Synthetic Elaboration of the Side Chain of (*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine: A New Regio- and Stereoselective Strategy to δ-Functionalized β-Amino Alcohols

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Received April 7, 1997[⊗]

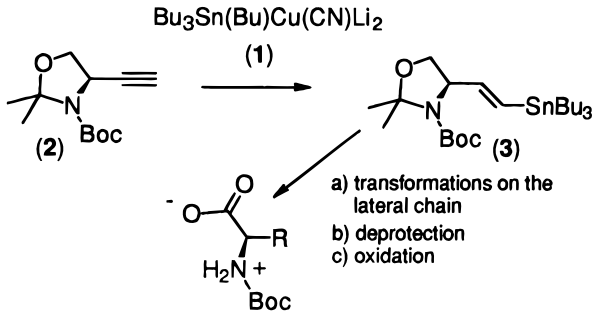
An investigation of the reactivity of ethynyloxazolidine **2** is presented. Functionalization at the acetylenic position has been found to occur very easily using the mild Sonogashira conditions. Addition of tributyltin cuprate **1** provided the corresponding stannylated (*E*)-ethenyloxazolidine **3**, a new chiral building block which has been reacted with electrophiles under Pd catalysis. The reaction sequence occurred without racemization and showed an easy and mild procedure for the regio- and stereoselective synthesis of unsaturated amino alcohols.

Introduction

Addition of (tributylstannyl)cuprate **1**[1] to substituted alkynes is a very powerful method for preparing geometrically defined trisubstituted alkenes.[2] The utility of this tin-based "dimetallic reagent", besides its high chemoselectivity, lies in the generation, after addition on terminal alkynes, of two stereo- and regiodefined vinyl organometallics which can be reacted stepwise with different electrophiles. Being interested in investigating the synthetic utility of this type of reaction,[3] we directed our efforts toward finding new simple acetylenic substrates, focusing our attention particularly on the synthesis of some new, highly functionalized unsaturated nitrogen compounds.[4,5] For example, we showed that *t*-Boc-protected chiral propargylic amines can be considered as very useful reagents for stannylcuprate addition.[6] These compounds, which were easily obtained with high enantiomeric purity from naturally occurring amino acids, reacted selectively with **1** to afford the corresponding 2-substituted γ-stannylated allylic amines. Coupling these stannylated amines with electrophiles under Pd catalysis provided a new mild and stereocontrolled procedure to chiral γ-substituted (*E*)-allylic amines, a class of compounds which proved to be useful intermediates in the synthesis of conformationally restricted peptide isosters.[7]

Attempting to extend this methodology toward more functionalized systems, we envisaged ethynyloxazolidine **2** as a useful substrate to synthesize vinylstannane **3** through stannylcupration. Because such oxazolidine moieties are widely employed as synthetic equivalents of α-amino acids,[8] compound **3** could be an interesting intermediate to be used in the stereoselective synthesis of nonnatural amino acids.

Scheme 1



The first synthesis of compound **2**, using naturally occurring serine as the chiral starting material, was recently reported by Meffre.[9] Its use as a direct precursor to optically active alkynylglycine derivatives was shown. We recently published[10] an alternative procedure to compound **2**, based on a modification[11] of the well-known Corey and Fuchs[12] aldehyde-to-alkyne omologation method, and pointed out the possibility to achieve a new class of substituted alkynes through different pathways. Here we report the full experimental details on the synthesis of compound **2** and related γ-functionalized derivatives. Its reactivity with (tributylstannyl)cuprate is also studied with the aim of preparing stannyl oxazolidine **3**. The potentiality of **3** as a chiral building block for the synthesis of δ-substituted β-amino alcohols will also be exploited.

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[⊗] Abstract published in *Advance ACS Abstracts*, August 1, 1997.

