Synthesis of Enantiomerically Pure α-Substituted Propargylic Amines by Reaction of Organoaluminum Reagents with Oxazolidines

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Received March 14, 2000

Various oxazolidines prepared in two steps from *(R)*-phenylglycinol react at 0 °C with dialkylalkynylalane−triethylamine complexes in the presence of trimethylaluminum in high yield and diastereoselectivity. Enantiomerically pure primary α-substituted propargylamines can be easily obtained in two steps after removal of ferrocenylmethyl protective group under smooth acidic conditions and oxidative cleavage of the chiral appendage.

Introduction

Enantiopure α-substituted propargylamines are useful synthetic intermediates and can also be encountered as part of bioactive compounds[1] or natural products.[2] Numerous synthetic pathways have been devised for the preparation of such compounds in racemic form, but methods for the obtention of enantiomerically pure material are still scarce.[3,4] Among all of the asymmetric preparative methods of optically pure α-substituted amines, the diastereoselective addition of organometallic reagents to the C=N bond of chiral imines or their derivatives often proved to be very efficient.[5] However, this strategy gives unsatisfying results for the preparation of propargylamines. Enders and co-workers described a general method in 1995 for the asymmetric synthesis of propargylamines with a key step involving a 1,2 addition of organocerium reagents to chiral α,β-unsaturated aldimines which had to be performed at −100 °C.[4d,e] The nucleophilic addition of alkynyl Grignard reagents on chiral oxazines has recently been reported to proceed in the presence of BF_3·Et_2O at a more elevated temperature but with moderate de (ca. 65%) in most cases.[4h,j] Nucleophilic ring opening of oxazolidines is known to proceed in a diastereoselective fashion with organometallic reagents, provided that the reaction proceeds via a two-step mechanism and that the transient iminium ion adopts a well-defined geometry. Troublesome competitive concerted S_N2-type reactions can however occur if organometallic reagents are too nucleophilic, leading to a decrease in diastereoselectivity.

We recently reported preliminary results on the nucleophilic opening of chiral oxazolidines with mixed alkynylaluminum compounds.[6] These species are indeed known to be good Lewis acids and poor nucleophiles and usually react by transferring preferentially their alkynyl group.[7] We report in this paper our full investigations in this field, as well as the use of this reaction for the fast and efficient preparation of enantiomerically pure α-substituted propargylamines.

Results and Discussion

We first investigated the reactivity of dialkylalkynylalanes with oxazolidines bearing a benzylic nitrogen protective group and *(R)*-phenylglycinol (**1**) as chiral amino alcohol. These oxazolidines were known to furnish, under acidic conditions, only one iminium, whose geometry is controlled by $A_{(1,3)}$ strain.[8] They were prepared according to reported procedures and used as such (Scheme 1).[9]

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(3) For recent examples of preparation of α-substituted propargylic amines in a racemic form, see: Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970 and references herein cited. For preparation of α-substituted propargylic hydroxylamines, see: Franz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

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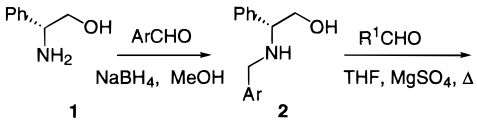
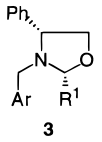
10.1021/jo0003706 CCC: $19.00
Published on Web 09/08/2000

Scheme 1

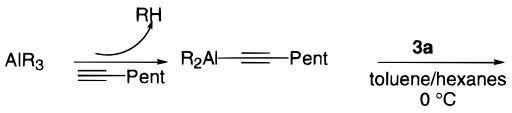


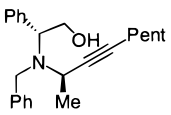


product	Ar	R1	Yield[a] (%)	de[b] (%)
3a	Ph	Me	95	83
3b	3,4-OMe-Ph	Me	92	82
3c	Ph	$(CH_2)_2Ph$	95	87

a) Overall yield from **1**. b) Determined by ^{1}H NMR of the crude reaction mixture

