyl-H), 6.30 (d, *J* = 3.2 Hz, 1H, furyl-H), 6.13 (t, *J* = 8.0 Hz, C*H*$(NHBoc)_2$), 5.50 (br s, 2H, NHBoc), 1.45 (s, 18H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.4, 151.7, 142.2, 110.5, 106.6, 80.4, 56.7, 28.3; HRMS (ESI): calcd. for $C_{15}H_{24}N_2NaO_5^+$ $(M+Na)^+$: 335.1577, found: 335.1572; IR (neat): 3321, 2978, 1701, 1551, 1514, 1250, 1180, 1012 cm^{-1}.

4.2.16. Di-tert-butyl (4,4-dimethylpent-2-yne-1,1-diyl)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.76 (t, *J* = 8.0 Hz, 1H, C*H*$(NHBoc)_2$), 5.55 (br s, 2H, NHBoc), 1.46 (s, 18H, $OC(CH_3)_3$), 1.20 (s, 9H, $CC(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.0, 91.4, 80.0, 75.2, 51.0, 30.6, 28.2, 27.1; HRMS (ESI): calcd for $C_{17}H_{30}N_2NaO_4^+$ $(M+Na)^+$ 349.2098 found 349.2098; IR (neat): 3312, 2974, 1695, 1535, 1499, 1246, 1171, 1015 cm^{-1}.

4.2.17. Dibenzyl (phenylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 15H, Ar-H), 6.28 (t, *J* = 8.0 Hz, 1H, C*H*$(NHCbz)_2$), 5.91 (br s, 2H, NHCbz), 5.11 (d, *J* = 12.4 Hz, 2H, OC*H*HPh), 5.07 (d, *J* = 12.4 Hz, 2H, OCH*H*Ph); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.4, 138.7, 136.0, 128.7, 128.5, 128.3, 128.2, 128.2, 125.8, 67.1, 62.0; HRMS (ESI): calcd. for $C_{23}H_{22}N_2NaO_4^+$ $(M+Na)^+$: 413.1472, found: 413.1489; IR (neat): 3292, 1701, 1553, 1514, 1344, 1312, 1236, 1067, 1022 cm^{-1}.

4.3. Procedures for Mannich reaction of N-Boc-aminals with diethyl malonate

To a solution of an *N*-Boc-aminal (0.10 mmol) and diethyl malonate (24 mg, 0.15 mmol) in dichloromethane (0.50 mL) was added $Cu(OTf)_2$ (3.6 mg, 0.010 mmol) at room temperature. After stirring for 24 h, the mixture was directly purified by silica gel chromatography and the target material was obtained as a white solid.

4.3.1. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-3-phenylprop-2-yne-1-yl)malonate

To a solution of di-*tert*-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and diethyl malonate (80 mg, 0.50 mmol) in DCE (1.0 mL) was added $\{Cu(OTf)\}_2 \cdot$tol (5.2 mg, 0.010 mmol) at room temperature. After stirring for 12 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as a white solid (26 mg, 0.067 mmol, 67%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H, Ph), 7.33-7.25 (m, 3H, Ph), 5.74 (br s, 1H, NHBoc), 5.35 (br s, 1H, C*H*NHBoc), 4.32-4.17 (m, 4H, O$CH_2$$CH_3$), 3.85 (d, *J* = 4.8 Hz, 1H, C*H*$(CO_2Et)_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.30 (t, *J* = 6.8 Hz, 3H, OCH_2CH_3), 1.29 (t, *J* = 6.8 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.3, 166.3, 154.6, 131.7, 128.5, 128.2, 122.2, 85.7, 83.7, 80.1, 61.9, 61.7, 56.2, 42.5, 28.2, 14.0, 13.9; HRMS (ESI): calcd. for $C_{21}H_{27}NNaO_6^+$ $(M+Na)^+$: 412.1731, found: 412.1729; IR (neat): 3374, 2980, 1722, 1489, 1369, 1248, 1159, 1028 cm^{-1}.

4.3.2. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-3-(4-methoxyphenyl)prop-2-yne-1-yl) malonate

To a solution of di-*tert*-butyl (3-(4-methoxyphenyl)prop-2-yne-1,1-diyl)dicarbamate (38 mg, 0.10 mmol) and diethyl malonate (80 mg, 0.50 mmol) in DCE (1.0 mL) was added $\{Cu(OTf)\}_2 \cdot$tol (5.2 mg, 0.010 mmol) at room temperature. After stirring for 12 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as colorless oil (31 mg, 0.074 mmol, 74%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.24 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.72 (br s, 1H, NHBoc), 5.33 (br s, 1H, C*H*NHBoc), 4.30-4.20 (m, 4H, O$CH_2$$CH_3$), 3.83 (d, *J* = 4.8 Hz, 1H, C*H*$(CO_2Et)_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.30 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.29 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.3, 166.3, 154.6, 133.2, 131.5, 122.8, 121.2, 86.9, 82.7, 80.3, 62.0, 61.8, 56.1, 42.5, 28.3, 14.1, 14.0; HRMS (ESI): calcd. for $C_{21}H_{26}BrNNaO_6^+$ $(M+Na)^+$: 490.0836, found: 490.0851; IR (neat): 2980, 1730, 1487, 1393, 1369, 1342, 1248, 1161, 1013 cm^{-1}.

4.3.3. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-3-(4-bromophenyl)prop-2-yne-1-yl) malonate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.24 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.72 (br s , 1H, NHBoc), 5.33 (br s, 1H, C*H*NHBoc), 4.30-4.20 (m, 4H, O$CH_2$$CH_3$), 3.83 (d, *J* = 4.8 Hz, 1H, C*H*$(CO_2Et)_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.30 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.29 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.3, 166.3, 154.6, 133.2, 131.5, 122.8, 121.2, 86.9, 82.7, 80.3, 62.0, 61.8, 56.1, 42.5, 28.3, 14.1, 14.0; HRMS (ESI): calcd. for $C_{21}H_{26}BrNNaO_6^+$ $(M+Na)^+$: 490.0836, found: 490.0851; IR (neat): 2980, 1730, 1487, 1393, 1369, 1342, 1248, 1161, 1013.

4.3.4. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-2-octyne-1-yl)malonate

To a solution of di-*tert*-butyl (2-octyne-1,1-diyl)dicarbamate (34 mg, 0.10 mmol) and diethyl malonate (120 mg, 0.75 mmol) in dichloromethane (1.0 mL) was added $\{Cu(OTf)\}_2 \cdot$tol (5.2 mg, 0.010 mmol) at room temperature. After stirring for 12 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as a white solid (19 mg, 0.057 mmol, 57%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.61 (br s, 1H, NHBoc), 5.08 (br s, 1H, C*H*NHBoc), 4.29-4.14 (m, 4H, O$CH_2$$CH_3$), 3.72 (d, *J* = 4.8 Hz, 1H, C*H*$(CO_2Et)_2$), 2.13 (td *J* = 7.2 Hz, 2.0 Hz, 2H, $CH_2C{\equiv}C$), 1.60 (br s, 2H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.30 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.27 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.35-1.25 (m, 4H, CH_2), 0.88 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 166.5, 154.6, 84.5, 79.9, 61.8, 61.6, 56.4, 42.2, 30.9, 29.7, 28.3, 28.1, 22.1, 18.5, 14.05, 13.97, 13.9; HRMS (ESI): calcd. for $C_{20}H_{33}NNaO_6^+$ $(M+Na)^+$: 406.2200, found: 406.2184; IR (neat): 3437, 2961, 2932, 1734, 1722, 1491, 1369, 1248, 1161, 1042 cm^{-1}.

4.3.5. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-3-cyclohexylprop-2-yne-1-yl)malonate

To a solution of di-*tert*-butyl (3-cyclohexylprop-2-yne-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and diethyl malonate (120 mg, 0.75 mmol) in DCE (1.0 mL) was added $\{Cu(OTf)\}_2 \cdot$tol (2.6 mg, 0.0050 mmol) at room temperature. After stirring for 12 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/50 to 1/9) to afford the product as colorless oil (22 mg, 0.055 mmol, 55%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.59 (br s, 1H, NHBoc), 5.09 (br s, 1H, C*H*NHBoc), 4.27-4.16 (m, 4H, O$CH_2$$CH_3$), 3.73 (d, *J* = 4.8 Hz, 1H, C*H*$(CO_2Et)_2$), 2.35 (br s, 1H, Cy), 1.72-1.62 (m, 5H, Cy), 1.45 (s, 9H, $C(CH_3)_3$), 1.45-1.25 (m, 4H, Cy), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.27 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 166.5, 154.6, 88.5, 79.8, 76.8, 61.8, 61.6, 56.6, 42.2, 32.3, 28.7, 28.3, 25.8, 24.5, 14.1, 14.0; HRMS (ESI): calcd. for $C_{21}H_{33}NNaO_6^+$ $(M+Na)^+$: 418.2200, found: 418.2203; IR (neat): 2931, 1732, 1719, 1489, 1368, 1248, 1233, 1159, 1043, 1024 cm^{-1}.

