Asymmetric Synthesis

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Catalytic Asymmetric Direct Henry Reaction of Ynals: Short Syntheses of (2*S*,3*R*)-(+)-Xestoaminol C and (−)-Codonopsinines**

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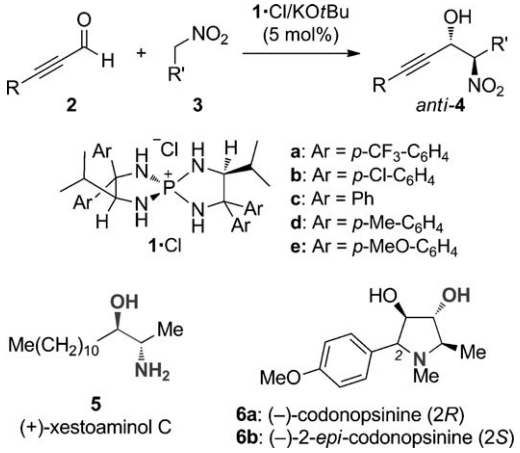
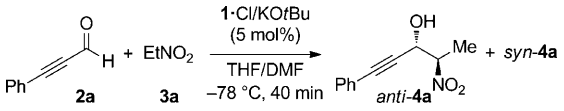
Optically active propargylic alcohols are versatile building blocks for the asymmetric synthesis of various biologically relevant complex molecules owing to the rich chemistry of the carbon–carbon triple bond, which allows its conversion into numerous other functional groups.[1] There are three principal approaches to the catalytic enantioselective construction of this important class of compounds: 1) the reduction of ynones,[2,3] 2) the addition of terminal alkynes to aldehydes,[4] and 3) the addition of an appropriate nucleophile to ynals.[5,6] Although the first two methods have been studied extensively, efforts for exploring the potential of the third approach have been rather limited despite the inherent flexibility in the structure of the nucleophilic component used in this method. Nitroalkanes appear to be an attractive candidate as nucleophiles for addressing this issue because their coupling reaction with ynals, namely the direct Henry reaction of ynals,[7–9] provides a straightforward entry to optically active β-nitro propargylic alcohols. These alcohols are extremely valuable intermediates that can be converted into various functionalized β-amino alcohols and α-hydroxy carbonyls. In particular, if the relative stereochemistry could be rigorously controlled, this unprecedented transformation would serve as a useful yet reliable process for the synthesis of *anti*- or *syn*-β-amino alcohols with structures that are not readily accessible by existing catalytic asymmetric methodologies. Herein, we report the first catalytic asymmetric direct Henry reaction of ynals efficiently mediated by a chiral tetraaminophosphonium salt **1d**·Cl with excellent *anti*-selectivity and enantioselectivity.[10,11] Furthermore, the synthetic utility of this new procedure is clearly demonstrated by its application in the short syntheses of (2*S*,3*R*)-(+)-xestoaminol C (**5**), (−)-codonopsinine (**6a**), and (−)-2-*epi*-codonopsinines (**6b**; Scheme 1).

We began our studies by examining the reaction of 3-phenylpropynal (**2a**) with nitroethane (**3a**) using **1a**·Cl, which contains *para*-trifluoromethylphenyl moieties, as the catalyst precursor.[10,12] When **2a** was treated with **3a** (10 equiv) under the influence of the iminophosphorane generated from **1a**·Cl and KO*t*Bu in tetrahydrofuran at −78 °C for 30 minutes, the desired Henry adduct *anti*-**4a** was obtained almost exclusively in 86 % *ee*, but in only 22 % yield (Table 1, entry 1). Although the stereoselectivity was promising, a substantial amount of **2a** remained unreacted. Analysis of the crude mixture revealed that the low conversion was primarily a result of the decomposition of **1a** during the initial stage of the reaction. As the aminophosphonium cation **1** was fairly stable



Scheme 1. Catalytic asymmetric direct Henry reaction of ynals mediated by **1**·Cl, and natural products concisely assembled from Henry adducts.

