Isomerization of Chiral Non-Racemic α-Substituted Propargylic Amines to Terminal Acetylenes

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Various α-substituted propargylamines, prepared in three steps from (*R*)-phenylglycinol, are readily isomerized at 0 °C with KAPA to form terminal acetylenic amines, without any detectable epimerization of the chiral center, as already observed for propargyl alcohols. Enantiomerically pure primary α-substituted alkynylamines can be easily obtained in two steps after removal of the ferrocenylmethyl protective group and oxidative cleavage of the chiral appendage.

Introduction

While ω-propargylic alcohols are common synthetic intermediates in natural product synthesis, their nitrogenated counterparts have been less studied.[1] The lack of a simple and straightforward preparation of ω-propargylic amines is probably one of the reasons for this fact.

One of the simplest ways of synthesizing alcohols bearing a terminal acetylenic function is the isomerization of internal triple bonds to terminal acetylenes with potassium 3-aminopropylamide (KAPA).[2] Furthermore, the use of this "acetylene zipper" with an optically active secondary propargylic alcohol enables the rapid isomerization of the acetylene unit away from the hydroxy center, *without racemization*.[3] Although the usefulness of this reaction has been proved both in several natural product total syntheses[4] and for the efficient preparation of polydeuterated long chain derivatives,[5] it has been mainly carried out only with dialkylacetylenes or alcohols.

We recently described a new access to enantiomerically pure α-substituted propargylic amines via the nucleophilic opening of chiral non-racemic oxazolidines with mixed organoaluminum reagents.[6] We report here that the isomerization of chiral α-substituted propargylic amines to terminal acetylenic compounds by KAPA also proceeds in an efficient manner, without racemization.

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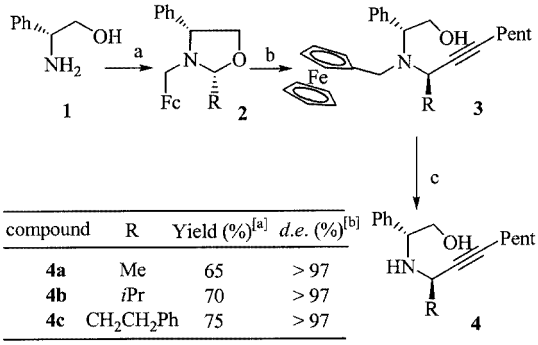
Results and Discussion

The chiral, non-racemic α-substituted amino alcohols **4a**−**c** were prepared from (*R*)-phenylglycinol **1** using our previously reported procedures (Scheme 1).

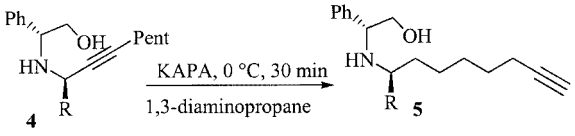


compound	R	Yield (%)[a]	*d.e.* (%)[b]
4a	Me	65	> 97
4b	*i*Pr	70	> 97
4c	CH_2CH_2Ph	75	> 97

[a] Isolated yield from **1**. [b] Determined by ^1H NMR.

Scheme 1. Reagents and conditions: (a) (i) FcCHO, $NaBH_4$, MeOH; (ii) RCHO, $MgSO_4$, THF; (b) PentCCAl(*i*Bu)$_2$·Et_3N, $AlMe_3$, toluene, 0 °C; (c) CH_2Cl_2, TFA 5%, Et_3SiH, 0 °C to room temp.

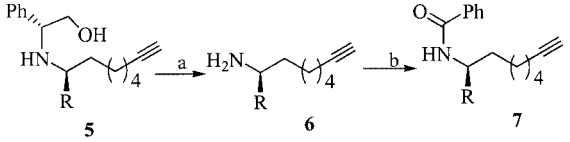
The clean preparation of KAPA was performed according to the procedure described by Cossy and co-workers.[7] The best results were obtained when this reagent was freshly prepared and used immediately. The isomerization reaction was carried out in 1,3-diaminopropane as solvent at 0 °C (Scheme 2). The terminal acetylenic amino alcohols **5a**−**c** were obtained in less than 30 min, in moderate to good yields, without any detectable epimerization.[8]



compound	R	Yield (%)
5a	Me	77
5b	*i*Pr	62
5c	CH_2CH_2Ph	55

Scheme 2

Final deprotection leading to the primary amines was performed by oxidative cleavage of the amino alcohols.[6,9,10] Although these compounds proved to be more stable than the previously described α-substituted propargylamines, they are hygroscopic and were therefore protected and stored as their benzamides **7a**−**c** (Scheme 3).