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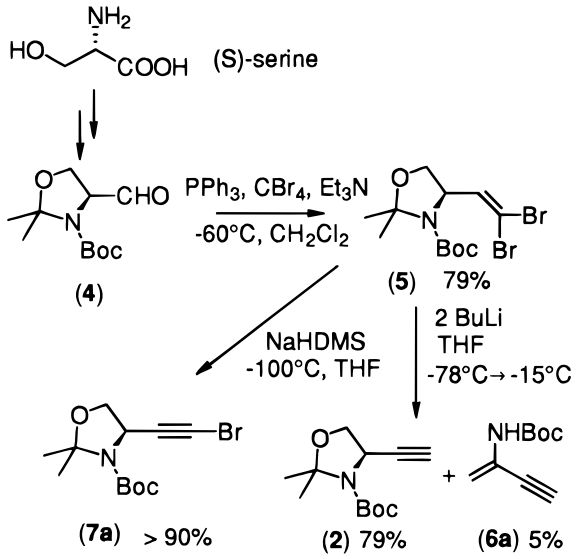
S0022-3263(97)00619-1 CCC: $14.00

Scheme 2



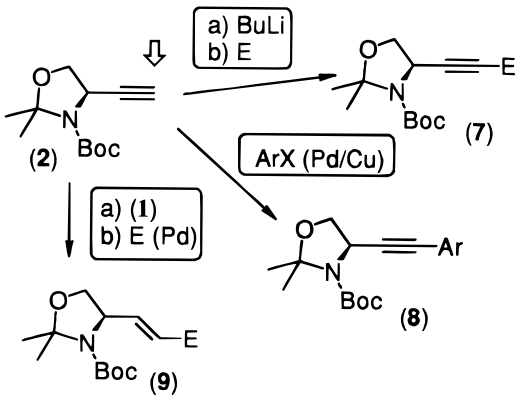
Results and Discussion

Synthesis of Compound 2 and Its Derivatives. Compound **2** was prepared using naturally occurring serine as the chiral starting material. The amino acid was transformed into the corresponding aldehyde **4** following the well-known procedure described by Garner.[13] The recently proposed reduction−oxidation sequence[14,15] can be alternatively followed to obtain good yields of the desired aldehyde which can be directly used, for our purposes, without any further purification. The synthesis of **5** has been described using the Corey−Fuchs conditions.[16] The modified procedure we used, in the presence of Et_3N at low temperature,[11] provided an efficient transformation to **5** which was easily isolated in 79% yield.

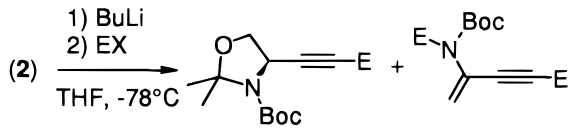
Intermediate **5** was quantitatively dehydrohalogenated in the presence of sodium bis(hexamethyldisilylamide) (NAHMDS) to the corresponding (bromoethynyl)oxazolidine derivative **7a**. Conversion into **2** was accomplished simply by treating with 2 equiv of BuLi at −78 °C.[12] The whole reaction sequence from **4** to **2** could also be performed without isolation of **5** in 74% yield after purification. Variable amounts of enamine **6a** were always formed in this transformation. The same result was also observed[17] when compound **2** was treated with BuLi. However, using our conditions, this byproduct was present in very small amounts (lower than 10%) and became predominant only when a large excess of base was used for prolonged reaction times.

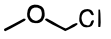
The enantiomeric purity of compound **2** was established by ^{1}H-NMR analysis of the diastereomeric Mosher amides.[18] These were prepared by reaction of both (*R*)-(−)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPACl) with the amino alcohol obtained by deprotection of **2** with Amberlist in MeOH/H_2O at room temperature. The two diastereomers were found to be clearly distinguishable and showed no contamination from racemized material.

Scheme 3



Scheme 4



Electrophile	(7/6)	Conversion	Isolated yield
$ClCOCH_3$	70/30	42%	-
ClCOOMe	80/20	>95%	(**7c**) 46% (**6c**) 8%
	70/30	>95%	-

We then examined the possibility of introducing new functional groups to the terminal position of the lateral chain of the oxazolidine ring. Three different pathways were considered as outlined in Scheme 3.