4.3.6. Diethyl 2-((E)-1-(N-tert-butoxycarbonylamino)-3-phenylprop-2-ene-1-yl)malonate

The titled product was obtained as a white solid (33 mg, 0.084 mmol, 84%), following the general procedure with di-*tert*-butyl ((*E*)-3-phenylprop-2-ene-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) at –20 °C for 72 h. Spectra data are in accordance with the literature.[19]

4.3.7. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-3-phenylpropyl)malonate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H, Ph), 7.19-7.13 (m, 3H, Ph), 5.45 (d, *J* = 10.0 Hz, 1H, NHBoc), 4.34-4.29 (m, 1H, C*H*NHBoc), 4.25-4.13 (m, 4H, O$CH_2$$CH_3$), 3.60 (d, *J* = 4.4 Hz, 1H, C*H*$(CO_2Et)_2$), 2.78-2.60 (m, 2H, Ph$CH_2$$CH_2$), 1.97-1.76 (m, 2H, Ph$CH_2CH_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.264 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.262 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.3, 167.8, 155.4, 141.4, 128.41, 128.36, 126.0, 79.3, 61.7, 61.5, 55.3, 50.1, 35.7, 32.7, 28.3, 14.00, 13.97; HRMS (ESI): calcd. for $C_{21}H_{32}NO_6^+$ $(M+H)^+$: 394.2224, found: 394.2218; IR (neat): 3433, 2978, 1717, 1497, 1368, 1240, 1159, 1024 cm^{-1}.

4.3.8. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-1-(2-tolyl)-methyl)malonate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26-7.25 (m, 1H, Ar-H), 7.17-7.14 (m, 3H, Ar-H), 6.25 (br s, 1H, NHBoc), 5.66 (br s, 1H, C*H*NHBoc), 4.27-4.04 (m, 4H, O$CH_2$$CH_3$), 3.73 (d, *J* = 4.4 Hz, 1H, C*H*$(CO_2Et)_2$), 2.46 (s, 3H, Ar-CH_3), 1.39 (s, 9H, $C(CH_3)_3$), 1.24 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.15 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.3, 167.4, 155.2, 138.2, 135.3, 131.0, 127.9, 126.4, 126.0, 79.9, 62.2, 61.9, 55.8, 50.7, 28.6, 19.4, 14.3, 14.2; HRMS (ESI): calcd. for

$C_{20}H_{29}NNaO_6^+$ (M+Na)$^+$: 402.1887, found: 402.1878; IR (neat): 3395, 2978, 1719, 1497, 1368, 1288, 1256, 1165, 1032 cm^{-1}.

4.3.9. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-1-(1-naphthyl)-methyl)malonate

^{1}H-NMR (400 MHz, $CDCl_3$,): δ 8.15 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.85 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.75 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.57 (ddd, *J* = 8.8 Ha, 7.2 Ha, 1.6 Hz, 1H, Ar-H), 7.50-7.46 (m, 2H, Ar-H), 7.42 (app t, *J* = 8.0 Hz, 1H, Ar-H), 6.45 (br s, 1H, NHBoc), 6.30 (br dd, *J* = 8.8 Hz, 4.0 Hz, 1H, C*H*NHBoc), 4.31-4.20 (m, 2H, OC*H*$_2$CH$_3$), 4.13-3.98 (m, 3H, OC*H*$_2$CH$_3$ and C*H*(CO$_2$Et)$_2$), 1.39 (s, 9H, C(CH$_3$)$_3$), 1.28 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.07 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.3, 167.3, 155.0, 135.1, 133.8, 130.1, 129.1, 128.4, 126.8, 125.7, 125.1, 123.7, 122.2, 79.7, 62.1, 61.5, 55.6, 50.1, 28.3, 14.0, 13.8; HRMS (ESI): calcd. for $C_{23}H_{29}NNaO_6^+$ (M+Na)$^+$: 438.1887, found: 438.1875; IR (neat): 3428, 2978, 2935, 1717, 1495, 1368, 1244, 1159, 1032, 1016 cm^{-1}.

4.3.10. Diethyl 2-(1-(N-tert-butoxycarbonylamino)-1-(2-furyl)-methyl)malonate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 1.6 Hz, 0.8 Hz 1H, Ar-H), 6.29 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H, Ar-H), 6.21 (ddd, *J* = 3.2, 1.2, 0.8 Hz, 1H, Ar-H), 5.93 (br s, 1H, NHBoc), 5.54 (br s, 1H, C*H*NHBoc), 4.28-4.12 (m, 4H, OC*H*$_2$CH$_3$), 4.00 (d, *J* = 4.8 Hz, 1H, C*H*(CO$_2$Et)$_2$), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.27 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.23 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.9, 166.8, 155.0, 152.5, 141.9, 110.4, 106.6, 79.9, 61.9, 61.6, 54.4, 48.3, 28.3, 13.95, 13.90; HRMS (ESI): calcd. for $C_{17}H_{25}NNaO_7^+$ (M+Na)$^+$: 379.1556, found: 379.1558; IR (neat): 3431, 2980, 2932, 1721, 1495, 1369, 1238, 1161, 1011 cm^{-1}.

4.4. General procedures of Mannich-type reaction of N-Boc-aminals with ethyl 2-oxocyclopentanecarboxylate

To a solution of the *N*-Boc-aminal (0.10 mmol) and ethyl 2-oxocylopentanecarboxylate (17mg, 0.11 mmol) in dichloromethane (1.0 mL) was added Cu(OTf)$_2$ (3.6 mg, 0.010 mmol) at 0 °C. After stirring for 24 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as an oil.

4.4.1. Ethyl 1-(((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentanecarboxylate

The titled compound was obtained as white solid (36 mg, 0.099 mmol, 99%, dr: *anti*/*syn* = 6.0/1), following the general procedure with di-*tert*-butyl (phenylmethylene)dicarbamate (32 mg, 0.10 mmol) and molecular sieve 4A (50 mg); spectra data of *syn* isomer are in accordance with the literature.[7] *anti* isomer ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.22 (m, 5H, Ph), 6.73 (br d, *J* = 8.8 Hz, 1H, NHBoc), 5.08 (br s, 1H, C*H*NHBoc), 4.31-4.18 (m, 2H, OC*H*$_2$CH$_3$), 2.42-2.28 (m, 2H, CH$_2$), 2.04-1.65 (m, 4H, CH$_2$), 1.37 (s, 9H, C(CH$_3$)$_3$), 1.29 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 216.8, 171.2, 154.8, 138.5, 128.4 (two peaks overlap), 127.8, 79.4, 63.0, 61.9, 57.7, 39.6, 32.9, 28.3, 19.4, 14.1; HRMS (ESI): calcd. for $C_{20}H_{27}NNaO_5^+$ (M+Na)$^+$ 384.1781, found 384.1774; IR (neat): 3424, 2976, 1743, 1715, 1493, 1366, 1229, 1161, 1020 cm^{-1}.

4.4.2. Ethyl 1-(1-((tert-butoxycarbonyl)amino)-3-phenylprop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

The titled compound was obtained as an oil (37 mg, 0.097 mmol, 97%, dr = 1.3/1), following the general procedure with di-*tert*-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and ethyl 2-oxocylopentanecarboxylate (17 mg, 0.11 mmol) at 0 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): both diastereomers δ 7.39-7.36 (m, 2H, Ph), 7.33-7.26 (m, 3H, Ph), 6.07 (br s, 0.44H, NHBoc), 5.43 (br s, 0.56H, NHBoc), 5.21 (br d, *J* = 10.0 Hz, 1H, C*H*NHBoc), 4.29-4.14 (m, 2H, OC*H*$_2$CH$_3$), 2.69-1.90 (m, 6H, CH$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$), 1.28 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.27 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): both diastereomers, δ 210.3, 170.0, 168.9, 154.9, 154.7, 131.8, 131.7, 128.55, 128.52, 128.2, 122.3, 122.2, 85.7, 85.4, 84.5, 84.0, 80.3, 80.0, 64.9, 61.9, 46.0, 45.6, 39.0, 37.7, 32.9, 31.6, 31.2, 28.3, 28.2, 19.7, 19.1, 14.1, 14.0; HRMS (ESI): calcd. for $C_{22}H_{27}NNaO_5^+$ (M+Na)$^+$: 408.1781, found: 408.1797; IR (neat): 3429, 2978, 1751, 1721, 1489, 1231, 1161, 1024 cm^{-1}.