Table 1: Effect of *N*,*N*-dimethylformamide concentration and catalyst structure.[a]



Entry	**1**·Cl	DMF [v/v %]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	**1a**	0	22	>20:1	86
2	**1a**	5	49	14:1	82
3	**1a**	10	>99	12:1	83
4	**1b**	10	82	>20:1	98
5	**1c**	10	93	11:1	94
6	**1d**	10	94	>20:1	98
7	**1e**	10	>99	11:1	97

[a] The reaction was performed with 0.20 mmol of **2a** and 2.0 mmol of **3a** in the presence of **1**·Cl/KO*t*Bu (5 mol %) in THF/DMF (2.0 mL) at −78 °C under an argon atmosphere. [b] Yield of isolated product. [c] Diastereomeric ratio (d.r.) was determined by ^{1}H NMR (400 MHz) spectroscopic analysis of an aliquot of the crude reaction mixture. [d] Enantiomeric excess was determined by HPLC on a chiral stationary phase. Absolute and relative configurations were assigned by analogy to **4b** and **4h**.

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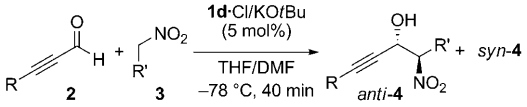
in the reactions with aromatic or aliphatic aldehydes under similar conditions,[10] we assumed that the origin of this decomposition would be the relatively low pK_a of the in situ generated secondary propargylic alkoxide,[13] which might prevent the facile proton abstraction from the aminophosphonium cation. Rather, the intermediate would attack the cationic phosphorus center, thus triggering the collapse of **1a**. To gain information about this presumably unique behavior of the β-nitro secondary propargylic alkoxide, we prepared the Henry adduct of **2a** and 2-nitropropane, 4-methyl-4-nitro-1-phenylpent-1-yn-3-ol, and treated it with the iminophosphorane preformed from **1c**·Cl and KO*t*Bu in tetrahydrofuran. ^{31}P NMR spectroscopic analysis of the resulting mixture at −98 °C revealed that the original sharp signal of iminophosphorane at $\delta = 47.2$ ppm had disappeared and a new broad signal was observed upfield ($\delta = 37.7$ ppm), corresponding to the tetraaminophosphonium cation,[10,12] which confirmed the formation of the corresponding aminophosphonium alkoxide by an acid–base reaction.[14] This observation is quite different to the result obtained with the benzaldehyde-derived Henry adduct, 2-methyl-2-nitro-1-phenylpropan-1-ol,[15] and supports our assumption regarding the influence of pK_a of the product **4**. Interestingly, our attempts to tackle this problem found that the catalyst decomposition pathway could be suppressed by adding *N*,*N*-dimethylformamide as a co-solvent and that the conversion of the starting ynal **2a** improved gradually as the concentration of *N*,*N*-dimethylformamide was increased, at the slight expense of stereoselectivity (Table 1, entries 2 and 3). This trend is probably because the overall polarity of the solvent system has a beneficial effect on the stabilization of the aminophosphonium alkoxide intermediate.[16] These optimized condition allowed us to investigate the effect of the aromatic substituents of **1** (Ar) on the diastereo- and enantioselectivities (Table 1, entries 4–7), and steric bulk, rather than the electronic effects of a *para* substituent on the aromatic groups, seemed to be important. Eventually, the use of **1d**·Cl, which contains *para*-tolyl groups, afforded quantitative formation of **4a** with an *anti*/*syn* ratio of greater than 20:1; the enantiomeric excess of the *anti* isomer was determined to be 98% (Table 1, entry 6).