In the first two cases, a direct introduction of substituents on the triple bond was considered in order to obtain the corresponding ethynyloxazolidine derivatives **7** or **8**. Alternatively, the synthesis of (*E*)-ethenyloxazolidine derivatives **9** was accomplished through the corresponding γ-stannylated intermediate **3**, *via* a palladium-catalyzed Stille coupling.[19]

It was already shown that the introduction of new functional groups at the terminal position in propargyl aminic systems can be easily achieved through metalation and further reaction with electrophiles.[20] The same approach was successfully applied in the alkylation and silylation of compound **2**;[17] therefore, we tried to extend this procedure to a wider series of electrophiles. Unfortunately, as shown in Scheme 4, discouraging results were obtained. When acetyl chloride was used, for example, the desired product **7b** was formed only in low yield. Conversely, with more reactive electrophiles like methyl chloroformate or methoxymethyl chloride, the starting material was completely transformed to **7c**,**d**; however, in both cases variable amounts of byproducts **6c**,**d** were recovered.

In order to circumvent this problem, we decided to turn to a milder procedure, taking into consideration the

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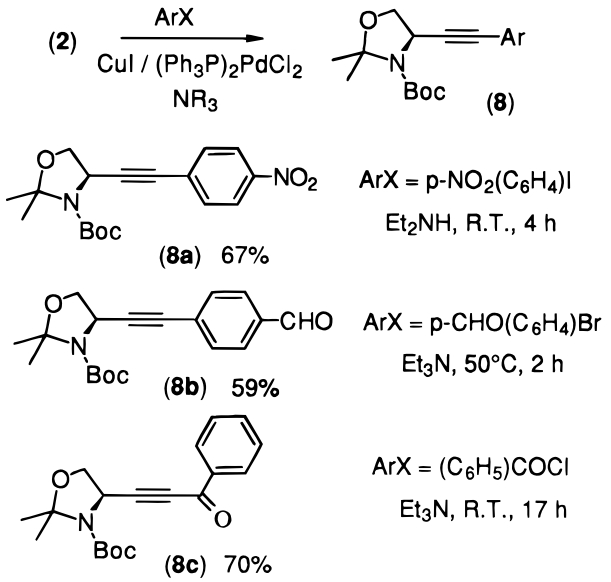
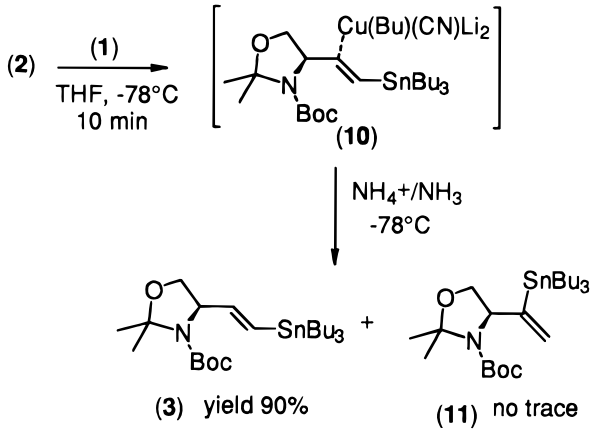
Scheme 5