4.4.3. Ethyl 1-((E)-1-((tert-butoxycarbonyl)amino)-3-phenylallyl)-2-oxocyclopentanecarboxylate

The titled compound was obtained as an oil (32 mg, 0.082 mmol, 82%, dr = 1.5/1), following the general procedure with di-*tert*-butyl ((*E*)-3-phenylprop-2-ene-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and ethyl 2-oxocylopentanecarboxylate (52 mg, 0.33 mmol); ^{1}H-NMR (400 MHz, $CDCl_3$): both diastereomers δ 7.36-7.22 (m, 5H, Ph), 6.58 (d, *J* = 16.0 Hz, 0.4H, PhC*H*=CH), 6.21 (dd, *J* = 16.0 Hz, 8.0 Hz, 0.6H, PhCH=C*H*), 6.04 (dd, *J* = 16.0 Hz, 8.0 Hz, 0.6H, PhCH=C*H*), 5.94 (br d, *J* = 5.6 Hz, 0.4H, NHBoc), 5.38 (br s, 1H, NHBoc), 4.77-4.69 (m, 1H, C*H*NHBoc), 4.27-4.09 (m, 2H, OC*H*$_2$CH$_3$), 2.56-2.34 (m, 2H, CH$_2$), 2.25-1.86 (m, 4H, CH$_2$), 1.43 (s, 3.6H, C(CH$_3$)$_3$), 1.42 (s, 5.4H, C(CH$_3$)$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.23 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): both diastereomers, δ 211.8, 171.6, 171.0, 155.0, 136.3, 133.8, 133.5, 128.51, 128.50, 127.9, 126.6, 126.5, 125.3, 125.2, 79.7, 79.4, 64.5, 63.3, 61.7, 61.6, 55.2, 54.6, 38.9, 37.5, 32.7, 28.32, 28.28, 19.5, 18.9, 14.0; HRMS (ESI): calcd. for $C_{22}H_{29}NNaO_5^+$ (M+Na)$^+$: 410.1938, found: 410.1931; IR (neat): 3429, 2976, 1748, 1717, 1491, 1368, 1229, 1161, 1026 cm^{-1}.

4.4.4. Ethyl 1-(1-((tert-butoxycarbonyl)amino)-3-phenylpropyl)-2-oxocyclopentanecarboxylate

Titled compound was obtained as an oil (29 mg, 0.075 mmol, 75%, dr = 1.4 /1), following the general procedure with di-*tert*-butyl (3-phenylpropane-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and ethyl 2-oxocylopentanecarboxylate (52mg, 0.33 mmol). Spectra data are in accordance with the literature.[20]

4.5. General procedures of Mannich-type reaction of N-Boc-aminals with trimethyl((1-phenylvinyl)oxy)silane

To a solution of the *N*-Boc-aminal (0.10 mmol) and trimethyl((1-phenylvinyl)oxy)silane (21 mg, 0.11 mmol) in dichloromethane (1.0 mL) was added Cu(OTf)$_2$ (3.6 mg, 0.010 mmol) at room temperature. After stirring for 3-120 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as a white solid.

4.5.1. tert-Butyl (3-oxo-1,3-diphenylpropyl)carbamate

The titled compound was obtained as a white solid (25 mg, 0.077 mmol, 77%), following the general procedure with di-*tert*-butyl (phenylmethylene)dicarbamate (32 mg, 0.10 mmol) and molecular sieve 4A (50 mg) for 24 h. Spectra data are in accordance with the literature. [21]

4.5.2. tert-Butyl (5-oxo-1,5-diphenylpent-1-yn-3-yl)carbamate

To a solution of di-*tert*-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and trimethyl((1-phenylvinyl)oxy)silane (21 mg, 0.11 mmol) in chloroform (1.0

mL) was added {Cu(OTf)}$_2$tol (2.6 mg, 0.010 mmol) at room temperature. To this mixture was added trimethyl((1-phenyl)oxy)silane (21×2 mg, 0.11×2 mmol) after 4 h and 24 h. After stirring for 48 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as a white solid (26 mg, 0.073 mmol, 73%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98-7.97 (m, 2H, Ar-H), 7.60-7.55 (m, 1H, Ar-H), 7.49-7.45 (m, 2H, Ar-H), 7.34-7.32 (m, 2H, Ar-H), 7.25-7.23 (m, 3H, Ar-H), 5.56 (br s, 1H, NHBoc), 5.18 (br s, 1H, C*H*NHBoc), 3.61 (br d, *J* = 16.8 Hz, 1H, C*H*HCOPh), 3.36 (dd, *J* = 16.8 Hz, 5.6 Hz, 1H, CH*H*COPh), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.9, 154.7, 136.7, 133.4, 131.7, 128.6, 128.2, 128.12, 128.08, 122.5, 87.8, 83.0, 80.0, 43.8, 40.0, 28.3; HRMS (ESI): calcd. for $C_{22}H_{23}NNaO_3^+$ $(M+Na)^+$: 372.1570, found: 372.1569; IR (neat): 3350, 2976, 2930, 1688, 1489, 1366, 1246, 1163, 1022 cm^{-1}.

4.5.3. tert-Butyl (E)-(5-oxo-1,5-diphenylpent-1-en-3-yl)carbamate

The titled compound was obtained as a white solid (64 mg, 0.090 mmol, 90%), following the general procedure with di-*tert*-butyl ((*E*)-3-phenylprop-2-ene-1,1-diyl)dicarbamate (70 mg, 0.10 mmol) under stirring for 3 h; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (app d, J = 7.6 Hz, 2H, Ar-H), 7.57 (app t, *J* = 7.6 Hz, 1H, Ar-H), 7.47 (app t, *J* = 7.6 Hz, 2H, Ar-H), 7.33 (app d, *J* = 7.2 Hz, 2H, Ar-H), 7.27 (app t, *J* = 7.2 Hz, 2H, Ar-H), 7.22-7.19 (m, 1H, Ar-H), 6.56 (d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 6.32 (dd, *J* = 16.0 Hz, 6.4 Hz, 1H, PhCH=C*H*), 5.43 (br s, 1H, NHBoc), 4.85-4.78 (m, 1H, C*H*NHBoc), 3.49 (br d, *J* = 15.6 Hz, 1H, C*H*HCOPh), 3.33 (dd, *J* = 15.6 Hz, 5.6 Hz, 1H, CH*H*COPh), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 198.3, 155.2, 136.8, 136.5, 133.3, 130.7, 129.1, 128.6, 128.4, 128.1, 127.5, 126.4, 79.5, 49.5, 43.3, 28.3; HRMS (ESI): calcd. for $C_{22}H_{25}NNaO_3^+$ $(M+Na)^+$: 374.1727, found: 374.1727; IR (neat): 3362, 2976, 2928, 1688, 1493, 1366, 1246, 1165, 1045, 1022 cm^{-1}.

4.5.4. tert-Butyl (5-oxo-1,5-diphenylpentan-3-yl)carbamate

To a solution of di-*tert*-butyl (3-phenylpropane-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and trimethyl((1-phenylvinyl)oxy)silane (21 mg, 0.11 mmol) in dichloromethane (0.50 mL) was added $Cu(OTf)_2$ (7.2 mg, 0.020 mmol) at room temperature. To this mixture was added trimethyl((1-phenylvinyl)oxy)silane (21×2 mg, 0.11×2 mmol) after 12 h and 24 h. After stirring for 120 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/30 to 1/9) to afford the product as a white solid (11 mg, 0.030 mmol, 30%). Spectra data are in accordance with the literature.[22]

4.6. The Procedure for preparation of the hemiaminal ether from the N-Boc-phenylalkynylaminal and ethanol

To a mixture of di-*tert*-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate (35 mg, 0.10 mmol) and diphenyl phosphate (2.5 mg, 0.010 mmol) was added EtOH (2.0 mL) at room temperature. After stirring for 4 h at 60 ˚C, the reaction mixture was quenched with aq. $NaHCO_3$ and evaporated to remove EtOH. The residue was diluted with AcOEt and extracted with the same solvent. The combined organic layers were dried over Na_2SO_4 and then concentrated. The residue was purified by flush column chromatography on silica gel (eluting with hexane/AcOEt = 9/1) to afford the corresponding hemiaminal (25 mg, 0.090 mmol, 90 % yield). Spectra data of the hemiaminal ether is in accordance with the literature[14]

4.7. Preparation of chiral phosphoric acid catalysts

The procedure for the synthesis of chiral phosphoric acids[15b,23] was modified. To a solution of BINOL derivative (0.37 mmol) in pyridine (8.0 mL) was added phosphoryl chloride (160 μL, 1.5 mmol) at room temperature. Followed by stirring for 5 h at 95 °C, the mixture was added water (1.7 mL) at 0 °C. After stirring for 5 h at 95 °C, the mixture was allowed to cool to room temperature and diluted with dichloromethane. The solvent pyridine was removed by washing with 1N HCl (50 ml ×3), and the aqueous layer was extracted with dichloromethane (50 ml ×3). The combined organic layer was dried over sodium sulfate anhydrate. Filtered solution was evaporated in vacuo. The obtained material was purified by silica gel column chromatography (dichloromethane/methanol = 80/1). The purified compound was dissolved in chloroform (50 ml) and washed with 6N HCl. The organic layer was directly evaporated, and a little amount of water included in the mixture was removed by azeotropic process with toluene at three times.