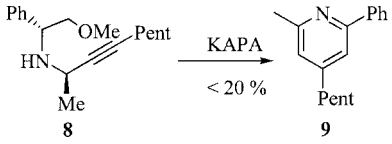


compound	R	Yield (%)[a]
7a	Me	85
7b	*i*Pr	67
7c	CH_2CH_2Ph	59

[a] Isolated overall yield from **5**

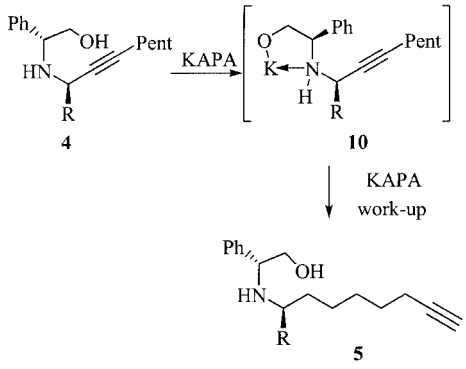
Scheme 3. Reagents and conditions: (a) (i) H_5IO_6, $MeNH_2$; (ii) HCl/MeOH, (iii) K_2CO_3; (b) PhCOCl, iPr_2EtN, CH_2Cl_2

All the attempts to isomerize N-protected compounds **3a**−**c** led to extensive degradation, probably because of the base-sensitive ferrocenyl moiety.[11] The presence of the free hydroxyl group proved to be essential for achieving completion of the reaction. Indeed, when submitted to KAPA isomerization, the O-protected compound **8** led to a complex mixture of by-products, among which the rearranged derivative **9** could be separated and characterized in less than 20% yield (Scheme 4).[12]



Scheme 4

In the case of the isomerization of propargyl alcohols, the absence of racemization was explained by the quantitative formation of the negatively charged alkoxide, leading to a decrease of the acidity of the neighboring protons, and therefore to the protection of the base-sensitive stereogenic center. In this study, the formation of the potassium alkoxide avoids epimerization and degradation by protecting the base-sensitive protons α to the nitrogen atom, probably by the formation of a five-membered chelate **10** with nitrogen (Scheme 5).



Scheme 5

Conclusion

We have described a new application of KAPA-induced isomerization, leading in a simple and efficient way to optically pure α-substituted amines bearing a terminal acetylenic function. These compounds could be useful synthetic intermediates for the elaboration of cyclic or acyclic enantiopure amino derivatives.

Experimental Section

General Procedures: NMR spectra were obtained at 300 MHz (^1H field value) on a Bruker AC 300. Routine infrared spectra (IR) were recorded neat on a Perkin−Elmer 1600 spectrophotometer as thin films, unless otherwise stated. Optical rotation measurement were performed using a 1 dm path-length cell. Elemental analyses were obtained from the Service de microanalyse of the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France. Product purification was performed by flash chromatography on silica gel (Merck, 230−400 mesh). Mass spectral data were recorded in the chemical ionization mode (NH_3) on a AEI MS-9 spectrometer. High-resolution mass spectra were obtained on a Kratos MS 80RF spectrometer.

