Resolution of (±)-1-Aryl-2-propynylamines via Acyltransfer Catalyzed by *Candida antarctica* Lipase

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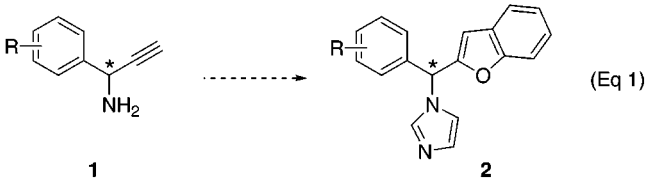
Chiral 1-ethynylbenzylamines (**1**) are important building blocks for the stereoselective synthesis of numerous biologically active compounds, such as conformationally restricted peptide isosteres,[1] oxotremorine analogues,[2] and benzo[*b*]furan compounds of general structure **2** (eq 1), which have been shown to display antifungal and aromatase inhibiting activities.[3]



1 **2** (Eq 1)

Unlike aryl propargylic alcohols,[4] however, no report on the synthesis of homochiral 1-arylpropargylamines has appeared up to now in the literature. In view of our previous studies related to the synthesis of chiral synthons of high enantiomeric purity useful for the preparation of bioactive compounds in nonracemic form,[5] we turned our attention to the synthesis of enantiomerically pure propargylamines **1**. Our first approaches based either on the diastereoselective addition of nucleophiles to the C=N bonds of imines containing removable chiral auxiliaries,[6] or the functional group modification of enantiopure 2-arylglycines, proved to be unsuccessful.[7] In fact, lithium acetylide and ethynylmagnesium bromide (even in the presence of cerium chloride) failed to react with enantiopure *N*-sulfinyl benzaldimine,[8] due to their low nucleophilicity toward carbon−nitrogen double bonds conjugated with an aromatic ring.[9] On the other hand, synthetic transformations of the carboxyl groups of α-amino acids mostly involve conversion into N-protected α-amino aldehydes,[10] which are relatively unstable, both chemically and configurationally,[10,11] and whose preparation from the corresponding acids via esters or active amides is lengthy.[12] In particular, only one laborious procedure for the preparation of *N*-protected 2-phenylglycinal has been claimed so far (no experimental data).[13]

Therefore, in an attempt to provide an easy access to the required compounds and based on our previous experience in this field,[4a,5] we decided to explore the possibility of obtaining the title compounds **1** via lipase-catalyzed resolution of the corresponding racemates. Some recent papers have described the preparation of chiral non racemic amines by stereoselective amidation via acyltransfer reactions using lipases from *Candida antarctica* (CAL)[14] and *Pseudomonas aeruginosa*[15] or the protease subtilisin A.[16] Schmidt et al.[17] have reported the kinetic resolution of racemic amines by enantioselective hydrolysis of the corresponding amides catalyzed by CAL, while Crout et al.[18] used the same enzyme to obtain enantiopure amines by hydrolysis of the corresponding oxalamic esters. On the basis of these reports, we decided to test CAL (in the immobilized form Novozym 435 from Novo Nordisk) in the enantioselective acylation of (±)-**1**.

The racemic starting materials **1a**−**f** were readily prepared (Scheme 1, Table 1) in 30−70% overall yield by hydrolysis of the corresponding acetamides **3a**−**f**, which were in turn obtained from aryl propargylic alcohols **4a**−**f**[4a] via Ritter reaction (acetonitrile/sulfuric acid), using the procedure described by Hacksell for the preparation of **1a**.[19] We then investigated the acetylation

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Scheme 1

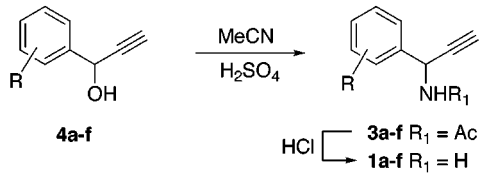
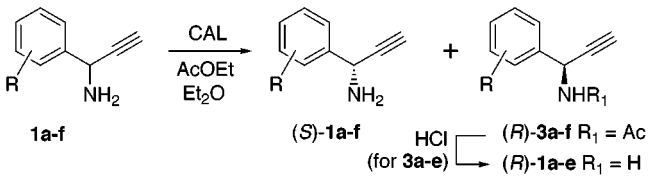


Table 1. Preparation of (±)-*N*-(1-Aryl-2-propynyl)acetamides 3a−f and (±)-1-Aryl-2-propynylamines 1a−f

compd	R	*t* (h)	yield (%)	mp (°C)
3a	H	48	91	89−90 (lit.[a] 82.5−84)
3b	4-Cl	18	60	116−118
3c	4-F	12	96	118−119
3d	3-F	16	71	101−103
3e	3-Me	18	60	105−107
3f	2-Me	24	45	145−148
1a	H	6	72	oil
1b	4-Cl	17	65	oil
1c	4-F	12	63	oil
1d	3-F	18	76	oil
1e	3-Me	72	77	oil
1f	2-Me	12	60	oil

[a] See reference 19.