*4.7.1. Catalyst (S)-**1***

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 4H, Ar-H), 7.47 (s, 2H, Ar-H), 7.11 (s, 8H, Ar-H), 7.03 (s, 2H, Ar-H), 6.79 (s, 4H, Ar-H), 2.87-2.72 (m, 6H, CH_2), 2.44-2.37 (m, 2H, CH_2), 2.15 (s, 24H, CH_3), 1.88-1.81 (m, 6H, CH_2), 1.72-1.65 (m, 2H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 143.1, 143.0, 141.7, 141.2, 138.0, 137.9, 137.1, 134.89, 134.87, 131.9, 131.80, 131.76, 128.7, 127.2, 126.92, 126.90, 125.4, 125.1, 29.1, 27.9, 22.75, 22.71, 21.1; ^{31}P-NMR (200 MHz, $CDCl_3$): δ 1.3 (s); HRMS (ESI): calcd for $C_{64}H_{60}O_4P^-$ $(M-H)^-$ 923.4224 found 923.4216; IR (neat): 3628, 3362, 2924, 2855, 1589, 1447, 1246, 1098 cm^{-1}; $[\alpha]_D^{26}$ 180.2 (*c* 1.0, $CHCl_3$).

*4.7.2. Catalyst (S)-**2***

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59 (app d, *J* = 1.2 Hz, 4H, Ar-H), 7.54 (app t, *J* = 1.2 Hz, 2H, Ar-H), 7.47-7.45 (m, 8H, Ar-H), 7.18 (s, 2H, Ar-H), 7.17-7.09 (m, 12H, Ar-H), 2.96-2.75 (m, 6H, CH_2), 2.47 (app dt, *J* = 16.8 Hz, 4.8 Hz, 2H, CH_2), 1.92-1.84 (m, 6H, CH_2), 1.74-1.66 (m, 2H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 141.6, 141.0, 138.0, 137.6, 135.1, 131.71, 131.67, 131.5, 128.5, 127.4, 127.08, 127.06, 127.0, 125.1, 29.2, 27.9, 22.7, 22.6; ^{31}P-NMR (200 MHz, $CDCl_3$): δ 0.4 (s); HRMS (ESI): calcd for $C_{56}H_{44}O_4P^-$ $(M-H)^-$ 811.2972 found 811.2976; IR (neat): 2924, 2853, 1593, 1449, 1435, 1404, 1263, 1219, 1190, 1018 cm^{-1}; $[\alpha]_D^{23}$ 193.4 (*c* 1.0, $CHCl_3$).

*4.7.3. Catalyst (S)-**3***

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 4H, Ar-H), 7.60 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.51-7.41 (m, 8H, Ar-H), 7.28-7.25 (m, 10H, Ar-H), 6.79 (app t, *J* = 8.0 Hz, 8H, Ar-H), 5.52 (br s, 1H, OH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.3 (d, $J_{C\text{-}F}$ = 247.7 Hz), 144.3 (d, $J_{C\text{-}F}$ = 9.1 Hz), 140.6, 137.6, 136.7, 133.7, 132.0, 131.5, 128.9, 128.8, 128.7, 127.2, 127.04, 126.97, 126.4, 125.1, 122.3, 115.3 (d, $J_{C\text{-}F}$ = 21.4 Hz); ^{19}F-NMR (500 MHz, $CDCl_3$): δ –115.3 (s); ^{31}P-NMR (200 MHz, $CDCl_3$): δ 5.1 (s); HRMS (ESI): calcd for $C_{56}H_{32}F_4O_4P^-$ $(M-H)^-$ 875.1969 found 875.1976; IR (neat): 1604, 1510, 1230, 1159, 1016 cm^{-1}; $[\alpha]_D^{25}$ 202.4 (*c* 1.0, $CHCl_3$).

*4.7.4. Catalyst (S)-**4***

Spectra data are in accordance with the literature.[24]

4.8. Enantioselective Mannich-type reaction of N-Boc-alkynylaminal and acetylacetone

4.8.1. tert-Butyl (3-acetyl-2-oxoundec-5-yn-4-yl)carbamate

To a suspension of molecular sieve 5A (50 mg), di-*tert*-butyl (2-octyne-1,1-diyl)dicarbamate (34 mg, 0.10 mmol) in the mixture of dichloromethane (0.33 mL) and AcOEt (0.67 mL) were added the chiral phosphoric acid catalyst (*S*)-**1** (9.3 mg,

0.010 mmol) and acetylacetone (50 mg, 0.50 mmol) at room temperature. After stirring for 48 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/9) to afford the product as white solid (26 mg, 0.080 mmol, 80%, 88% ee). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.27 (br s, 1H, NHBoc), 5.08 (app t, *J* = 8.0 Hz, 1H, C*H*NHBoc), 4.01 (d, *J* = 6.8 Hz, 1H, $CHAc_2$), 2.27 (s, 3H, Ac), 2.22 (s, 3H, Ac), 2.12 (td, *J* = 7.2 Hz, 2.0 Hz, 2H, $CH_2C{\equiv}C$), 1.47-1.43 (m, 2H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.32-1.26 (m, 4H, CH_2), 0.89 (t, *J* = 6.8 Hz, 3H, CH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 202.9, 202.0, 154.8, 85.1, 80.3, 77.2, 70.8, 42.1, 30.9, 30.3, 30.1, 28.2, 28.1, 22.1, 18.5, 13.9; HRMS (ESI): calcd for $C_{18}H_{29}NNaO_4^+$ $(M+Na)^+$ 346.1989 found 346.1994; IR (neat): 3350, 2932, 1701, 1489, 1366, 1250, 1161 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AS-H, hexane/EtOH = 20/1, flow rate = 0.5 mL/min, λ = 205 nm, retention time; t_R = 11.3 min (major), 16.6 min (minor); $[\alpha]_D^{22}$ 26.7 (*c* 1.0, $CHCl_3$, 88% ee).

4.8.2. tert-Butyl (3-acetyl-7,7-dimethyl-2-oxooct-5-yn-4-yl)carbamate

To a suspension of molecular sieve 5A, di-*tert*-butyl (4,4-dimethylpent-2-yne- 1,1-diyl)dicarbamate (33 mg, 0.10 mmol) in the mixture of dichloromethane (0.33 mL) and AcOEt (0.67 mL) were added the chiral phosphoric acid catalyst (*S*)-**2** (8.1 mg, 0.010 mmol) and acetylacetone (30 mg, 0.30 mmol) at 40 °C. After stirring for 48 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/9) to afford the product as white solid (25 mg, 0.080 mmol, 80%, 92% ee). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.25 (br s, 1H, NHBoc), 5.07 (app t, *J* = 8.4 Hz, 1H, C*H*NHBoc), 4.01 (d, *J* = 6.8 Hz, 1H, $CHAc_2$), 2.27 (s, 3H, Ac), 2.23 (s, 3H, Ac), 1.43 (s, 9H, $OC(CH_3)_3$), 1.16 (s, 9H, $CC(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 202.8, 201.9, 154.7, 93.2, 80.2, 75.2, 71.0, 42.0, 30.6, 30.3, 30.1, 28.2, 27.2; HRMS (ESI): calcd for $C_{17}H_{27}NNaO_4^+$ $(M+Na)^+$ 332.1832 found 332.1834; IR (neat): 3352, 2970, 1726, 1692, 1520, 1364, 1265, 1252, 1167, 1057, 1018 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H, hexane/EtOH = 50/1, flow rate = 1.0 mL/min, λ = 204 nm, retention time; t_R = 8.2 min (minor), 11.6 min (major); $[\alpha]_D^{24}$ 25.9 (*c* 1.0, $CHCl_3$, 92% ee).