Scheme 2

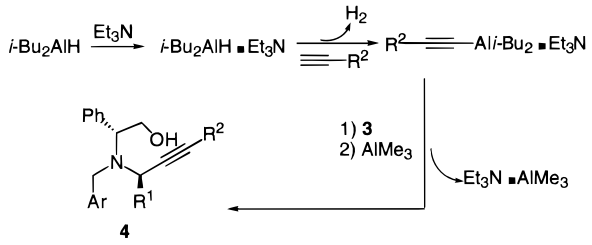




R	Yield[a] (%)	de[b] (%)
Me	93	74
Et	90	83
i-Bu	<50	94

a)Isolated yield . b) Determined by ^{1}H NMR of the crude reaction mixture

Scheme 3



Dialkylalkynylalanes were prepared by stirring trialkylalanes and alkynes in nonpolar solvents for several hours. Their reactivity was first checked with compound **3a** (Scheme 2). Two equivalents of alanes were necessary for complete conversion of oxazolidine.[10]

Increasing the size of alkyl groups led to an improvement of diastereoselectivity. However, with *i*-Bu_3Al, a large amount of competitive hydroalumination was observed when preparing mixed alane, leading to a dramatic decrease of chemical yield. Since the *i*-Bu group appeared to be crucial for a good diastereoselectivity, a new procedure was developed (Scheme 3).

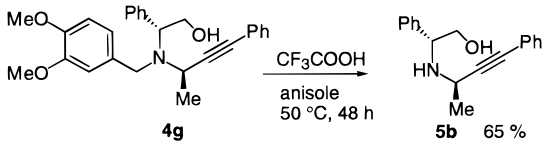
Alkynes metalation was performed with a DIBAH−Et_3N complex, which had been described to enable total conversion of alkyne.[11] However, the resulting tertiary amine complexes did not react with oxazolidines, probably because the Lewis acidity of the alane was lost. The reactivity of mixed alkynylalanes could be recovered by adding 1 equiv of Me_3Al to the reaction mixture, after the addition of the oxazolidine. Following this procedure,

Table 1

compound	Ar	R^1	R^2	yield (%)[a]	d.e.(%)[b]
4a	Ph	Me	pent	69	94
4b	Ph	Me	Ph	79	91
4c	Ph	$(CH_2)_2Ph$	pent	69	>97
4d	Ph	$(CH_2)_2Ph$	Ph	77	>97
4e	Ph	Me	*t*-Bu	69	78[c]
4f	Ph	$(CH_2)_2Ph$	*t*-Bu	72	91[c]
4g	3,4-OMe-Ph	Me	Ph	71	92
4h	3,4-OMe-Ph	$(CH_2)_2Ph$	Ph	75	96

[a] Isolated overall yield from **1**. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Metalation was performed with $AlMe_3$.

Scheme 4



various *N*-protected propargylamines were obtained, with an overall good yield and excellent diastereoselectivity, under simple experimental conditions (0 °C, toluene, 1 h) (Table 1).

Removal of dimethoxybenzyl group was then performed on compound **4g** under acidic conditions[12] without any detectable epimerization to give **5b** whose absolute configuration was determined by X-ray analysis (Scheme 4).

However, when applying these harsh conditions on substrate **4h**, amino alcohol **2b** was obtained as the major reaction product. This result showed that, with compound **4h**, the propargylic bound was more prone to be cleaved than the benzylic one, probably because the benzylic cationic leaving group was not stabilized enough.

We therefore decided to change the dimethoxyphenyl for a ferrocenyl group. This group should induce analogue allylic strain that with phenyl derivatives in the transition state and therefore lead to analogue diastereomeric excesses. Moreover, thanks to the great stability of methylene ferrocenyl cations, this protective group should be easily cleaved under smooth acidic conditions already described on amides and lactams, avoiding the competitive propargylic bound cleavage.[13]

N-Protected oxazolidines **7** were prepared by classical procedure and reacted with mixed organoaluminum compounds in excellent overall yield and diastereoselectivity (Scheme 5 and Table 2). Interestingly, the presence of basic heteroaromatic groups (furyl, pyridine) did not interfere with the alkynylation process.