Scheme 2



of (±)-**1** using CAL as the catalyst, ethyl acetate as acyl donor, and diethyl ether as solvent (Scheme 2, Table 2). The reaction was monitored by GC on a chiral column, allowing the simultaneous determination of (a) conversion and (b) the enantiomeric purities of both educt and product. The transformations were terminated as soon as the desired conversion (ca. 50%) was achieved. Following usual workup, compounds (*R*)-**3** and (*S*)-**1** were easily purified by flash chromatography and their ee determined again by chiral GC. In no case was observed a loss of ee due to the workup and silica gel chromatography. As can be seen from the data reported in Table 2, CAL proved to be an effective catalyst ($E > 100$)[20] in the enantioselective acetylation of (±)-**1a**−**e**. On the contrary, (±)-**1f** proved to be resistant to bioconversion under these conditions, and even after 120 h reaction both (*R*)-**3f** and (*S*)-**1f** were obtained only in negligible chemical yield and low enantiomeric purity. To assign the absolute configurations of **1** and **3**, the propargylamine (+)-**1a** was hydrogenated (H_2, 10% Pd/C, 30 psi) leading to (−)-1-phenylpropylamine. Comparison of its specific rotation with reported data for (*R*)-(+)-1-phenylpropylamine[21] established the *S*-configuration for **1** and, consequently, the *R*-configuration for the amides **3**. This result is in perfect agreement with the reported preference of CAL for the acylation of (*R*)-amines.[14,22]

Chemical hydrolysis of acetamides (*R*)-**3a**−**e** under the same experimental conditions as described for their racemic counterparts afforded amines (*R*)-**1a**−**e** without loss of enantiomeric purity (Table 3).

In summary, CAL-mediated kinetic resolution of 1-aryl-2-propynylamines opens up for the first time a very profitable avenue, both in terms of chemical yield and stereoselectivity, to (*R*)- and (*S*)-propargylamines, valuable intermediates for the synthesis of biologically relevant compounds in nonracemic form. Studies in this area are in progress in our laboratories and will be reported in due course.

Experimental Section

General. Reagents were obtained from commercial suppliers and used without further purification. Merck silica gel 60 was used for both column chromatography (70−230 mesh) and flash chromatography (230−400 mesh). Melting points are uncorrected. ^{1}H NMR spectra were measured at 200 MHz. Chemical shifts are reported relative to $CDCl_3$ at δ 7.24 ppm and tetramethylsilane at δ 0.00 ppm. EI low-resolution mass spectra were recorded with an electron beam of 70 eV. Elemental analyses (C, H, N) were performed in-house.

General Procedure for the Preparation of (±)-*N*-(1-Aryl-2-propynyl)acetamides (3b−f). A solution of 96% sulfuric acid (490 mg, 5 mmol) in dry acetonitrile (2.0 mL) was added to a stirred mixture of 1-aryl-2-propynyl-1-ol (1 mmol) and anhydrous sodium sulfate (142.0 mg, 1 mmol) in dry acetonitrile (3.1 mL) at −20 °C. The mixture was allowed to reach room temperature, and stirring was continued for the required time. The mixture was concentrated, poured on ice, and extracted with ether and dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography, using as eluants hexanes:Et_2O 1:1 followed by Et_2O, afforded pure *N*-(1-aryl-propynyl)acetamides (see Table 1).

(±)-*N*-[1-(4-Chlorophenyl)-2-propynyl]acetamide (3b): ^{1}H-NMR ($CDCl_3$) δ 7.43−7.26 (4H, m, J = 8.3 Hz), 6.19 (1H, br d, J = 8.2 Hz), 5.95 (1H, dd, J = 8.2, 2.0 Hz), 2.47 (1H, d, J = 2.0 Hz), 1.98 (3H, s). MS: 210/208 $(M + H)^+$, 209/207 (M^+), 130 (100%). Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N 6.75. Found: C, 63.88; H, 4.80; N, 6.66.