General Procedure for the Preparation of Propargylamines 3: The preparation of compound **3b** is representative. Freshly distilled triethylamine (920 μL, 6.6 mmol) was slowly added to a DIBAL solution (1 M in toluene, 6.3 mL, 6.3 mmol) under argon. The solution was stirred for 15 min, cooled to 0 °C and heptyne (1.6 mL, 12.2 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred until hydrogen evolution stopped. It was then cooled to 0 °C and a solution of oxazolidine **2b** (1.17 g, 3.0 mmol) in toluene (10 mL) was slowly added over 30 min, followed by Me_3Al solution (2 M in heptane, 3.3 mL, 6.6 mmol). The solution was stirred for another 30 min at 0 °C and

allowed to reach room temperature. The mixture was slowly poured onto a cold solution of saturated Rochelle's salts and, after vigorous stirring, the aqueous layer was extracted twice with diethyl ether (25 mL each). The organic layer was dried over anhydrous $MgSO_4$, the solvent was evaporated and the crude residue was purified by column chromatography (silica gel: 9:1 cyclohexane/ethyl acetate) to give **3b** (1.21 g, 2.37 mmol, 83% from **1**).

(*1R,2R*)-2-[Ferrocenylmethyl(1-methyloct-2-ynyl)amino]-2-phenylethanol (3a): Red-brown oil. $[\alpha]_D = +8.8$ ($c = 1.0$, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, $J = 7.1$ Hz, 3 H), 1.12 (d, $J = 6.9$ Hz, 3 H), 1.30−1.43 (m, 4 H), 1.44−1.56 (m, 2 H), 2.19 (td, $J = 7.1$, 1.9 Hz, 2 H), 2.71 (br. s, 1 H), 3.59 (d, $J = 14.1$ Hz, 1 H), 3.75 (d, $J = 14.1$ Hz, 1 H), 3.78−3.89 (m, 3 H), 3.96−4.14 (m, 5 H), 4.09 (s, 5 H), 4.19 (d, $J = 11.6$ Hz, 2 H), 7.35−7.24 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.5, 20.9, 22.0, 28.4, 30.9, 45.3, 46.5, 61.4, 64.0, 67.6−69.6, 81.2, 84.6, 86.3, 127.1−128.4, 139.7 ppm. IR (neat): $\tilde{\nu}$ = 3452 cm^{-1}, 3090, 2928, 2859, 1601. MS (CI, NH_3): *m/z* = 458 [MH^+]. $C_{28}H_{35}FeNO$ (457.4): C 73.52, H 7.71, N 3.06; found C 73.33, H 7.84, N 3.02.

(*1R,2R*)-2-[Ferrocenylmethyl(1-isopropyloct-2-ynyl)amino]-2-phenylethanol (3b): Orange oil. $[\alpha]_D = +48$ ($c = 1.2$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.64 (d, $J = 6.5$ Hz, 3 H), 0.91 (m, 6 H), 1.36 (m, 4 H), 1.48 (m, 2 H), 1.67 (m, 1 H), 2.19 (td, $J = 7.0$, 1.7 Hz, 2 H), 2.50 (br. s., 1 H), 3.02 (dd, $J = 10.0$, 1.4 Hz, 1 H), 3.65 (d, $J = 14.0$ Hz, 1 H), 3.72 (d, $J = 14.0$ Hz, 1 H), 3.98 (m, 2 H), 4.13 (m, 9 H), 7.22 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.6, 19.9, 20.5, 22.1, 28.6, 31.0, 32.2, 46.4, 59.0, 61.7, 64.9, 67.4, 70.3, 86.3, 127.0, 127.8, 128.8, 139.7 ppm. IR (neat): $\tilde{\nu}$ = 3427 cm^{-1}, 3085, 1598, 1490. MS (CI, NH_3): *m/z* = 486 [MH^+]. $C_{30}H_{39}FeNO$ (485.5): calcd. C 74.22, H 8.10, N 2.89; found C 73.97, H 8.35, N 2.79.