4.8.3. tert-Butyl (4-acetyl-5-oxo-1-(trimethylsilyl)hex-1-yn-3-yl)carbamate

To a suspension of molecular sieve 5A, di-*tert*-butyl (3-(trimethylsilyl)prop-2-yne-1,1'-diyl)dicarbamate (34 mg, 0.10 mmol) in dichloromethane (1.0 mL) were added the chiral phosphoric acid catalyst (*S*)-**1** (8.0 mg, 0.010 mmol) and acetylacetone (50 mg, 0.50 mmol) at room temperature. After stirring for 72 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/9) to afford the product as white solid (24 mg, 0.073 mmol, 73%, 90% ee). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.31 (br s, 1H, NHBoc), 5.11 (app t, *J* = 8.0 Hz, 1H, C*H*NHBoc), 4.03 (d, *J* = 6.8 Hz, 1H, $CHAc_2$), 2.27 (s, 3H, Ac), 2.23 (s, 3H, Ac), 1.43 (s, 9H, $C(CH_3)_3$), 0.13 (s, 9H, $Si(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 202.6, 201.6, 154.7, 101.9, 89.3, 80.5, 70.2, 42.5, 30.4, 30.1, 28.2, –0.3; HRMS (ESI): calcd for $C_{16}H_{27}NNaO_4Si^+$ $(M+Na)^+$ 348.1602 found 348.1606; IR (neat): 3350, 2965, 2176, 1705, 1491, 1366, 1250, 1163, 1053 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AS-H, hexane/EtOH = 50/1, flow rate = 0.5 mL/min, λ = 204 nm, retention time; t_R = 11.5 min (major), 12.1 min (minor); $[\alpha]_D^{32}$ 31.8 (*c* 1.0, $CHCl_3$, 90% ee).

4.9. Enantioselective Mannich-type reaction of N-Boc-alkynylaminal and α-substituted β-ketoesters

To a mixture of an *N*-Boc-aminal (0.10 mmol), an α-substituted β-ketoester (0.30 mmol) and molecular sieve 5A (50 mg) in dichloromethane (1.0 mL) was added catalyst (*S*)-**3** (8.8 mg, 0.010 mmol) at room temperature. After stirring for 36 h, the mixture was directly purified by silica gel chromatography (AcOEt/hexane = 1/25 to 1/9) to afford the corresponding adduct. The diastereo-mixture of the Mannich adduct could be separated by preparative HPLC on a silica gel column (Cosmosil 5SL-II, AcOEt/hexane = 1/30).

4.9.1. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-3-phenylprop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.36 (m, 2H, Ph), 7.32-7.26 (m, 3H, Ph), 6.08 (br d, *J* = 9.6 Hz, 1H, NHBoc), 5.21 (br d, *J* = 9.6 Hz, 1H, C*H*NHBoc), 4.27-4.14 (m, 2H, OCH_2CH_3), 2.70-2.52 (m, 1H, CH_2), 2.44-2.36 (m, 2H, CH_2), 2.32-2.22 (m, 1H, CH_2), 2.10-2.08 (m, 1H, CH_2), 1.96-1.92 (m, 1H, CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.27 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 214.8, 170.0, 154.7, 131.8, 128.5, 128.2, 122.2, 85.7, 84.5, 79.9, 62.9, 61.8, 46.0, 39.0, 32.9, 28.3, 19.7, 14.0; HRMS (ESI): calcd. for $C_{22}H_{27}NNaO_5^+$ $(M+Na)^+$: 408.1781, found: 408.1788; IR (neat): 3426, 2978, 1718, 1489, 1367, 1228, 1159, 1035 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 254 nm, retention time; t_R = 23.9 min (minor), 25.1 min (major); $[\alpha]_D^{25}$ 79.7 (*c* 1.0, $CHCl_3$, 94% ee).

4.9.2. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-3-(4-bromophenyl)prop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.23 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.06 (br d, *J* = 9.6 Hz, 1H, NHBoc), 5.18 (br d, *J* = 9.6 Hz, 1H, C*H*NHBoc), 4.27-4.14 (m, 2H, OCH_2CH_3), 2.68-2.51 (m, 1H, CH_2), 2.46-2.21 (m, 3H, CH_2), 2.13-2.04 (m, 1H, CH_2), 2.01-1.88 (m, 1H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 210.2, 169.9, 154.7, 133.2, 131.5, 122.8, 121.1, 86.9, 83.4, 80.0, 62.8, 61.9, 45.9, 38.9, 32.9, 28.3, 19.6, 14.0; HRMS (ESI): calcd. for $C_{22}H_{26}BrNNaO_5^+$ $(M+Na)^+$: 486.0887, found: 486.0893; IR (neat): 3426, 2978, 1748, 1718, 1486, 1367, 1229, 1159, 1011 cm^{-1}; HPLC analysis: Daicel CHIRALCEL OZ-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 254 nm, retention time; t_R = 14.0 min (minor), 18.7 min (major); $[\alpha]_D^{25}$ 41.0 (*c* 1.0, $CHCl_3$, 94% ee).

4.9.3. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-3-(4-methylphenyl)prop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.09 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.07 (br d, *J* = 10.0 Hz, 1H, NHBoc), 5.20 (br d, *J* = 10.0 Hz, 1H, C*H*NHBoc), 4.27-4.13 (m, 2H, OCH_2CH_3), 2.69-2.50 (m, 1H, CH_2), 2.43-2.39 (m, 2H, CH_2), 2.36-2.22 (m, 1H, CH_2), 2.33 (s, 3H, Me), 2.12-2.03 (m, 1H,CH_2), 1.99-1.89 (m, 1H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 214.9, 170.0, 154.7, 138.7, 131.6, 128.9, 119.1, 85.0, 84.6, 79.8, 62.8, 61.8, 46.1, 39.0, 32.9, 28.3, 21.4, 19.6, 14.0; HRMS (ESI): calcd. for $C_{23}H_{29}NNaO_5^+$ $(M+Na)^+$: 422.1938, found: 422.1948; IR (neat): 3428, 2978, 1749, 1719, 1510, 1487, 1367, 1228, 1159, 1037, 1021 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 254 nm, retention time; t_R = 23.6 min (major), 30.2 min (minor); $[\alpha]_D^{22}$ 69.2 (*c* 1.0, $CHCl_3$, 93% ee).

4.9.4. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-3-(1-cyclohexenyl)prop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.04 (app quin., *J* = 2.0 Hz, 1H, CH=C), 5.97 (d, 1H, *J* = 9.2 Hz, C*H*NHBoc), 5.07 (d, *J* = 8.0

Hz, 1H, NHBoc), 4.25-4.11 (m, 2H, OC*H*$_2$CH$_3$), 2.62-2.48 (m, 1H, CH$_2$), 2.41-2.30 (m, 2H, CH$_2$), 2.29-2.18 (m, 1H, CH$_2$), 2.11-2.04 (m, 5H, CH$_2$), 1.97-1.84 (m, 1H, CH$_2$), 1.63-1.52 (m, 4H, CH$_2$), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 214.9, 170.0, 154.6, 135.6, 119.8, 86.3, 82.8, 79.7, 62.9, 61.7, 46.0, 39.1, 32.9, 29.0, 28.3, 25.5, 22.1, 21.3, 19.6, 14.0; HRMS (ESI): calcd. for $C_{22}H_{31}NNaO_5^+$ (M+Na)$^+$: 412.2094, found: 412.2110; IR (neat): 3429, 2977, 2932, 1718, 1487, 1366, 1228, 1158, 1036 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 226 nm, retention time; t_R = 17.3 min (minor), 19.4 min (major); $[\alpha]_D^{23}$ 54.8 (*c* 1.0, CHCl$_3$, 94% ee).

4.9.5. Ethyl (1S)-1-((S,E)-1-((tert-butoxycarbonyl)amino)-5-phenylpent-4-en-2-yn-1-yl)- 2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.38-7.25 (m, 5H, Ph), 6.89 (d, *J* = 16.4 Hz, 1H, PhC*H*=CH), 6.09 (dd, *J* = 16.4 Hz, 2.4 Hz, 1H, PhCH=C*H*), 6.04 (br d, *J* = 9.6 Hz, 1H, NHBoc), 5.15 (br d, *J* = 9.6 Hz, 1H, C*H*NHBoc), 4.28-4.13 (m, 2H, OC*H*$_2$CH$_3$), 2.67-2.51 (m, 1H, CH$_2$), 2.45-2.23 (m, 3H, CH$_2$) 2.14-2.04 (m, 1H, CH$_2$), 2.00-1.87 (m, 1H, CH$_2$), 1.44 (s, 9H, C(CH$_3$)$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 214.9, 170.0, 154.7, 142.1, 135.9, 128.8, 128.7, 126.2, 107.2, 87.7, 83.7, 79.9, 62.8, 61.8, 46.2, 38.9, 32.9, 28.3, 19.6, 14.0; HRMS (ESI): calcd. for $C_{24}H_{29}NNaO_5^+$ (M+Na)$^+$: 434.1938, found: 434.1949; IR (neat): 3426, 2978, 1717, 1489, 1367, 1319, 1298, 1229, 1158, 1036 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-3, hexane/EtOH = 20/1, flow rate = 0.5 mL/min, λ = 254 nm, retention time; t_R = 29.9 min (major), 40.2 min (minor); $[\alpha]_D^{24}$ 79.1 (*c* 1.0, CHCl$_3$, 90% ee)