As expected, deprotection could be performed using smooth acidic conditions (5% TFA solution in dichloromethane, 0 °C) and led to secondary amines without any cleavage of the propargylic bound. No epimerization could be detected at this stage (Scheme 6 and Table 3).

The use of triethylsilyl hydride as cation scavenger appeared to be unnecessary for completion of this deprotection and can be avoided, but work-up procedures are simplified when this reagent is present in the reaction mixture.

(10) The use of 1 equiv of alane lead to only 50% conversion. This prompted us to propose a late dissociated transition state model, with two molecules of alane involved in the alkynylation process (see ref 5a). A synchronous retentive alkylation has been proposed for the opening of oxazines with trimethylaluminum: Andrés, C.; Nieto, J.; Pedrosa, R.; Villamanan, N. *J. Org. Chem.* **1996**, *61*, 4130. It is however not clear why, starting from diastereomerically pure material, a synchronous retentive S_Ni-like reaction requires 4 equiv of alanes and lead to compounds with de between 33 and 99%.

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Scheme 5

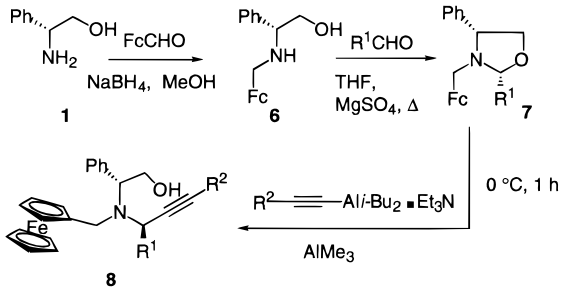


Table 2

compound	R^1	R^2	yield (%)[a]	d.e.(%)[b]
8a	Me	pent	81	94
8b	Me	Ph	78	92
8c	$(CH_2)_2Ph$	pent	86	>97
8d	$(CH_2)_2Ph$	Ph	87	>97
8i	2-furyl	pent	75	92
8j	3-pyridyl	pent	78	91

[a] Isolated overall yield from **1**. [b] Determined by ^1H NMR of the crude reaction mixture.

Scheme 6

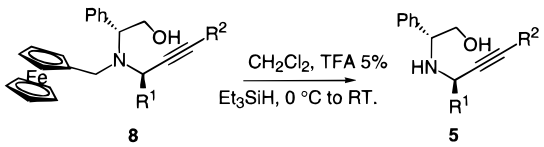
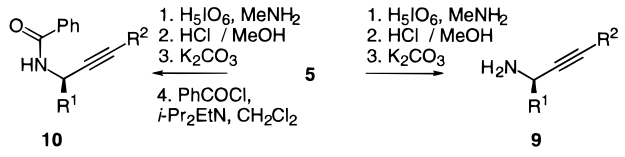


Table 3

compound	R^1	R^2	yield (%)[a]
5a	Me	pent	80
5b	Me	Ph	72
5c	$(CH_2)_2Ph$	pent	87
5d	$(CH_2)_2Ph$	Ph	87
5i	2-furyl	pent	73
5j	3-pyridyl	pent	73

[a] Isolated yield of diastereomerically pure material from **8**.

Scheme 7



compound	R^1	R^2	Yield (%)
10a	Me	Pent	66
10d	$(CH_2)_2Ph$	Ph	61
10i	2-Fur	Pent	65

compound	R^1	R^2	Yield (%)
9a	Me	Pent	70[a]
9b	Me	Ph	68
9c	$(CH_2)_2Ph$	Pent	62
9d	$(CH_2)_2Ph$	Ph	51[a]
9i	2-Fur	Pent	56[a]

a) unstable

Final deprotection was performed using standard oxidative cleavage of chiral amino alcohol.[14] Primary amines **9** could be isolated in good yield but most of them proved to be quite unstable.[15] They could however be handled and stored without any problem as benzamides **10** (Scheme 7).