(*1R,2R*)-2-[Ferrocenylmethyl(1-phenethyloct-2-ynyl)amino]-2-phenylethanol (3c): red-brown oil. $[\alpha]_D = +9.4$ ($c = 1.1$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, $J = 7.0$ Hz, 3 H), 1.32−1.40 (m, 4 H), 1.44−1.53 (m, 2 H), 1.64−1.76 (m, 2 H), 2.21 (dt, $J = 6.9$, 2.0 Hz, 2 H), 2.43−2.50 (m, 2 H), 2.59 (br. s, 1 H), 3.53−3.61 (m, 1 H), 3.63 (d, $J = 14.0$ Hz, 1 H), 3.77 (d, $J = 14.0$ Hz, 1 H), 3.82−3.92 (m, 1 H), 3.98−4.09 (m, 4 H), 4.07 (s, 5 H), 4.11−4.13 (m, 1 H), 4.20−4.22 (m, 1 H), 6.96−7.29 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.6, 22.1, 28.5, 31.0, 32.7, 36.6, 45.9, 51.2, 61.5, 64.5, 67.8, 68.4, 69.6, 69.9, 80.1, 85.8, 86.3, 125.6, 127.2, 128.3−129.1, 139.6 141.7 ppm. IR (neat): $\tilde{\nu}$ = 3446 cm^{-1}, 3086, 3027, 2926, 2858, 1602, 1495, 1454, 1266, 1231, 1106, 1024. *m/z* = 548 [MH^+]. $C_{35}H_{41}FeNO$ (547.6): C 76.77, H 7.55, N 2.56; found C 76.47, H 7.36, N 2.57.

General Procedure for the Preparation of Propargylamines 4: The preparation of compound **4b** is representative. Triethylsilane (1.2 mL, 7.5 mmol) and a solution of trifluoroacetic acid (1.2 mL, 15 mmol) in dichloromethane (15 mL) were added successively to a cold (0 °C) solution of propargylamine **3b** (1.45 g, 3.0 mmol) in dry dichloromethane (10 mL). The reaction mixture was allowed to reach room temperature, stirred for 2 h and quenched with water and a saturated aqueous solution of K_2CO_3. The aqueous layer was extracted twice with dichloromethane, the organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude residue was purified by column chromatography (silica gel, two successive elutions: 9:1 cyclohexane/ethyl acetate then 1:1 cyclohexane/ethyl acetate) to give **4b** (723 mg, 84%).

(*1R,2R*)-2-(1-Methyloct-2-ynylamino)-2-phenylethanol (4a): Oil. $[\alpha]_D = -13.6$ ($c = 1.25$, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, $J = 7.0$ Hz, 3 H), 1.28 (d, $J = 6.6$ Hz, 3 H), 1.28−1.37 (m, 4 H), 1.38−1.46 (m, 2 H), 2.08 (td, $J = 6.9$, 2.0 Hz, 2 H), 2.48 (br. s, 2 H), 3.52 (qt, $J = 6.6$, 2.0 Hz, 1 H), 3.57 (dd, $J = 10.9$, 6.7 Hz, 1 H), 3.71 (dd, $J = 10.9$, 4.7 Hz, 1 H), 3.98 (dd, $J = 6.7$, 4.7 Hz, 1 H), 7.24−7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.5, 22.0, 22.4, 28.4, 30.9, 43.0, 61.4, 65.4, 82.2, 83.1, 127.2−128.4, 141.1 ppm. IR (neat): $\tilde{\nu}$ = 3330 cm^{-1}, 2931, 2859, 1603. MS (CI, NH_3): *m/z* = 260 [MH^+]. $C_{17}H_{25}NO{\cdot}1/2H_2O$ (258.4): calcd. C 76.08, H 9.71, N 5.22; found C 76.48, H 9.35, N 5.03.

(*1R,2R*)-2-(1-Isopropyloct-2-ynylamino)-2-phenylethanol (4b): Oil. $[\alpha]_D = -13$ ($c = 1.15$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, $J = 7.0$ Hz, 3 H), 0.97 (d, $J = 6.6$ Hz, 3 H), 0.99 (d, $J = 6.6$ Hz, 3 H), 1.31 (m, 4 H), 1.42 (m, 2 H), 1.83 (m, 1 H), 2.11 (td, $J = 6.6$, 2.6 Hz, 2 H), 3.22 (m, 1 H), 3.53 (dd, $J = 10.7$, 6.2 Hz, 1 H), 3.72 (dd, $J = 10.7$, 4.7 Hz, 1 H), 3.99 (dd, $J = 6.2$, 4.7 Hz, 1 H), 7.29 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 17.4, 18.5, 19.6, 22.0, 28.4, 30.9, 32.2, 54.3, 61.8, 65.1, 79.7, 84.8, 127.3−128.5, 141.6 ppm. IR (neat): $\tilde{\nu}$ = 3349 cm^{-1}, 2930, 2871, 2244. MS (CI, NH_3): *m/z* = 288 [MH^+].

