Enantioselective Synthesis

Highly Enantioselective Construction of a Chiral Tertiary Carbon Center by Alkynylation of a Cyclic *N*-Acyl Ketimine: An Efficient Preparation of HIV Therapeutics**

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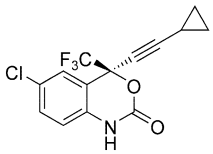
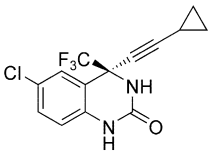
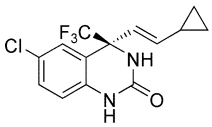
Recently great efforts have been made on developing methodology for generating secondary carbinols as well as secondary propargyl alcohol and propargyl amine by enantioselective alkynylation of aldehydes and aldimines.[1] However, the asymmetric synthesis of tertiary carbinols and carbinamines by addition of carbon nucleophiles to ketones and ketimines has experienced considerable frustration. Human immunodeficiency virus (HIV) is prone to mutation, which in turn leads to drug resistance. Dihydroquinazolines DPC 961 and DPC 083 are second-generation HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) with enhanced potency when compared to Efavirenz (Sustiva).[2] DPC 961 is currently undergoing clinical evaluation owing to its activity against wild-type HIV-1 and its increased potency toward the K103N-containing HIV as well as other NNRTI-resistant mutant viruses.[3]



Efavirenz (Sustiva)



DPC 961



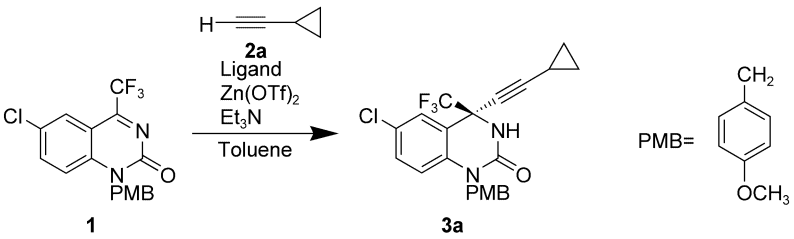
DPC 083

The challenge for synthesizing this class of NNRTIs is to form a tertiary carbinamine in an asymmetric manner. The syntheses of these compounds include diastereoselective 1,4-addition of a magnesium acetylide to 2(3*H*)-quinazolinone containing a chiral auxiliary substituent[4] or 1,2-enantioselective addition of a lithium acetylide to a cyclic *N*-acyl ketimines using lithium cinochona alkaloids[5] or lithium 4β-morpholinocaran-3α-ol as a chiral moderator.[6] The asymmetric addition step, for which the enantiomeric excess is consistently around 92% to 94%, requires the use of 3–5 equivalents of organometallic acetylide and low temperatures (−60 °C to −75 °C). In addition, the strongly basic conditions lead to decomposition of the product. Therefore, it is highly desirable to search for a practical asymmetric synthesis of this new class of dihydroquinazolinones which can then be scaled up to satisfy clinical demands.

The method involving a chiral additive appears to be the most advantageous because it avoids the step involving auxiliary attachment and removal and holds the potential for direct recovery and reuse of the unchanged chiral reagent. We have been developing a practical enantioselective preparation of chiral alchohols with C–C bond formation by alkynylation of a carbonyl group and activation of the C–H bond in terminal alkynes by a combination of zinc salt, tertiary amine, and a readily available chiral amino alcohol as the ligand.[7] We were interested in studying the enantioselective alkynylation of the cyclic *N*-acyl ketimine **1** (see Scheme 1) using a chiral amino alcohol as ligand by activation of the C–H bond in terminal alkynes.

To examine the possibility of alkynylation of ketimine **1** with a terminal acetylene, the reaction was carried out in the presence of zinc salts and triethylamine without a chiral amino alcohol as ligand. Treatment of **1** with one equivalent of cyclopropyl acetylene (**2a**), $Zn(OTf)_2$, and triethylamine gave the racemic adduct **3a** in 95% yield at room temperature after 10 h (Scheme 1). The use of $ZnCl_2$ instead of $Zn(OTf)_2$ could not promote the reaction. This result stimulated us to investigate the asymmetric alkynylation of the ketimine using a chiral ligand.

We examined the alkynylation of the ketimine with derivatives of ephedrine as ligands since *N*-methyl ephedrine (**4a**)[8] and (1*S*, 2*S*)-**5a**[7b] have been successfully used in the asymmetric alkynylation of aldehydes



Scheme 1. The alkynylation of ketimine **1** with cyclopropylacetylene. OTf = trifluoromethanesulfonate.

with a terminal acetylene. However, the derivatives of ephedrine ligands **4a** and **4b** (Bn = benzyl) gave very poor enantioselectivity and low yields in the alkynylation reaction, even when 1.1 equivalents of ligand and zinc triflate were used (Table 1, entries 1 and 2). In consideration of cost and availability, we decided to improve the enantioselectivity by using derivatives of chloramphenicol base. Both enantiomers of chloramphenicol bases are easily obtained from commercial chloramphenicol synthesis. In the subsequent investigations, a series of derivatives (**5a**–**5d**, **6**; TMDMS = *tert*-