(±)-*N*-[1-(4-Fluorophenyl)-2-propynyl]acetamide (3c): ^{1}H-NMR ($CDCl_3$) δ 7.49 (2H, dd J = 5.5, 2.3 Hz), 7.02 (2H, m), 6.42 (1H, d, J = 8.6 Hz), 5.93 (1H, dd, J = 8.2, 1.8 Hz), 2.48 (1H, d, J = 1.6 Hz), 2.00 (3H, s). MS: 191 (M^+, 100%). Anal. Calcd for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N 7.33. Found: C, 68.91; H, 5.33; N, 7.50.

(±)-*N*-[1-(3-Fluorophenyl)-2-propynyl]acetamide (3d): ^{1}H-NMR ($CDCl_3$) δ 7.29−7.15 (3H, m), 6.99−6.95 (1H, m), 6.51 (1H, br d, J = 8.3 Hz), 5.96 (1H, dd, J = 8.4, 2.2 Hz), 2.47 (1H, d, J = 2.4 Hz). MS: 192 $(M + H)^+$, 148 (100%). Anal. Calcd for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N 7.33. Found: C, 69.29; H, 5.38; N, 7.19.

(±)-*N*-[1-(3-Methylphenyl)-2-propynyl]acetamide (3e): ^{1}H-NMR ($CDCl_3$) δ 7.27−7.07 (4H, m), 6.32 (1H, d, J = 7.6 Hz), 5.93 (1H, dd, J = 8.2, 1.9 Hz), 2.44 (1H, d, J = 1.9 Hz), 2.33 (3H, s), 1.96 (3H, s). MS: 187 (M^+, 100%). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N 7.48. Found: C, 77.19; H, 6.88; N, 7.32.

(±)-*N*-[1-(2-Methylphenyl)-2-propynyl]acetamide (3f): ^{1}H-NMR ($CDCl_3$) δ 7.63−7.59 (1H, m), 7.24−7.14 (3H, m), 6.04 (1H, dd, J = 8.1, 2.1 Hz), 5.79 (1H, bs), 2.43 (1H, d, J = 2.6 Hz), 2.35 (3H, s), 1.98 (3H, s). MS: 188 $(M + H)^+$, 128 (100%). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N 7.48. Found: C, 77.23; H, 7.10; N, 7.21.

General Procedure for the Preparation of (±)-1-Aryl-2-propynylamines (1b−f). A suspension of *N*-(1-aryl-2-propynyl)acetamide (1 mmol) and 3.0 N aqueous HCl (5.7 mL) was heated to 70 °C for the required time. The resulting solution was extracted with Et_2O (5 mL). The aqueous layer was alkalinized by addition of solid $NaHCO_3$ to pH 8.5 and extracted with Et_2O (4 × 5 mL). The combined organic solution was dried (K_2CO_3), filtered, and concentrated in vacuo. The oily residue was subjected to flash chromatography using as eluants hexanes:Et_2O 1:1, followed by Et_2O, affording pure 1-aryl-2-propynylamine (see Table 1).

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Table 2. CAL-Catalyzed Resolution of (±)-1-Aryl-2-propynylamines 1a−f

			(*S*)-**1**			(*R*)-**3**			
compd	time (h)	conversion (%)	yield (%)[a]	ee (%)[b]	$[\alpha]^{23}_D$[c]	yield (%)[a]	ee (%)[b]	$[\alpha]^{23}_D$[c]	*E*
1a	17	48.0	40.3	97	+30.4	45.2	>98	+61.6	>100 (310)
1b	25	49.8	39.8	98	+28.6	42.6	>98	+80.3	>100 (420)
1c	25	48.0	40.3	88	+8.65	38.2	98	+51.3	>100 (310)
1d	47	49.0	46.0	93	+22.5	38.9	>98	+59.1	>100 (360)
1e	48	49.7	32.9	98	+27.3	40.8	98	+58.9	>100 (410)
1f	120	31	ND[d]	22	ND[d]	ND[d]	57	ND[d]	4.7

[a] Yield refer to isolated and purified materials. [b] Determined by chiral GC. [c] Measured in $CHCl_3$ solution (*c* 1.0). [d] ND = not determined.