4.9.6. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-oct-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): 5.96 (br d, *J* = 8.8 Hz, 1H, C*H*NHBoc), 4.94 (br d, *J* = 9.2 Hz, 1H, NHBoc), 4.24-4.10 (m, 2H, OC*H*$_2$CH$_3$), 2.63-2.48 (m, 1H, CH$_2$), 2.36-2.32 (m, 2H, CH$_2$), 2.29-2.01 (m, 2H, CH$_2$), 2.12 (td, *J* = 7.2 Hz, 2.0 Hz, 2H, CH$_2$), 1.96-1.86 (m, 1H, CH$_2$), 1.48-1.43 (m, 2H, CH$_2$), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.32-1.27 (m, 4H, CH$_2$), 1.24 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 0.89 (t, *J* = 6.8 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 215.0, 170.1, 154.8, 85.2, 79.6, 76.5, 62.8, 61.7, 45.7, 39.0, 32.9, 30.9, 28.3, 28.2, 22.1, 19.6, 18.5, 14.0, 13.9; HRMS (ESI): calcd. for $C_{21}H_{33}NNaO_5^+$ (M+Na)$^+$: 402.2251, found: 402.2253; IR (neat): 3429, 2961, 2932, 1750, 1720, 1489, 1228, 1159 cm^{-1}; HPLC analysis: Daicel CHIRALPAK IC, hexane/*i*PrOH = 10/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R = 21.3 min (minor), 37.3 min (major); $[\alpha]_D^{25}$ 35.4 (*c* 1.0, CHCl$_3$, 92% ee).

4.9.7. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-5-phenylpent-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.30-7.26 (m, 2H, Ph), 7.22-7.16 (m, 3H, Ph), 5.96 (br d, *J* = 10.0 Hz, 1H, NHBoc), 4.90 (br d, *J* = 10.0 Hz, 1H, C*H*NHBoc), 4.22-4.07 (m, 2H, OC*H*$_2$CH$_3$), 2.76 (t, *J* = 7.2 Hz, 2H, PhC*H*$_2$CH$_2$), 2.49-2.44 (m, 2H, PhCH$_2$C*H*$_2$), 2.44-2.36 (m, 1H, CH$_2$), 2.28-2.22 (m, 1H, CH$_2$), 2.15-2.07 (m, 1H, CH$_2$), 2.00-1.76 (m, 3H, CH$_2$), 1.42 (s, 9H, C(CH$_3$)$_3$), 1.22 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 215.1, 170.1, 154.7, 140.3, 128.4, 128.3, 126.2, 84.2, 79.6, 77.3, 62.7, 61.7, 45.6, 38.8, 34.5, 32.7, 28.3, 20.4, 19.6, 13.9; HRMS (ESI): calcd. for $C_{24}H_{31}NNaO_5^+$ (M+Na)$^+$: 436.2094, found: 436.2108; IR (neat): 3427, 2977, 1716, 1487, 1366, 1319, 1299, 1226, 1155, 1033 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R = 23.3 min (minor), 29.5 min (major); $[\alpha]_D^{24}$ 43.7 (*c* 1.0, CHCl$_3$, 91% ee).

4.9.8. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-3-cyclohexylprop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.94 (br d, *J* = 10.0 Hz, NHBoc), 4.95 (d, *J* = 10.0 Hz, 1H, C*H*NHBoc), 4.24-4.10 (m, 2H, OC*H*$_2$CH$_3$), 2.63-2.47 (m, 1H, CH$_2$), 2.40-2.28 (m, 3H, CH$_2$, C*H*CH$_2$), 2.26-2.15 (m, 1H, CH$_2$), 2.11-1.99 (m, 1H, CH$_2$), 1.96-1.83 (m, 1H, CH$_2$), 1.72-1.62 (m, 4H, Cy), 1.49-1.21 (m, 6H, Cy), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.24 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 210.4, 170.1, 154.8, 89.2, 79.6, 77.2, 62.9, 61.7, 45.7, 39.1, 32.9, 32.5, 28.7, 28.3, 25.8, 24.6, 19.7, 14.0; HRMS (ESI): calcd. for $C_{22}H_{33}NNaO_5^+$ (M+Na)$^+$: 414.2251, found: 414.2260; IR (neat): 3430, 2977, 2930, 2854, 1750, 1720, 1489, 1366, 1228, 1159, 1036 cm^{-1}; HPLC analysis: Daicel CHIRALPAK IC, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R = 30.8 min (minor), 58.8 min (major); $[\alpha]_D^{23}$ 44.0 (*c* 1.0, CHCl$_3$, 95% ee).

4.9.9. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-3-cyclopropylprop-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.92 (br d, *J* = 8.8 Hz, 1H, NHBoc), 4.90 (br d, *J* = 8.8 Hz, 1H, C*H*NHBoc), 4.23-4.10 (m, 2H, OC*H*$_2$CH$_3$), 2.59-2.46 (m, 1H, CH$_2$), 2.35-2.16 (m, 3H, CH$_2$), 2.09-2.02 (m, 1H, CH$_2$), 1.95-1.83 (m, 1H, CH$_2$), 1.42 (s, 9H, C(CH$_3$)$_3$), 1.24 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.21-1.13 (m, 1H, CH), 0.75-0.70 (m, 2H, CHC*H*H), 0.62-0.58 (m, 2H, CHCH*H*); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 214.9, 170.1, 154.7, 88.2, 79.6, 71.6, 62.9, 61.7, 45.6, 39.0, 32.8, 28.3, 19.6, 14.0, 8.22, 8.19, –0.7; HRMS (ESI): calcd. for $C_{19}H_{27}NNaO_5^+$ (M+Na)$^+$: 372.1781, found: 372.1789; IR (neat): 3429, 2978, 1717, 1488, 1367, 1229, 1158, 1030 cm^{-1}; HPLC analysis: Daicel CHIRALCEL OZ-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R = 18.4 min (minor), 20.8 min (major); $[\alpha]_D^{25}$ 39.4 (*c* 1.0, CHCl$_3$, 93% ee).

4.9.10. Ethyl (1S)-1-((S)-1-((tert-butoxycarbonyl)amino)-4,4-dimethylpent-2-yn-1-yl)-2-oxocyclopentanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.90 (br d, *J* = 10.0 Hz, 1H, NHBoc), 4.93 (br d, *J* = 10.0 Hz, 1H, C*H*NHBoc), 4.23-4.10 (m, 2H, OC*H*$_2$CH$_3$), 2.64-2.47 (m, 1H, CH$_2$), 2.40-2.27 (m, 2H, CH$_2$), 2.23-2.14 (m, 1H, CH$_2$), 2.11-2.02 (m, 1H, CH$_2$), 1.96-1.83 (m, 1H, CH$_2$), 1.43 (s, 9H, OC(CH$_3$)$_3$), 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.16 (s, 9H, CC(CH$_3$)$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 214.8, 170.1, 154.7, 93.3, 79.6, 75.2, 63.0, 61.6, 45.6, 39.2, 32.9, 30.8, 28.3, 27.2, 19.6, 14.0; HRMS (ESI): calcd. for $C_{20}H_{31}NNaO_5^+$ (M+Na)$^+$: 388.2094, found: 388.2105; IR (neat): 3430, 2970, 1719, 1489, 1366, 1321, 1299, 1227, 1159, 1036 cm^{-1}; HPLC analysis: Daicel CHIRALCEL OZ-H, hexane/*i*PrOH = 50/1, flow rate = 0.5 mL/min, λ = 209 nm, retention time; t_R = 12.1 min (minor), 16.6 min (major); $[\alpha]_D^{24}$ 42.2 (*c* 1.0, CHCl$_3$, 95% ee).

4.9.11. Ethyl 1-(1-((tert-butoxycarbonyl)amino)-3-phenylprop-2-yn-1-yl)-2-oxocyclohexanecarboxylate

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.41-7.35 (m, 2H, Ph), 7.31-7.25 (m, 3H, Ph), 5.89 (br d, *J* = 10.4 Hz, 1H, NHBoc), 4.97 (br d, *J* = 10.4 Hz, 1H, C*H*NHBoc), 4.22 (qd, *J* = 7.2 Hz, 1.2 Hz, 2H, OC*H*$_2$CH$_3$), 2.69-2.56 (m, 1H, CH$_2$), 2.58-2.48 (m, 2H, CH$_2$), 2.11 (td, *J* = 13.2 Hz, 3.2 Hz, 1H, CH$_2$), 2.06-2.00 (m, 1H, CH$_2$), 1.86 (app d, *J* = 13.2 Hz, 1H, CH$_2$), 1.72-1.51 (m, 2H, CH$_2$), 1.42 (s, 9H, C(CH$_3$)$_3$), 1.29 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C-NMR

(100 MHz, $CDCl_3$): δ 207.1, 170.4, 154.7, 131.8, 128.3, 128.1, 122.6, 86.2, 84.3, 79.7, 65.1, 62.0, 47.7, 41.2, 34.7, 28.3, 26.3, 22.2, 14.0; HRMS (ESI): calcd. for $C_{23}H_{29}NNaO_5^+$ $(M+Na)^+$: 422.1938, found: 422.1952; IR (neat): 3449, 2978, 2935, 1715, 1484, 1226, 1168, 1022 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 206 nm, retention time; t_R = 15.3 min (minor), 23.1 min (major); $[\alpha]_D^{25}$ –2.3 (*c* 1.0, $CHCl_3$, 95% ee).