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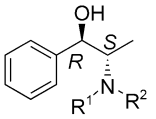
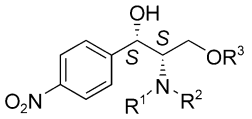


4a: R^1=Me;R^2=Me
4b: R^1=Me; R^2=Bn



5a: R^1=Me; R^2=Me; R^3=TMDMS
5b: R^1=Me; R^2=Me; R^3=Tr
5c: R^1=Me; R^2=Me; R^3=*t*Bu
5d: R^1=Me; R^2=Bn; R^3=Tr

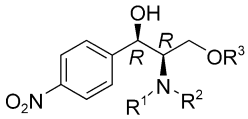


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Table 1: Effect of the chiral ligand on the selectivity of the alkynylation of ketimine **1** with cyclopropylacetylene (see Scheme 1).[a]

Entry	Ligand (equiv)	$Zn(OTf)_2$ [equiv]	NEt_3 [equiv]	*T* [°C]	*t* [h]	Yield of **3a** [%][b]	*ee* **3a** [%][c]	Config. of **3a**[d]
1	**4a** (1.1)	1.1	2.5	25	14	34	44.1	(−)-*S*
2	**4b** (1.1)	1.1	2.5	25	10	24	23.5	(+)-*R*
3	(*S*,*S*)-**5a** (1.1)	1.1	2.5	25	10	95	99.1	(+)-*R*
4	(*S*,*S*)-**5b** (1.1)	1.1	2.5	25	10	93	98.0	(+)-*R*
5	(*S*,*S*)-**5c** (1.1)	1.1	2.5	25	10	91	99.3	(+)-*R*
6	(*S*,*S*)-**5d** (1.1)	1.1	2.5	25	10	90	42.1	(−)-*S*
7	(*S*,*S*)-**5c** (1.1)	1.1	1.5	60	10	64	99.0	(+)-*R*
8	(*S*,*S*)-**5c** (1.1)	1.1	2.5	25	6	95	99.3	(+)-*R*
9	(*R*,*R*)-**6** (1.1)	1.1	2.5	25	6	95	99.2	(−)-*S*

[a] All reactions were performed on 0.5-mmol scale. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase, Chiralcel OD, *i*PrOH/hexane 10/90, 0.7 mL min^{-1}, 254 nm. [d] The absolute configuration is based on comparison with the literature.[4a, 9]

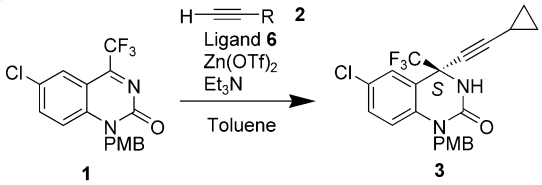
butyldimethylsilyl, Tr = triphenylmethyl) were evaluated as ligands in an effort to obtain more efficient enantioselective alkynylation.

The substituents on the 2-nitrogen and 3-oxygen atoms greatly affected the enantioselectivity of the reaction. The derivatives of chloramphenicol base with an amino group bearing two methyl groups and a C3-oxygen atom attached to a tertiary carbon atom gave excellent enantioselectivities and yields (Table 1, entries 3–5). When one of the amino substituents was changed to benzyl, the enantioselectivity was severely decreased (entry 6). The inexpensive yet effective chiral ligand **5c** and its enantiomer (1*R*, 2*R*)-**6** gave excellent enantioselectivities in the alkynylation reactions (entries 8 and 9). Thus treatment of the cyclic *N*-acyl ketimine **1** with 1.1 equivalents of cyclopropylacetylene, 1.1 equivalents of $Zn(OTf)_2$, 1.1 equivalents of (1*R*, 2*R*)-**6**, and 2.5 equivalents of Et_3N in toluene at room temperature for 6 h provided adduct **3a** (isolated in 95% yield with 99.2% *ee*). Reducing the amount of Et_3N to 1.5 equiv caused a decrease in the chemical yield (entry 7). Removal of the *p*-methoxybenzyl (PMB) group in (−)-**3a**[9] with ceric ammonium nitrate gave (−)-(*S*)-DPC 961 with a specific rotation of $[\alpha]_D^{20} = -63$ (c = 0.275, MeOH), which is identical to the reported value.[4a] Therefore, the stereochemistry of the adduct (−)-**3a** obtained using (1*R*, 2*R*)-**6** as the ligand was assigned the *S* configuration.

In a brief exploration of the scope of this novel asymmetric reaction, other acetylenes were studied by using (1*R*, 2*R*)-**6** as the ligand. All of the phenyl-, alkyl-, and silyl-substituted terminal alkynes gave excellent enantioselectivities (up to 99.5% *ee*) and high yields (Table 2). When the reaction was run on a 100-gram scale, **3a** was obtained in 96% yield and with 99.1% *ee* (Table 2, entry 1). Simple recrystallization from heptane afforded **3a** in 95% yield with over 99% *ee*. The chiral amino alcohol ligand **6** could be recovered unchanged (90% recovery) by basification of the acid aqueous extracts. The recovered ligand was of suitable purity to be recycled directly (entry 2). Acetylenes containing bulky substituents gave the adducts with up to 99.5% *ee* (entries 6–8).