Further experiments were then conducted to probe the substrate scope. The representative results listed in Table 2 show not only the generality of this reaction but also the intriguing relationship between the structures of the reactants and the concentration of *N*,*N*-dimethylformamide required for efficient catalysis. In the reactions of aromatic ynals, the electronic properties of the terminal aromatic substituents affected the estimation of the suitable amount of *N*,*N*-dimethylformamide, which again agrees with our conjecture that the pK_a of the in situ generated secondary propargylic alkoxide is related to the decomposition of **1**. For instance, the amount of *N*,*N*-dimethylformamide can be reduced in the coupling of *para*-anisyl-substituted ynal **2b** with **3a**, and should be increased when electron-withdrawing *para*-chlorophenyl-substituted ynal **2c** is employed (Table 2, entry 1 versus 2). In both cases, high levels of diastereo- and enantioselectivities were maintained. On the other hand, the addition of 5% (v/v) of *N*,*N*-dimethylformamide was generally sufficient for facilitating a smooth reaction with aliphatic ynals, and excellent stereoselectivities were uniformly obtained irrespective of their steric demands (Table 2, entries 3–6). In addition to nitroethane (**3a**), other nitroalkanes were used as the nucleophilic component by simply tuning the *N*,*N*-dimethylformamide concentration according to their polarity (Table 2, entries 7 and 8).

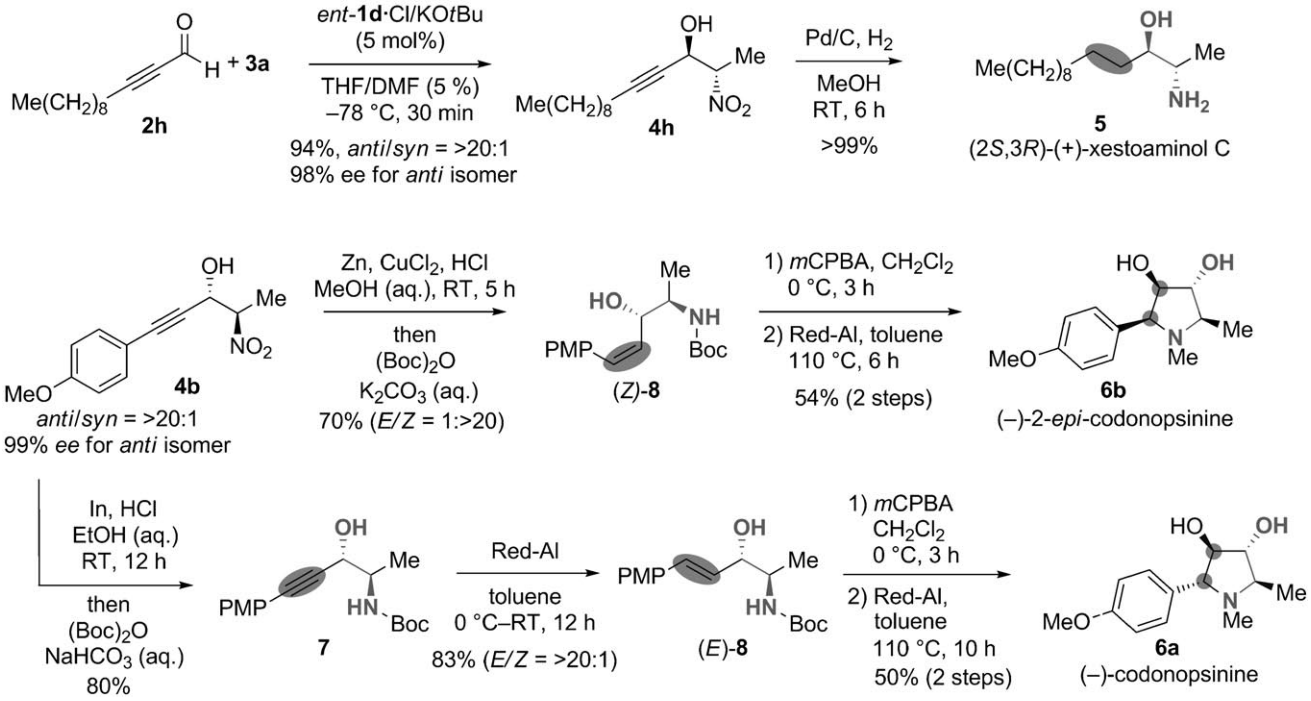
The synthetic utility of this catalytic, highly *anti*-selective and enantioselective direct Henry reaction of ynals was demonstrated by its application to the concise asymmetric syntheses of several naturally occurring, biologically active compounds (Scheme 2). The treatment of 2-dodecynal (**2h**) and nitroethane (**3a**) with 5 mol% of *ent*-**1d**·Cl/KO*t*Bu in tetrahydrofuran/*N*,*N*-dimethylformamide (95:5) at −78 °C for 30 minutes resulted in the predominant formation of *anti*-β-nitro propargylic alcohol **4h** (*anti*/*syn* = > 20:1) in 94% yield and 98% *ee*. Subsequent simultaneous reduction of the triple