4.9.12. Ethyl 2-acetyl-2-benzyl-3-((tert-butoxycarbonyl)amino)-5-phenylpent-4-ynoate

^{1}H-NMR (400 MHz, $CDCl_3$): both diastereomers δ 7.42-7.39 (m, 2H, Ph), 7.32-7.25 (m, 8H, Ph), 5.79 (br d, *J* = 10.0 Hz, 0.66H, NHBoc), 5.54 (br s, 0.34H, NHBoc), 5.27 (br d, *J* = 10.0 Hz, 0.66H, C*H*NHBoc), 5.21 (br s, 0.69H, C*H*NHBoc), 4.31 (q, *J* = 7.2 Hz, 1.31H, OCH_2CH$_3$), 4.14 (qd, *J* = 7.2 Hz, 2.8 Hz, 0.69H, OCH_2CH$_3$), 3.45-3.39 (m, 2H, PhCH_2), 2.29 (s, 1.0H, Ac), 1.99 (s, 2.0H, Ac), 1.44 (s, 5.9H, C(CH_3)$_3$), 1.43 (s, 3.1H, C(CH_3)$_3$), 1.31 (t, *J* = 7.2 Hz, 2.0H, OCH$_2$CH_3), 1.16 (t, *J* = 7.2 Hz, 1.0H, OCH$_2$CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): both diastereomers, δ 205.4, 205.3, 170.5, 169.8, 154.9, 154.7, 135.2, 135.0, 131.75, 131.71, 130.3, 130.2, 128.61, 128.58, 128.5, 128.4, 128.30, 128.27, 127.4, 127.3, 122.4, 122.3, 86.3, 85.8, 85.1, 80.3, 68.8, 68.1, 62.0, 61.6, 46.2, 45.8, 39.2, 39.1, 30.1, 29.4, 28.3 (two peaks overlap), 14.1, 13.8, 1.0, 0.0; HRMS (ESI): calcd. for $C_{27}H_{31}NNaO_5^+$ $(M+Na)^+$: 472.2094, found: 472.2098; IR (neat): 3430, 2979, 1716, 1489, 1367, 1246, 1165, 1017 cm^{-1}; HPLC analysis: Daicel CHIRALPAK IF, hexane/*i*PrOH = 50/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R = 27.7 min (minor), 31.8 min (major); $[\alpha]_D^{25}$ 27.2 (*c* 1.0, $CHCl_3$, 89% ee).

4.9.13. Ethyl 2-acetyl-2-hexyl-3-((tert-butoxycarbonyl)amino)-5-phenylpent-4-ynoate

^{1}H-NMR (500 MHz, $CDCl_3$): both diastereomers δ 7.38-7.35 (m, 2H, Ph), 7.31-7.26 (m, 3H, Ph), 5.76 (d, *J* = 10.0 Hz, 0.71H, NHBoc), 5.57 (br s, 0.29H, NHBoc), 5.24-5.19 (m, 1H, C*H*NHBoc), 4.34-4.28 (m, 1.42H, OCH_2CH$_3$), 4.27-4.18 (m, 0.58H, OCH_2CH$_3$), 2.32 (s, 0.87H, Ac), 2.25 (s, 2.13H, Ac), 2.11-2.05 (m, 1H, C*H*HCC), 1.95 (ddd, *J* = 14.0 Hz, 12.5 Hz, 4.5 Hz, 0.29H, CH*H*CC), 1.86 (ddd, *J* = 14.0 Hz, 12.5 Hz, 4.5 Hz, 0.71H, CH*H*CC), 1.55-1.41 (m, 2H, CH$_2$), 1.46 (s, 9H, OC(CH_3)$_3$), 1.41-1.18 (m, 6H, CH$_2$), 1.33 (t, *J* = 7.5 Hz, 3H, OCH$_2$CH_3), 0.87 (t, *J* = 6.5 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$): both diastereomers, δ 204.8, 204.6, 170.9, 170.6, 154.9, 154.8, 131.70, 131.67, 128.5, 128.3, 128.24, 128.17, 122.6, 122.4, 86.4, 85.9, 84.2, 84.0, 80.3, 80.0, 68.0, 66.8, 61.6, 46.7, 45.6, 33.8, 33.3, 31.4, 29.8, 28.6, 28.3, 27.7, 24.6, 24.2, 22.5, 14.14, 14.05, 14.0; HRMS (ESI): calcd. for $C_{26}H_{37}NNaO_5^+$ $(M+Na)^+$: 466.2564 found: 466.2553; IR (neat): 2931, 1716, 1488, 1367, 1328, 1242, 1168, 1018 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AD-H connected with Daicel CHIRALPAK AD-3, hexane/*i*PrOH = 20/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R = 24.6 min (minor), 25.5 min (major); $[\alpha]_D^{33}$ 40.2 (*c* 1.0, $CHCl_3$, 91% ee).

4.10. Enantioselective Mannich-type reaction of N-Boc-alkynylaminal and aldehydes

To a solution of *N*-Boc-aminal (0.10 mmol) and (*S*)-**4** (5.0 mg, 0.010 mmol) in the appropriate solvent (2.0 mL) were added aldehyde (0.30 mmol) and 3,4-dihydro-2*H*-pyran (DHP) (18 μL, 0.20 mmol) at room temperature. After stirring for 96 h, the reaction mixture was added MeOH (2.0 mL) and $NaBH_4$ (11 mg, 0.30 mmol) at 0 ˚C. After stirring for 2 h at 0 ˚C, the reaction mixture was quenched with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/AcOEt = 7/1, then toluene/AcOEt = 20/1) to afford the corresponding Mannich adduct.

4.10.1. tert-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-phenylpent-1-yn-3-yl)carbamate

The reaction was carried out in the mixed solvent of $PhCF_3$/AcOEt (1/1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46-7.43 (m, 2H, Ar-H), 7.33-7.31 (m, 3H, Ar-H), 7.30-7.25 (m, 4H, Ar-H), 7.22-7.19 (m, 1H, Ar-H), 5.10 (d, 1H, *J* = 8.0 Hz, NH), 4.77 (t, 1H, app *J* = 8.0 Hz, C*H*NH), 3.73 (d, 1H, *J* = 11.6 Hz, C*H*HOH), 3.51 (m, 1H, CH*H*OH), 3.03 (dd, 1H, *J* = 9.6, 4.4 Hz, C*H*HPh), 2.81-2.87 (m, 1H, CH*H*Ph), 2.75 (br s, 1H, OH), 1.95 (m, 1H, C*H*CH$_2$OH), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 156.1, 140.2, 131.7, 129.3, 128.5, 128.3, 126.1, 122.5, 87.6, 84.6, 80.5, 59.8, 49.1, 45.2, 33.9, 28.3; HRMS (ESI): calcd. for $C_{23}H_{27}NNaO_3^+$ $(M+Na)^+$: 388.1883, found: 388.1884; IR (neat): 3392, 2927, 1690, 1491, 1367, 1248, 1167, 1046 cm^{-1}; HPLC analysis: Daicel CHIRALPAK IC, hexane/*i*PrOH = 50/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t_R = 33.6 min (major), 55.7 min (minor).