Scheme 6

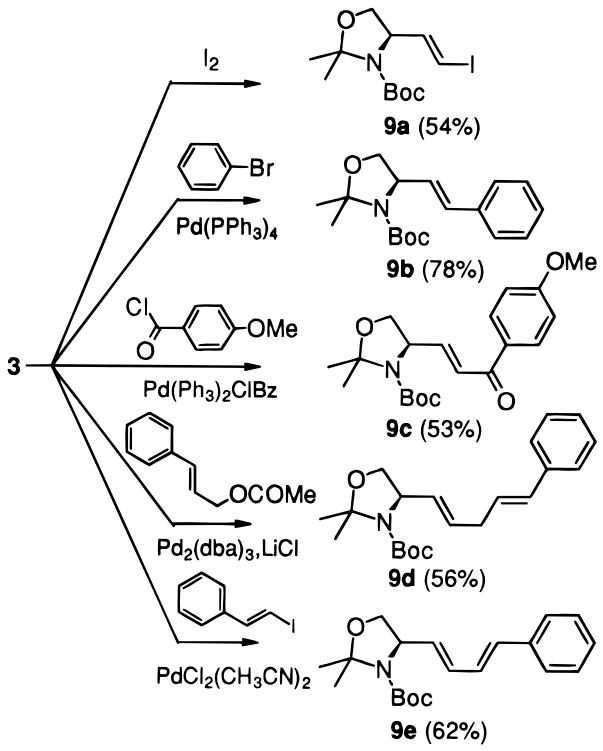


Sonogashira[21] copper−palladium-catalyzed coupling of terminal alkynes with aromatic halides. This reaction is known[22] to be efficient, high yielding, and tolerant of a wide range of functional groups which might allow us to insert on the lateral chain consisting of a large variety of differently substituted aromatic rings. This could be very useful, for example, if our sequence had to be employed to investigate structure−activity relationships within a series of compounds. Our results are reported in Scheme 5.

We attempted this simple procedure with three different electrophiles. In all cases a clean reaction was observed and the corresponding coupled products **8a**−**c** were isolated after chromatography with satisfactory yields.

Stannylcupration of 2 and Some Synthetic Applications of Vinylstannane 3. (Tributylstannyl)cyanocuprate **1**[1] was found to add efficiently to compound **2** at low temperature, affording the corresponding γ-stannylated (*E*)-ethenyloxazolidine **3** in a regio- and stereoselective manner. Remarkably, the opposite regioisomer **11** was not detected as determined by ^{1}H-NMR analysis

Scheme 7



of the crude mixture. The 19.4 Hz coupling we measured for the vinyl protons in the ^{1}H-NMR spectrum was in good agreement for the assigned *E*-geometry of **3**.[4]

As we have previously mentioned, the main feature of this reaction is that it can provide,[4] through the bismetallic intermediate adduct **10**, an efficient entry to the stepwise β,γ-substitution of the lateral chain. This was demonstrated by reacting **3** with several electrophiles which resulted in a new series of γ-substituted (*E*)-ethenyloxazolidines (**9a**−**e**). Iododestannylation was performed first, and iodo derivative **9a** was obtained selectively with high yield. Aryl and vinyl halides as well as anisoyl chloride and cinnamyl acetate were then used following the well-known Pd-catalyzed procedure described by Stille.[19] Experimental details and results are reported in Scheme 7.

In each case the reaction proceeded with retention of configuration with respect to the vinyl−tin bond, as confirmed by ^{1}H-NMR analysis, and the corresponding cross-coupled products were obtained and isolated in good yields. Since stannylcupration and Stille coupling conditions have already proved[6,23] not to alter the enantiomeric excesses in chiral compounds, we can conclude that this mild method can be widely used for obtaining chiral ethenyloxazolidines with a predictable *E*-geometry.

Cleavage of the oxazolidine ring was tested on compounds **9b**,**d**. The best reaction conditions were found using PTSA in wet methanol at room temperature. Amino alcohols **12b**,**d** were obtained in satisfactory yields. Conveniently deprotection can be carried out avoiding purification of oxazolidine **9** as we proved in the case of **9b**, from which **12b** was obtained in 71% overall yield from **3**.

Amino alcohols of type **12** are of interest as unnatural (not coded) amino acids precursors. A limitation to their use results in the lack of oxidative methods compatible with the presence of unsaturations on the backbone. It

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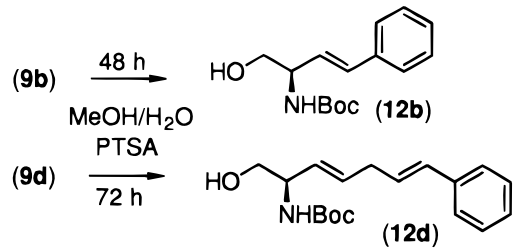
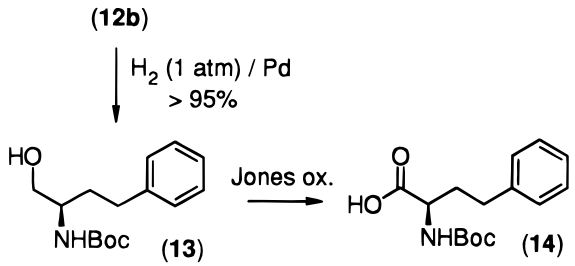
Scheme 8