(*1R,2R*)-2-(1-Phenethyloct-2-ynylamino)-2-phenylethanol (4c): Oil. $[\alpha]_D = -57.5$ ($c = 0.8$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, $J = 7.0$ Hz, 3 H), 1.27−1.39 (m, 4 H), 1.39−1.48 (m, 2 H), 1.78−2.02 (m, 2 H), 2.11 (td, $J = 6.9$, 2.0 Hz, 2 H), 2.12 (m, 2 H), 2.67−2.88 (m, 2 H), 3.40 (ddt, $J = 7.7$, 5.7, 2.0 Hz, 1 H), 3.54 (dd, $J = 10.8$, 6.6 Hz, 1 H), 3.70 (dd, $J = 10.8$, 4.7 Hz, 1 H), 3.97 (dd, $J = 6.6$, 4.7 Hz, 1 H), 7.15−7.34 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.6, 22.2, 28.4, 31.0, 32.1, 37.7, 47.8, 61.6, 65.3, 81.0, 84.6, 125.8−128.4, 141.4, 141.7 ppm. IR (neat): $\tilde{\nu}$ = 3321 cm^{-1}, 3026, 2930, 2859, 1603, 1495, 1454, 1330, 1107, 1030. MS (CI, NH_3): *m/z* = 350 [MH^+]. $C_{24}H_{31}NO{\cdot}1/4H_2O$ (348.5): calcd. C 80.89, H 8.76, N 4.10; found C 80.69, H 8.58, N 3.77.

General Procedure for the Isomerization of Propargylamines 4: The preparation of compound **5b** is representative. 1,3-Diaminopropane (8 mL) was added to potassium hydride (328 mg, 8.2 mmol) at 0 °C under argon. The suspension was stirred at room temperature for 30 min and cooled to 0 °C. Propargylamine **4b** (470 mg, 1.64 mmol) in 1,3-diaminopropane (2 mL) was then added slowly, the reaction mixture was stirred for 30 min and treated with a saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was extracted twice with diethyl ether, the organic layers were washed with a saturated aqueous sodium chloride solution, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude residue was purified by column chromatography (silica gel, 9:1 cyclohexane/ethyl acetate) to give **5b** (291 mg, 62%).

(*1R,2R*)-2-(1-Methyloct-7-ynylamino)-2-phenylethanol (5a): Oil. $[\alpha]_D = -59$ ($c = 1.15$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, $J = 6.2$ Hz, 3 H), 1.29 (m, 6 H), 1.47 (m, 2 H), 1.89 (t, $J = 2.6$ Hz, 1 H), 2.12 (td, $J = 6.9$, 2.6 Hz, 2 H), 2.24 (m, 1 H) 2.51 (br. s, 2 H) 3.48 (dd, $J = 10.6$, 8.6 Hz, 1 H), 3.67 (dd, $J = 10.6$, 4.5 Hz, 1 H), 3.87 (dd, $J = 8.6$, 4.5 Hz, 1 H), 7.29 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 19.8, 25.3, 28.2, 28.6, 37.8, 49.3, 61.2, 66.7, 68.1, 84.5, 127.1, 127.3, 128.4, 141.1 ppm. IR (neat): $\tilde{\nu}$ = 3300 cm^{-1}, 2934, 2858. MS (CI, NH_3): *m/z* = 260 [MH^+]. $C_{17}H_{25}NO$ (259.4): calcd. C 78.72, H 9.71, N 5.40; found C 78.53, H 9.87, N 5.36.