Because of the great unstability of primary substituted propargylamines, we checked that the oxidative cleavage conditions were not racemizing.[16] Optical purity of compound **10i** was determined by chiral HPLC to be 99.4%. Since this reagent was probably the most likely to epimerize if any loss of stereochemical purity was to occur, the other derivatives prepared by the same method are expected to be of comparable purity.

In conclusion, we performed a straightforward and simple access to enantiopure α-substituted propargylamines. The key step for the introduction of chirality does not require low temperature and proceeds in very good yield. Crucial points were the method for preparation of fully metalated terminal alkynes, their in situ decomplexation, and the use of methylene ferrocenyl group as cleavable nitrogen "benzylic" protective group. The use of this new methodology for the elaboration of allylic amines and their transformations is under investigation in our laboratory.

Experimental Section

General Comments. NMR spectra were obtained at 300 MHz (^1H field value). IR spectra were recorded as thin film 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.

General Procedure for the Preparation of Amino Alcohols 2 and 6. The preparation of amino alcohol **6** is representative. To a solution of (*R*)-phenylglycinol (4 g, 29.2 mmol) in MeOH (40 mL) was added ferrocenecarboxaldehyde (6.38 g, 29.2 mmol) in one portion. The mixture was stirred for 1 h and cooled at 0 °C. $NaBH_4$ (1.6 g, 42 mmol) was then slowly added. After overnight stirring, the reaction was quenched with water (40 mL) and the aqueous phase extracted twice with dichloromethane (40 mL). Organic layer was washed with a saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$. Recrystallization of the crude reaction mixture from cyclohexane/ethyl acetate 1:1 gave 9.3 g of **6** (95%).

(2*R*)-Ferrocenylmethylamino-2-phenyl-ethanol 6: orange crystals, mp = 76 °C (Et_2O), $[\alpha]_D = -54$ (*c* 1.15, MeOH); ^1H NMR ($CDCl_3$) δ ppm: 2.76 (br. s, 1H), 3.32 (d, $J = 12.9$ Hz, 1H), 3.46 (d, $J = 12.9$ Hz, 1H), 3.53 (dd, $J = 10.6$, 8.5 Hz, 1H), 3.69 (dd, $J = 10.6$, 4.0 Hz, 1H), 3.81 (dd, $J = 8.5$, 4.0 Hz, 1H), 4.03 (s, 5H), 4.04−4.18 (m, 4H), 5.22 (br. s, 1H), 7.25−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ ppm 46.3, 64.0, 66.7, 67.7, 67.8, 68.2, 68.4, 86.6, 127.4, 127.5, 128.7, 140.5. IR (cm^{-1}, neat): 3378, 3092, 2926, 2868, 1492, 1453. MS: 336 (MH^+), 199. Anal. Calcd for $C_{19}H_{21}FeNO$: C, 68.08; H, 6.31; N, 4.18. Found: C 67.78, H 6.33, N 4.17.

General Procedure for the Preparation of Oxazolidines 3 and 7a. The preparation of oxazolidine **7a** is representative. To a solution of of *N*-ferrocenylmethyl-(*R*)-phenylglycinol (**6**, 1 g, 2.98 mmol) in dichloromethane (10 mL) in the presence 3 Å molecular sieves was added acetaldehyde (504 μL, 8.94 mmol). The mixture was stirred at room temperature for 2 h and filtered over Celite, and the solvent and excess aldehyde were evaporated to furnish oxazolidine **7** as an orange oil (quantitative). For other nonvolatile aldehydes, a slight excess is used (maximum 2 equiv), and the reaction is rapidly washed with aqueous saturated metabisulfite solution, dried over anhydrous $MgSO_4$, and solvent is evaporated. Oxazolidine was used as such in the next step.