Table 3. Preparation of (*R*)-1 by Hydrolysis of (*R*)-3

product	yield (%)[a]	ee (%)[b]	$[\alpha]^{23}_D$[c]
(*R*)-**1a**	60	98	−31.3
(*R*)-**1b**	65	98	−27.5
(*R*)-**1c**	83	97	−32.8 (*c* 0.8)
(*R*)-**1d**	70	98	−19.7
(*R*)-**1e**	54	97	−29.7 (*c* 0.7)

[a] Yield refer to isolated and purified materials. [b] Determined by chiral GC. [c] Measured in $CHCl_3$ solution (*c* 1.0, unless otherwise stated).

(±)-1-(4-Chlorophenyl)-2-propynylamine (1b): ^{1}H-NMR ($CDCl_3$) δ 7.48−7.29 (4H, m), 4.72 (1H, d, J = 1.9 Hz), 2.48 (1H, d, J = 1.9 Hz), 1.75 (2H, br d). MS: 167/165 (M^+), 166/164 $(M - H)^+$, 130 (100%). HRMS calcd for C_9H_8ClN 165.03452, found 165.03470.

(±)-1-(4-Fluorophenyl)-2-propynylamine (1c): ^{1}H-NMR ($CDCl_3$) δ 7.50 (2H, dd, J = 8.7, 5.7 Hz), 7.01 (2H, m), 4.74 (1H, d, J = 2.2), 2.48 (1H, d, J = 1.9), 1.78 (2H, bs). MS: 148 $[(M - H)^+$, 100%]. HRMS calcd for C_9H_8FN 149.06408, found 149.06369.

(±)-1-(3-Fluorophenyl)-2-propynylamine (1d): ^{1}H-NMR ($CDCl_3$) δ 7.36−7.24 (3H, m), 7.03−6.91 (1H, m), 4.75 (1H, d, J = 2.3 Hz), 2.49 (1H, d, J = 2.3 Hz), 1.78 (2H, s). MS: 149 (M+), $[148 (M - H)^+$, 100%]. HRMS calcd for C_9H_8FN 149.06408, found 149.06444.

(±)-1-(3-Methylphenyl)-2-propynylamine (1e): ^{1}H-NMR ($CDCl_3$) δ 7.33−7.24 (3H, m), 7.10 (1H, d, J = 7.1 Hz), 4.73 (1H, d, J = 2.0 Hz), 2.47 (1H, d, J = 2.0 Hz), 2.35 (3H, s), 1.88 (2H, s). MS: 145 (M^+), 128 (100%). HRMS calcd for $C_{10}H_{11}N$ 145.08915, found 145.08870.

(±)-1-(2-Methylphenyl)-2-propynylamine (1f): ^{1}H-NMR ($CDCl_3$) δ 7.64−7.61 (1H, m), 7.23−7.17 (3H, m), 4.92 (1H, d, J = 2.0 Hz), 2.44 (1H, d, J = 2.0 Hz), 2.43 (3H, s), 1.75 (1H, bs). MS: 145 (M^+), 128 (100%). HRMS calcd for $C_{10}H_{11}N$ 145.08915, found 145.08945.

General Procedure for the CAL-Catalyzed Resolution of (±)-1-Aryl-2-propynylamines (1a−f). A mixture of (±)-**1** (2 mmol), EtOAc (0.78 mL, 8 mmol), and lipase B from *Candida antarctica* (immobilized form NOVOZYM 435) (100 mg) in Et_2O (5 mL) was strirred at room temperature, and the reaction was monitored by GC on a FS-cyclodex BETA I/P column. After the desired conversion was reached, the reaction mixture was diluted with Et_2O and filtered to remove the enzyme. The organic layer was washed twice with 3.0 N HCl, and the two phases were separated. The organic layer, containing the amide was washed once with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude (*R*)-**3**.

The aqueous phase containing (*S*)-**1** hydrochloride was alkalinized with solid $NaHCO_3$ to pH 7−8 and then extracted three times with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give the crude (*S*)-**1**. The crude products were purified by flash chromatography on silica gel (EtOAc:hexanes 1:1). The enantiomeric excess of purified products was determined by GC on the above-mentioned chiral column (for yields, ee and conversion, see Table 2).

Amines (*R*)-**1a**−**e** were prepared by hydrolysis (see Table 3) of the corresponding amides (*R*)-**3a**−**e** following the same procedure described for the hydrolysis of their racemic counterparts.

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