(*1S,2R*)-2-(1-Isopropyloct-7-ynylamino)-2-phenylethanol (5b): Oil. $[\alpha]_D = -74$ ($c = 1.05$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, $J = 6.7$ Hz, 3 H), 0.88 (d, $J = 6.7$ Hz, 3 H), 1.15 (m, 6 H), 1.38 (m, 2 H), 1.85 (m, 1 H), 1.90 (t, $J = 2.6$ Hz, 1 H), 2.06 (td, $J = 6.9$, 2.6 Hz, 2 H), 2.18 (br. s., 2 H), 2.25 (m, 1 H) 3.47 (dd,

J = 10.4, 8.8 Hz, 1 H), 3.64 (dd, J = 10.4, 4.5 Hz, 1 H), 3.78 (dd, J = 8.8, 4.5 Hz, 1 H), 7.28 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 18.2, 18.7, 25.7, 28.2, 28.6, 29.2, 29.9, 59.2, 62.1, 66.4, 68.1, 84.5, 127.2, 127.4, 128.4, 141.5 ppm. IR (neat): ṽ = 3307 cm^{-1}, 2935, 2863. MS (CI, NH_3): m/z = 288 [MH^+]. $C_{19}H_{29}NO$ (287.4): calcd. C 79.39, H 10.17, N 4.87; found C 79.37, H 10.29, N 4.79.

(*1S,2R*)-2-(1-Phenethyloct-7-ynylamino)-2-phenylethanol (5c): Oil. $[\alpha]_D$ = −89 (c = 1.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (m, 8 H), 1.71 (m, 2 H), 1.92 (t, J = 2.6 Hz, 1 H), 2.18 (td, J = 7.0, 2.6 Hz, 2 H), 2.24 (br. s., 2 H), 2.60 (m, 3 H) 3.49 (dd, J = 10.6, 8.7 Hz, 1 H), 3.64 (dd, J = 10.6, 4.5 Hz, 1 H), 3.79 (dd, J = 8.7, 4.5 Hz, 1 H), 7.24 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 24.1, 28.3, 28.7, 31.3, 34.4, 35.4, 53.6, 61.7, 66.5, 68.1, 84.5, 125.6, 128.5, 141.3, 142.5 ppm. IR (neat): ṽ = 3300 cm^{-1}, 2932, 2857, 1602. MS (CI, NH_3): m/z = 350 [MH^+]. $C_{24}H_{31}NO$ (349.5): calcd. C 82.47, H 8.94, N 4.01; found C 82.31, H 9.13, N 4.06.

General Procedure for the Oxidative Cleavage: The preparation of compound **6b** is representative. Aqueous methylamine (40% solution, 1 mL) and, slowly, an aqueous solution of periodic acid (845 mg, 3.72 mmol in 7.5 mL H_2O) were added to a cold (0 °C) solution of propargylamine **5b** (410 mg, 1.43 mmol) in methanol (8.5 mL). The turbid solution was stirred at room temperature for 3 h and became limpid. The reaction mixture was extracted twice with diethyl ether. After evaporation of the diethyl ether, the methanolic solution was treated with 3 M aqueous HCl, the methanol was evaporated and the aqueous phase was washed twice with diethyl ether. The aqueous phase was then treated with an aqueous saturated solution of K_2CO_3 to reach pH 9 and extracted twice with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and the primary amine was purified by column chromatography (silica gel, ethyl acetate) to give **6b** (222 mg, 93%).

(*R*)-1-Methyloct-7-ynylamine (6a): Oil. $[\alpha]_D$ = −8 (c = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.6 Hz, 3 H), 1.36 (m, 6 H), 1.53 (m, 2 H), 1.66 (br. s, 2 H), 1.93 (t, J = 2.6 Hz, 1 H), 2.18 (td, J = 6.6, 2.6 Hz, 2 H), 2.87 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 23.9, 25.8, 28.3, 28.7, 39.9, 46.8, 68.1, 84.6 ppm. IR (neat): ṽ = 3306 cm^{-1}, 2931, 2857, 2116. MS (CI, NH_3): m/z = 140 [MH^+].