(2*R*,4*R*)-3-Ferrocenylmethyl-2-methyl-4-phenyl-oxazolidine (7a): ^1H NMR ($CDCl_3$) δ ppm 1.30 (d, $J = 5.1$ Hz, 1H), 3.43 (d, $J = 14.4$ Hz, 1H), 3.57 (t, $J = 7.8$ Hz, 1H), 3.64 (d, *J*

(14) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475.

(15) The unstability of primary α-substituted propargylamines has already been noticed, see: ref 4j.

(16) Partial racemization of α-substituted amines has been suspected in the oxidative cleavage step with $Pb(OAc)_4$: Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002. It can be avoided if the reaction is "carefully controlled": Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. No racemization has been noticed with H_5IO_6 as oxidizing reagent (see ref 14).

= 14.4 Hz, 1H), 3.81 (t, J = 8.0 Hz, 1H), 4.03 (m, 10 H), 4.27 (q, J = 5.1 Hz, 1H) 7.27−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ ppm 20.4, 47.3, 65.1, 67.8, 68.2, 68.4, 70.0, 70.4, 73.0, 81.2, 90.5, 127.6−128.5, 139.8. IR (cm^{-1}, neat) 2989, 1554; MS 362 (MH^+), 199.

General Procedure for the Preparation of Propargylamines 4 and 8. The preparation of compound **8a** is representative. To a DIBAL solution (1 M in toluene, 6.3 mL, 6.3 mmol) under argon was slowly added freshly distilled triethylamine (920 μL, 6.6 mmol). The solution was stirred for 15 min and cooled to 0 °C, and heptyne (1.6 mL, 12.2 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature, stirred until hydrogen evolution stopped, and cooled to 0 °C, and a solution of oxazolidine **7** (1.08 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 on a cold solution of saturated Rochelle's salts,[17] and after vigorous stirring, the aqueous layer was twice extracted with diethyl ether. Organic layer was dried over anhydrous $MgSO_4$, the solvent was evaporated, and the crude residue was purified by column chromatography (silica gel, two successive elutions 9/1 cyclohexane/ethyl acetate then 7/3 cyclohexane/ethyl acetate to give **8a** (1.08 g, 2.37 mmol, 75% from **1**).

(1*R*,2*R*)-2-[Ferrocenylmethyl-(1-methyl-oct-2-ynyl)-amino]-2-phenylethanol 8a: red-brown oil, yield = 75%, $[\alpha]_D$ = +8.8 (c = 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ ppm 0.89 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.30−1.43 (m, 4H), 1.44−1.56 (m, 2H), 2.19 (td, J = 7.1, 1.9 Hz, 2H), 2.71 (br. s, 1H), 3.59 (d, J = 14.1 Hz, 1H), 3.75 (d, J = 14.1 Hz, 1H), 3.78−3.89 (m, 3H), 3.96−4.14 (m, 5H), 4.09 (s, 5H), 4.19 (d, J = 11.6 Hz, 2H), 7.35−7.24 (m, 5H); ^{13}C NMR ($CDCl_3$) δ ppm 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; IR (cm^{-1}, neat) 3452, 3090, 2928, 2859, 1601; MS 458 (MH^+), 199. Anal. Calcd for $C_{28}H_{35}NOFe$: C, 73.52; H, 7.71; N, 3.06. Found: C, 73.33; H, 7.84; N, 3.02.

General Procedure for the Preparation of Propargylamines 5. The preparation of compound **5a** is representative. To a cold (0 °C) solution of propargylamine (1.36 g, 3.0 mmol) in dry dichloromethane (10 mL) were added successively triethylsilane (1.2 mL, 7.5 mmol) and a solution of trifluoroacetic acid (1.2 mL, 15 mmol) in dichloromethane (15 mL). The reaction was allowed to reach room temperature, stirred for 2 h, and quenched with water and 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 **5a** (621 mg, 80%).