Table 2: Substrate profile.[a]



Entry	R (**2**)	R′ (**3**)	DMF [v/v %]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]	**4**
1	*p*-MeO-C_6H_4 (**2b**)	Me (**3a**)	5	> 99	> 20:1	99	**4b**
2	*p*-Cl-C_6H_4 (**2c**)	Me (**3a**)	15	94	16:1	95	**4c**
3	$Me(CH_2)_5$ (**2d**)	Me (**3a**)	5	> 99	> 20:1	98	**4d**
4	cyclohexyl (**2e**)	Me (**3a**)	5	89	> 20:1	98	**4e**
5	$PhCH_2O(CH_2)_2$ (**2f**)	Me (**3a**)	5	> 99	14:1	98	**4f**
6	$tBuMe_2SiO(CH_2)_2$ (**2g**)	Me (**3a**)	5	98	> 20:1	> 99	**4g**
7	Ph (**2a**)	H (**3b**)	5	92	–	88	**4i**
8	Ph (**2a**)	Et (**3c**)	15	92	10:1	93	**4j**

[a] The reaction was performed with 0.20 mmol of **2** and 2.0 mmol of **3** in the presence of **1d**·Cl/KO*t*Bu (5 mol%) in THF/DMF (2.0 mL) at −78 °C under an argon atmosphere. [b] Yield of isolated product. [c] Diastereomeric ratio (d.r.) was determined by ^1H NMR (400 MHz) spectroscopic analysis of an aliquot of the crude reaction mixture. [d] Enantiomeric excess was determined by HPLC on a chiral stationary phase. Absolute and relative configurations of **4b** were determined from the establishment of the total synthesis (Scheme 2) and others were assigned by comparison to **4b** and **4h**.



Scheme 2. Short catalytic asymmetric syntheses of (2*S*,3*R*)-(+)-xestoaminol C (**5**) and (−)-codonopsinines (**6**). THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide, Boc = *tert*-butoxycarbonyl, PMP = *para*-methoxyphenyl, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, *m*CPBA = *meta*-chloroperbenzoic acid.