(*S*)-1-Isopropyloct-7-ynylamine (6b): Oil. $[\alpha]_D$ = −18 (c = 1.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 1.44 (m, 11 H), 1.92 (t, J = 2.6 Hz, 1 H), 2.19 (td, J = 6.6, 2.6 Hz, 2 H), 2.52 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 18.3, 19.1, 26.0, 28.4, 28.8, 33.1, 34.4, 56.4, 68.1, 84.5 ppm. IR (neat): ṽ = 3308 cm^{-1}, 2933, 2860, 2116. MS (CI, NH_3): m/z = 168 [MH^+].

(*S*)-1-Phenethyl-7-ynylamine (6c): Amorphous − $[\alpha]_D$ = +5 (c = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (m, 11 H), 1.72 (m, 1 H), 1.95 (t, J = 2.6 Hz, 1 H), 2.19 (td, J = 7.0, 2.6 Hz, 2 H), 2.69 (m, 3 H), 7.17 (m, 3 H), 7.28 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 25.5, 28.3, 28.7, 32.5, 37.9, 39.8, 50.7, 68.1, 84.5, 125.6, 128.3, 142.3 ppm. IR (neat): ṽ = 3303 cm^{-1}, 3026, 2931, 2856, 2116. MS (CI, NH_3): m/z = 230 [MH^+].

General Procedure for the Preparation of Benzamides 7: The preparation of compound **7b** is representative. Freshly purified primary amine **6b** (120 mg, 0.72 mmol) was dissolved in dichloromethane (10 mL). Benzoyl chloride (337 μL, 2.9 mmol) and triethylamine (407 μL, 2.9 mmol) were added and the reaction mixture was stirred overnight, and then washed with water. The organic layer was dried over anhydrous $MgSO_4$ and the solvents evaporated. The crude residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 7:3) to give **7b** (141 mg, 67% from **5b**).

(*R*)-*N*-(1-Methyloct-7-ynyl)benzamide (7a): White solid. M.p. 57 °C. $[\alpha]_D$ = −13 (c = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, J = 6.6 Hz, 3 H), 1.44 (m, 8 H), 1.92 (t, J = 2.6 Hz, 1 H), 2.17 (td, J = 6.9, 2.6 Hz, 2 H), 4.17 (m, 1 H) 6.28 (d, J = 8.0 Hz, 1 H), 7.39 (m, 3 H), 7.68 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 20.8, 25.5, 28.2, 28.4, 36.7, 45.5, 68.1, 84.4, 126.7, 128.3, 131.1, 134.8, 166.7 ppm. IR (neat): ṽ = 3303 cm^{-1}, 2935, 2859, 1634. MS (CI, NH_3): m/z = 244 [MH^+]. $C_{16}H_{21}NO$ (243.3): calcd. C 78.97, H 8.70, N 5.76; found C 78.33, H 8.66, N 5.62.

(*S*)-*N*-(1-Isopropyloct-7-ynyl)benzamide (7b): White solid. M.p. 64 °C. $[\alpha]_D$ = −14 (c = 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.53 (m, 8 H), 1.85 (m, 1 H), 1.92 (t, J = 2.6 Hz, 1 H), 2.17 (td, J = 6.8, 2.6 Hz, 2 H), 4.03 (m, 1 H), 5.86 (d, J = 9.3 Hz, 1 H), 7.46 (m, 3 H), 7.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 18.3, 19.2, 25.8, 28.3, 28.7, 32.1, 32.3, 54.5, 68.1, 84.5, 126.7, 128.6, 131.2, 135.1, 167.3 ppm. IR (neat): ṽ = 3298 cm^{-1}, 2937, 2857, 1631. MS (CI, NH_3): m/z = 272 [MH^+]. $C_{18}H_{25}NO$ (271.4): calcd. C 79.66, H 9.28, N 5.16; found C 79.38, H 9.30, N 4.98.