(1*R*,2*R*)-2-(1-Methyloct-2-ynylamino)-2-phenyl-ethanol 5a: oil, $[\alpha]_D$ = −13.6 (c = 1.25, MeOH); ^{1}H NMR ($CDCl_3$) δ ppm 0.88 (t, J = 7.0 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H), 1.28−1.37 (m, 4H), 1.38−1.46 (m, 2H), 2.08 (td, J = 6.9, 2.0 Hz, 2H), 2.48 (br. s, 2H), 3.52 (qt, J = 6.6, 2.0 Hz, 1H), 3.57 (dd, J = 10.9, 6.7 Hz, 1H), 3.71 (dd, J = 10.9, 4.7 Hz, 1H), 3.98 (dd, J = 6.7, 4.7 Hz, 1H), 7.24−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ ppm 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; IR (cm^{-1}, neat) 3330, 2931, 2859, 1603; MS: 260 (MH^+). Anal. Calcd for $C_{17}H_{25}NO\cdot 0.5H_2O$: C, 76.08; H, 9.71; N, 5.22. Found: C, 76.48; H, 9.35; N, 5.03.

General Procedure for the Oxidative Cleavage. The preparation of compound **9a** is representative. To a cold (0 °C) solution of propargylamine **5a** (370 mg, 1.43 mmol) in methanol (8.5 mL) were added 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). The turbid solution was stirred at room temperature for 3 h and became limpid. The reaction mixture was extracted twice with ether. After evaporation of ether, the methanolic solution was treated with 3 M aqueous HCl, methanol was evaporated, and the aqueous phase was washed twice with ether. Then, the aqueous phase was 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 **9a** (139 mg, 70%).

(1*R*)-Methyloct-2-ynylamine 9a: oil, $[\alpha]_D$ = +24.1 (c = 1.6, $CHCl_3$) (unstable, fully characterized as benzamide **10a**); ^{1}H NMR ($CDCl_3$) δ ppm 0.89 (t, J = 7.1 Hz, 3H), 1.32 (d, J = 6.7 Hz, 3H), 1.29−1.36 (m, 4H), 1.49 (quint, J = 7.1 Hz, 2H), 1.61 (br. s, 2H), 2.16 (dt, J = 7.1, 2.0 Hz, 2H), 3.69 (qt, J = 6.7, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ ppm 13.9, 18.6, 22.1, 24.9, 28.5, 31.0, 38.9, 81.6, 84.7.

General Procedure for Preparation of Benzamides 10. The preparation of compound **10a** is representative. Freshly purified primary amine **9a** (100 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 washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. Crude residue was purified by column chromatography (silica gel, 7/3 cyclohexane/ethyl acetate) to give **10a** (166 mg, 66% from **8a**).

(1*R*)-*N*-(1-Methyloct-2-ynyl)benzamide 10a: white solid, mp 70 °C, $[\alpha]_D$ = + 41.6 (c = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ ppm 0.90 (t, J = 7.0 Hz, 3H), 1.30−1.38 (m, 4H), 1.48 (d, J = 6.9 Hz, 3H), 1.47−1.53 (m, 2H), 2.17 (td, J = 7.0, 5.1 Hz, 2H), 4.94−5.07 (m, 1H), 6.27−6.48 (br. s, 1H), 7.38−7.53 (m, 3H), 7.69 (d, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 14.0, 18.6, 22.2, 22.9, 28.3, 31.0, 37.9, 80.2, 83.1, 126.9, 128.5, 131.5, 134.2, 166.1; IR (cm^{-1}, neat) 3286, 2928, 1632; MS 244 (MH^+). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.51; H, 8.46; N, 5.66.

Acknowledgment. One of us (J.B.) thanks MENRT for a grant.

Supporting Information Available: Characterization of compounds **3c**, **4a**−**h**, **5b**−**j**, **8b**−**j**, **9b**, **9c**, **9d**, **9i**, **10d**, and **10i** and NMR spectra of compounds **5a**, **6**, **7a**, **8a**, **9a**, and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org..

JO0003706

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