bond and the nitro functionality under the hydrogenation conditions enabled the two-step, catalytic asymmetric synthesis of the long-chain vicinal amino alcohol (2*S*,3*R*)-(+)-xestoaminol C (**5**),[17,18] which displays a reverse transcriptase inhibition. Attaining high *anti* selectivity in the asymmetric direct Henry reaction of aliphatic aldehydes remains an important problem to be solved in view of making a short synthetic route to saturated *anti*-vicinal amino alcohols, such as **5**. As such, Henry reaction is particularly desirable for accessing this class of chiral building blocks. Furthermore, the exposure of *para*-methoxyphenyl-substituted *anti*-**4b** (99% *ee*; Table 2, entry 1) to hydrochloric acid in the presence of indium metal gave rise to *N*-Boc-*anti*-amino propargylic alcohol **7**, leaving the triple bond intact, and it can be exclusively converted into the corresponding *E*-allylic alcohol (*E*)-**8** with Red-Al. Meanwhile, the use of zinc powder with a catalytic amount of cupric chloride in methanol followed by protection of the nitrogen atom with $(Boc)_2O$ selectively afforded *Z*-allylic alcohol (*Z*)-**8** in good yield. These simple procedures allow for the facile synthesis of various *E*- and *Z*-configured *anti*-amino allylic alcohols and thus offer a unique opportunity for rapidly constructing the structural and stereochemical frameworks of poly-functionalized molecules. Indeed, (*E*)-**8** and (*Z*)-**8** were effectively transformed into (−)-codonopsinine (**6a**)[19–21] and (−)-2-*epi*-codonopsinine (**6b**),[20b,c] respectively, where the olefin geometry of **8** was reflected in the C2 stereochemistry of the pyrrolidine skeleton. To the best of our knowledge, this is the first example of a catalytic asymmetric synthesis of these pyrrolidine alkaloids, which exhibit antibiotic and hypotensive activities without affecting the central nervous system.[22]

In conclusion, we have achieved the first efficient, highly *anti*-selective and enantioselective direct Henry reaction of ynals through the identification of *N*,*N*-dimethylformamide as a crucial co-solvent for facilitating the catalysis of chiral tetraaminophosphonium chlorides of type **1**·Cl. Moreover, we have clearly shown that the synthetic potential of this new method relies on the usefulness of optically active *anti*-β-nitro propargylic alcohols as a precursor for the preparation of a range of stereochemically uniform, saturated, and unsaturated *anti*-vicinal amino alcohols, including the accomplishment of the short syntheses of (2*S*,3*R*)-(+)-xestoaminol C (**5**) and (−)-codonopsinines (**6**). We believe this study greatly expands the potential of this approach, through the addition of an appropriate nucleophile to ynals, toward the preparation of synthetically valuable, optically active propargylic alcohols.

Experimental Section

Tetraaminophosphonium chloride **1d**·Cl (0.011 mmol, 6.90 mg) was treated with a solution of KO*t*Bu (1.0 M in THF; 0.010 mmol, 10.0 μL) in the presence of nitroethane (**3a**) (2.0 mmol, 145.0 μL) in 2.0 mL of THF contaminating DMF (5%) at −78 °C for 30 min. A 0.67 M solution of **2a** in THF/DMF (95:5; 0.20 mmol, 320 μL) was slowly added to the catalyst solution and allowed to stir for 30 min. Introduction of a 0.5 M toluene solution of trifluoroacetic acid (100 μL) at −78 °C was followed by pouring the reaction mixture into a saturated aqueous solution of NH_4Cl. Extractive workup with ethyl acetate was performed and the resulting organic phase was dried over Na_2SO_4. Evaporation of the volatiles gave a crude residue and the diastereomeric ratio was analyzed by 400 MHz ^1H NMR spectroscopy. Purification of the residue by column chromatography on

silica gel (*n*-hexane/ethyl acetate = 4:1) afforded **4a** in quantitative yield. Enantiomeric excess of the *anti* isomer was determined to be 98% *ee* by HPLC on a chiral stationary phase (Daisel Chiralpak AD-H, *n*-hexane/2-propanol/EtOH = 90:4.5:5.5, flow rate 1.0 mL min^{-1}).

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[15] When a slight excess of the Henry adduct of benzaldehyde and 2-nitropropane, 2-methyl-2-nitro-1-phenylpropan-1-ol, was added to a solution of the iminophosphorane in THF, a sharp signal at $\delta = 44.8$ ppm and a broad peak at $\delta = 40.2$ ppm were observed in the ^{31}P NMR spectrum at −98 °C.

[16] A similar ^{31}P NMR experiment with 4-methyl-4-nitro-1-phenylpent-1-yn-3-ol and the iminophosphorane in THF/DMF (5%) gave a sharper signal at $\delta = 35.8$ ppm. However, the precise role of DMF is still unclear at present.

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