(*S*)-*N*-(1-Phenethyloct-7-ynyl)benzamide (7c): White solid. M.p. 91 °C. $[\alpha]_D$ = −63.0 (c = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (m, 8 H), 1.85 (m, 2 H), 1.91 (t, J = 2.6 Hz, 1 H), 2.16 (td, J = 6.8, 2.6 Hz, 2 H), 2.71 (t, J = 7.9 Hz, 2 H), 4.22 (m, 1 H) 6.02 (d, J = 9.1 Hz, 1 H), 7.17 (m, 3 H), 7.22 (m, 2 H), 7.43 (m, 3 H), 7.69 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 25.4, 28.2, 28.6, 32.3, 35.2, 36.9, 49.7, 68.2, 84.5, 125.8, 131.3, 134.8, 141.8, 167.1 ppm. IR (neat): ṽ = 3302 cm^{-1}, 2938, 2856, 2116, 1632. MS (CI, NH_3): m/z = 334 [MH^+]. $C_{23}H_{27}NO$ (333.5): calcd. C 82.84, H 8.16, N 4.20; found C 82.76, H 8.35, N 4.05.

2-Methyl-4-pentyl-6-phenylpyridine (9): Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.31 (m, 4 H), 1.62 (m, 2 H), 2.57 (s, 3 H), 2.61 (t, J = 7.6 Hz, 2 H), 6.92 (s, 1 H), 7.39 (m, 3 H), 7.97 (d, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.5, 30.2, 31.4, 35.4, 118.3, 122.0, 127.1, 128.6, 152.9, 156.9, 158.0 ppm. IR (neat): ṽ = 3038 cm^{-1}, 2927, 2856, 2232, 1728, 1604. MS (CI, NH_3): m/z = 240 [MH^+].

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[1] For examples of intramolecular hydroaminations of aminoalkynes, see: Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771 and references therein. For the reactivity of terminal alkynes, see: K. Sonogashira, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon: New York, **1991**; vol. 3, pp. 521−548.

[2] [2a] C. A. Brown, A. Yamashita, *J. Am. Chem. Soc.* **1975**, *97*, 891−892. [2b] C. A. Brown, A. Yamashita, *J. Chem. Soc., Chem. Commun.* **1976**, 959−960.

[3] [3a] M. M. Midland, R. L. Halterman, C. A. Brown, A. Yamaichi, *Tetrahedron Lett.* **1981**, *39*, 4171−4172. [3b] M. M. Midland, P. E. Lee, *J. Org. Chem.* **1981**, *46*, 3933−3934.

[4] [4a] C. H. Heathcock, J. C. Kath, R. B. Ruggeri, *J. Org. Chem.* **1995**, *60*, 1120−1130. [4b] J. Cossy, D. Belotti, J.-P. Pete, *Tetrahedron* **1990**, *46*, 1859−1870.
[5] [5a] S. R. Abrams, *J. Org. Chem.* **1984**, *49*, 3587−3590. [5b] W. Fitz, D. Arigoni, *J. Chem. Soc., Chem. Commun.* **1992**, 1533−1534.
[6] J. Blanchet, M. Bonin, L. Micouin, H.-P. Husson, *J. Org. Chem.* **2000**, *65*, 6423−6426.
[7] J. Cossy, B. Gille, V. Bellosta, *J. Org. Chem.* **1998**, *63*, 3141−3146.
[8] The diastereomeric purity of isomerized compounds was checked by ^{1}H and ^{13}C NMR spectroscopy.
[9] Z.-Y. Chang, R. M. Coates, *J. Org. Chem.* **1990**, *55*, 3475−3483.
[10] H_5IO_6-mediated oxidative cleavage of similar substrates is known to occur without any racemization: see refs.[6,9]
[11] KAPA has been described to be basic enough to cause D/H exchange of [D_6]benzene: C. A. Brown, *J. Chem. Soc., Chem. Commun.* **1975**, 222−223.
[12] The exact mechanism of this unusual cycloaromatization process is unclear. As pointed out by one referee, compound **9** could result from a possible deprotonation α to the OMe group, leading to a 6-*endo*-dig cyclization and aromatization. This explanation implies that several metalated species involved in this process, bearing a C−N bond in the β-position, undergo cyclization or protonation faster than β-elimination.

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