In conclusion, a novel and highly enantioselective alkynylation of cyclic ketimine has been developed for the synthesis of tertiary amines in excellent yield and with high enantioselectivity. This approach has provided an efficient method for the synthesis of the important second-generation non-nucleoside reverse transcriptase inhibitors. The advantages of the enantioselective reaction include the following: 1) only 1.1 equivalents of acetylene is required; 2) the reaction is carried out under standard conditions, avoiding low temperatures and harmful reagents for generating organometallic acetylide; and 3) the chiral ligand based on a derivative of chloramphenicol is easily prepared from a pharmaceutical commodity source, and can be recovered and

Table 2: Effect of the terminal alkynes on the selectivity in the alkynylation of ketimine **1**.[a]



1 **3**

Entry	**2** (R=)	*T* [°C]	*t* [h]	Product **3** (yield [%])[b]	*ee* of **3** [%][c]
1	**2a** (cyclopropyl)	25	6	**3a** (96)	99.1[d]
2	**2a** (cyclopropyl)	25	10	**3a** (95)	99.1[e]
3	**2b** 2-phenylethyl)	25	12	**3b** (73)	98.2
4	**2c** (phenyl)	25	8	**3c** (88)	98.2
5	**2d** (*tert*-butyl)	30	15	**3d** (63)	98.5
6	**2e** (*n*-butyl)	25	6	**3e** (92)	>99.5
7	**2f** (trimethylsilyl)	25	8	**3f** (87)	>99.5
8	**2g** (cyclopentylmethyl)	25	6	**3g** (86)	>99.5

[a] All reactions were performed on 0.5-mmol scale, unless otherwise stated. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase, Chiralcel OD or AD. [d] The reaction was performed on a 100-gram scale. [e] The chiral ligand was recycled for three runs.

reused without decreasing enantioselectivity and chemical yield.

Experimental Section

In a typical experiment, cyclopropyl acetylene (**2a**; 73 mg, 1.1 mmol) was added under an argon atmosphere over 2 h at 25 °C to a solution of $Zn(OTf)_2$ (396 mg, 1.1 mmol), (1*R*, 2*R*)-**6** (326 mg, 1.1 mmol), and triethylamine (252 mg, 2.5 mmol) in dried toluene (1 mL). Then ketimine **1** (369 mg, 1 mmol) was added. After 6 h the mixture was cooled to 0 °C, and 6 N HCl (10 mL) was added. The mixture was extracted with EtOAc (3 × 5 mL; Ac = acetyl). The combined organic layer was washed with 6 N HCl (3 × 5 mL), saturated Na_2CO_3 aqueous, and brine and then dried with Na_2SO_4. After removal of solvent under vacuum, the residue was purified by flash chromatography on silica gel (hexane/EtOAc 6/1) to afford **3a** (412 mg, 95 % yield, 99.3 % *ee*). $[\alpha]_D^{20} = -74.1$ ($c = 0.6$ in methanol); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 9.00$ (s, 1H), 7.46 (br s, 1H), 7.41 (dd, $J = 2.8$ and 8.9 Hz, 1H), 7.13 (d, $J = 8.2$ Hz, 2H), 6.96 (d, $J = 8.7$ Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.12 (d, $J = 16.4$ Hz, 1H), 4.93 (d, $J = 16.5$ Hz, 1H), 3.69 (s, 3H), 1.52 (m, 1H), 0.93–0.87 (m, 2H), 0.77–0.72 ppm (m, 2H); ^{19}F NMR (282 MHz, [D$_6$]DMSO): $\delta = -81.3$ ppm (s, 3F); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 158.3$, 151.2, 136.6, 130.8, 128.4, 127.6, 127.5, 125.8, 123.8 (q, $J = 289$ Hz), 117.1, 116.5, 114.0, 91.8, 68.0, 57.7 (q, $J = 32$ Hz), 54.9, 43.9, 8.3, 8.2, −1.2 ppm; MS (EI) $m/e = 434$ (M^+, 6.6), 365(13.8), 121(100); HR-EI-MS calcd for $C_{22}H_{18}ClF_3N_2O_2$: 434.1009, found: 434.0967.

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Keywords: alkynes · amino alcohols · drug design · ketimines · zinc

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[9] The specific rotation of **3a** {$[\alpha]_D^{25} = -31.6$ ($c = 0.6$, MeOH)} reported in reference [4a] was not corrected. The reaction with (1*R*, 2*R*)-**6** as ligand gave (−)-(*S*)-**3a** with a specific rotation $[\alpha]_D^{20} = -74.1$ ($c = 0.6$, MeOH), while using (1*S*, 2*S*)-**5c** gave (+)-(*R*)-**3a** with a specific rotation $[\alpha]_D^{20} = +74.3$ ($c = 0.6$, MeOH).