4.10.2. tert-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-(4-methoxyphenyl)pent-1-yn-3-yl)carbamate

The reaction was carried out in the mixed solvent of DCE/AcOEt (1/1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.31-7.18 (m, 5H, Ar-H), 6.84 (d, 2H, *J* = 9.2Hz, Ar-H), 5.08 (d, 1H, *J* = 8.4 Hz, NH), 4.74 (app t, 1H, *J* = 8.4 Hz, C*H*NH), 3.81 (s, 3H, OCH$_3$), 3.71 (d, 1H, *J* = 11.2 Hz, C*H*HOH), 3.49 (m, 1H, CH*H*OH), 3.02 (dd, 1H, *J* = 13.2, 4.0 Hz, C*H*HPh), 2.85-2.79 (m, 2H, CH*H*Ph, OH), 1.93 (m, 1H, C*H*CH$_2$OH), 1.46 (s, 9H, C(CH_3)$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.8, 156.0, 140.3, 133.2, 129.3, 128.4, 126.1, 114.7, 114.0, 86.2, 84.6, 80.4, 60.1, 55.3, 49.1, 45.4, 34.0, 28.3; HRMS (ESI): calcd. for $C_{24}H_{29}NNaO_4^+$ $(M+Na)^+$: 418.1989, found: 418.1987; IR (neat): 3399, 2931, 1689, 1606, 1509, 1367, 1247, 1170, 1032 cm^{-1}; HPLC analysis: Daicel CHIRALPAK IC, hexane/EtOH = 40/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t_R = 25.3 min (major), 27.2 min (minor).

4.10.3. tert-Butyl (3R,4S)-(4-(hydroxymethyl)-1-(4-methoxyphenyl)-5-methylhex-1-yn-3-yl) carbamate

The reaction was carried out in the mixed solvent of DCE/AcOEt (1/1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 2H, *J* = 8.4 Hz, Ar-H), 6.82 (d, 2H, *J* = 8.4 Hz, Ar-H), 5.43 (br d, 1H, *J* = 8.4 Hz , NH), 4.91 (m, 1H, C*H*NH), 4.07 (br d, 1H, *J* = 9.2 Hz, C*H*HOH), 3.95-3.85 (m, 1H, CH*H*OH), 3.80 (s, 3H, OCH$_3$), 2.35 (br s, 1H, OH), 2.13-2.08 (m, 1H, C*H*(CH$_3$)$_2$), 1.66 (m, 1H, C*H*CH$_2$OH), 1.47 (s, 9H, C(CH_3)$_3$), 1.06 (d, 3H, *J* = 6.4 Hz, CH(CH_3)$_2$), 1.05 (d, 3H, *J* = 6.4 Hz, CH(CH_3)$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.5, 155.8, 133.1, 115.0, 113.9, 87.3, 83.5, 80.0, 60.6, 55.3, 51.1, 44.3, 28.4, 26.5, 21.4, 19.7; HRMS (ESI): calcd. for $C_{20}H_{29}NNaO_4^+$ $(M+Na)^+$: 370.1989, found: 370.1982; IR (neat): 3391, 2963, 1688, 1607, 1509, 1247, 1171 cm^{-1}; HPLC analysis: Daicel CHIRALPAK AS-H, hexane/*i*-PrOH = 20/1, flow rate = 0.75 mL/min, λ = 254 nm, retention time; t_R = 10.8 min (major), 16.5 min (minor).

4.11. Carbamoyl groups exchange reaction between N-Boc- and N-Cbz-aminal

To a suspension of molecular sieve 4A (50 mg), di-*tert*-butyl (phenylmethylene)dicarbamate (16 mg, 0.050 mmol) and dibenzyl (phenylmethylene)dicarbamate (20 mg, 0.050 mmol) in dichloromethane (1.0 mL) was added $Cu(OTf)_2$ (3.6 mg, 0.010 mmol) at room temperature. After stirring for 24 h, the mixture was directly purified by silica gel column chromatography (AcOEt/hexane = 1/30 to 1/9) to afford di-*tert*-butyl

(phenylmethylene) dicarbamate (8.0 mg, 0.25 mmol, 25%), dibenzyl (phenylmethylene)dicarbamate (13 mg, 0.34 mmol, 34%) and benzyl *tert*-butyl (phenylmethylene)dicarbamate (7.4 mg, 0.021 mmol, 21%).

4.11.1. Benzyl tert-butyl (Phenylmethylene)dicarbamate

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 10H, Ar-H), 6.20 (t, *J* = 8.0 Hz, 1H, C*H*-Ph), 5.76 (br s, 1H, NHCbz), 5.53 (br s, 1H, NHBoc), 5.13 (s, 1H, OCH_2Ph), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.3, 154.7, 139.2, 136.2, 128.7, 128.5, 128.24, 128.18, 128.1, 125.8, 80.4, 67.0, 61.9, 28.3; HRMS (ESI): calcd. for $C_{20}H_{24}N_2NaO_4^+$ $(M+Na)^+$: 379.1628, found: 379.16278; IR (neat): 3310, 3032, 2978, 1701, 1545, 1506, 1240, 1171, 1016 cm^{-1}.

4.12. Hetero-Diels-Alder reaction of N-Boc-aminal with cyclopentadiene

To a mixture of di-*tert*-butyl (phenylmethylene)dicarbamate (32 mg, 0.10 mmol), cyclopenta-1,3-diene (42 μL, 0.5 mmol) and molecular sieves 5Å (50 mg) in dichloromethane (1.0 mL) was added a $Cu(OTf)_2$ (3.6 mg, 0.010 mmol) at 0 ˚C. After stirring for 96 h at the same temperature, the reaction mixture was quenched with aq. $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 20/1) to afford the correcponding hetero-Diels-Alder adduct (15.5 mg, 0.057 mmol, 57% yield).

4.12.1. tert-Butyl 3-phenyl-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate

The title compound was obtained as a single diastereomer, and exists as a mixture of rotamers in chloroform. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.31 (m, 4H, Ph), 7.23-7.21 (m, 1H, Ph), 6.54 (s, 0.5H, HC=CH), 6.45 (s, 1H, PhCHCHC*H*), 6.43 (s, 0.5H, HC=CH), 4.84 (s, 0.5H, HC=CH), 4.70 (s, 0.5H, HC=CH), 4.10 (s, 0.5H, PhC*H*), 4.01 (s, 0.5H, PhC*H*), 3.04 (s, 1H, PhCHC*H*), 1.81 (d, 1H, *J* = 8.8 Hz, C*H*H), 1.46 (s, 4.5H, $C(CH_3)_3$), 1.38 (d, 1H, *J* = 8.0 Hz, CH*H*), 1.22 (s, 4.5H, $C(CH_3)_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 156.7, 156.3, 142.2, 141.8, 137.9, 136.0, 135.4, 128.3, 128.0, 126.6, 126.5, 126.3, 79.4, 62.2, 61.4, 61.2, 60.8, 52.1, 51.5, 43.9, 43.5, 28.4, 28.2; HRMS (ESI) calcd. for $C_{17}H_{21}NNaO_2^+$ $(M+Na)^+$: 294.1465, found: 294.1469; IR (neat): 2975, 1695, 1364, 1162, 1122, 714 cm^{-1}.

4.13. Comparison of reactivity of aldehyde and encarbamate

tert-Butyl benzylidenecarbamate was synthesized according to the literature procedure.[25] To a mixture of diphenyl phosphate (2.5 mg, 0.010 mmol) and molecular sieve 5A (50 mg) in DCM (2.0 mL) were added 3-phenylpropanal (40 μL, 0.30 mmol) and *tert*-butyl benzylidenecarbamate (21 mg, 0.10 mmol) at room temperature. After stirring for 5 h, the mixture was added MeOH (2.0 mL) and $NaBH_4$ (11 mg, 0.30 mmol) at 0 ˚C. After stirring for 2 h at 0 ˚C, the reaction mixture was quenched with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/AcOEt = 7/1) to afford the Mannich adduct with trace yield as shown in Scheme 11A.

tert-Butyl (3-phenylprop-1-en-1-yl)carbamate was synthesized according to the literature procedure.[26] To a mixture of diphenyl phosphate (2.5 mg, 0.010 mmol), *tert*-butyl (3-phenylprop-1-en-1-yl)carbamate (70 mg, 0.30 mmol) and molecular sieve 5A (50 mg) in dichloromethane (2.0 mL) was added a *tert*-butyl benzylidenecarbamate (21 mg, 0.10 mmol) at room temperature. After stirring for 5 h, the mixture was added MeOH (2.0 mL) and $NaBH_4$ (11 mg, 0.30 mmol) at 0 ˚C. After stirring for 2 h at 0 ˚C, the reaction mixture was quenched with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/AcOEt = 10/1) to afford the adduct as shown in Scheme 11B (40 mg, 0.090 mmol, 90%, *E*/*Z* = 3.5/1).

To a solution of the adduct obtained from Scheme 10B (23 mg, 0.050 mmol) and diphenyl phosphate (1.3 mg, 0.0050 mmol) in DCM (1.0 mL) was added water (0.050 mmol, 0.9 μL) at room temperature. After stirring for 48 h, the reaction mixture was added MeOH (1.0 mL) and $NaBH_4$ (1.9 mg, 0.050 mmol) at 0 ˚C. After stirring for 2 h at 0 ˚C, the reaction mixture was quenched with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/AcOEt = 7/1) to afford the corresponding aminoalcohol as shown in Scheme 11C (14 mg, 0.039 mmol, 78%).

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