Scheme 9



was already shown,[24] for example, that aromatic alcohol **12b** can not be oxidized to the corresponding vinylglycine derivative. Nevertheless, we thought that amino alcohols **12** could be interesting substrates for the preparation of saturated amino acids, as we proved in the case of **12b**. Catalytic hydrogenation to saturated **13** was performed, and subsequent oxidation using Jones' conditions afforded *t*-Boc-homophenylalanine (**14**) with good optical purity $[\alpha]^{25}_D = +4.9$ (*c* 0.9, EtOH) [lit.[25] $[\alpha]_D = +5.9$ (*c* 1.4, EtOH)].

Conclusions

We have developed a novel procedure for the preparation of ethynyloxazolidine **2** and investigated some synthetic elaborations on the lateral chain which delivered the final products in essentially enantiomerically pure form. In particular, vinylstannane **3** has been highlighted as an interesting building block which, hopefully, can be used in the synthesis of molecules of biological and pharmaceutical interest.

Experimental Section

General. All reactions were carried out under a positive pressure of dry nitrogen. Ethereal extracts were dried with Na_2SO_4. The temperature of dry ice−ether baths is indicated as −100 °C, that of dry ice−ethanol as −78 °C, and that of ice−NaCl as −15 °C. Reactions were monitored by TLC on SiO_2; detection was made using a $KMnO_4$ basic solution. Flash column chromatography[26] was performed using glass columns (10−50 mm wide) and SiO_2 (230−400 mesh). ^{1}H-NMR spectra were recorded at 200 or 300 MHz. ^{13}C-NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, δ 7.26 for ^{1}H-NMR; $CHCl_3$, δ 77.0 for ^{13}C-NMR). Coupling constants (*J*) are reported in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), m (multiplet), bs (broad singlet), bt (broad triplet), and bq (broad quartet). For those compounds which are present as slowly interconverting rotamers, NMR experiments were performed at 50 °C and signals of the averaged spectrum are reported when possible. Mass spectra were obtained at a 70 eV ionization potential and are reported in the form *m*/*z* (intensity relative to base = 100). Organotin fragments are given for ^{120}Sn. Polarimetric measurements were performed in $CHCl_3$ solution at $\lambda = 589$ nm, and the temperature is specified case by case. IR spectra were recorded in CCl_4 solution.

Materials. Garner aldehyde **4** was prepared according to the literature.[13] Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification except TMSCl which was distilled over quinoline. THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was purified by the standard procedure, dried over $CaCl_2$, and stored over 4-Å molecular sieves. Toluene was distilled over sodium wire and stored over 4-Å molecular sieves. DMF was distilled over $CaCl_2$ and stored over 4-Å molecular sieves. Petroleum ether, unless specified, is the 40−70 °C boiling fraction.

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(2,2-dibromoethenyl)oxazolidine (5). CBr_4 (5.98 g, 18.0 mmol) was dissolved in CH_2Cl_2 (120 mL) and cooled at −20 °C. A solution of PPh_3 (4.67 g, 17.8 mmol) in CH_2Cl_2 (250 mL) was added, and the mixture was stirred for 30 min and then cooled to −60 °C. A solution of **4** (2.12 g, 9.0 mmol) and Et_3N (12.5 g, 8.9 mmol) in CH_2Cl_2 (100 mL) was added, and the mixture was kept at −60 °C for 30 min, then warmed at rt, and stirred overnight. The solution was diluted with pentane and filtered, the solvent evaporated, and the crude residue chromatographed on SiO_2 (CH_2Cl_2), affording 2.73 g (79%) of (*R*)-**5**[16] as a white solid: mp 55−56 °C; ^{1}H-NMR (300 MHz, 50 °C) δ 6.46 (d, $J = 8.1$ Hz, 1H), 4.59−4.44 (m, 1H), 4.10 (dd, $J = 6.6$, 9.3 Hz, 1H), 3.78 (dd, $J = 9.3$, 2.7 Hz, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 151.7, 138.5, 94.5, 89.9, 80.4, 67.3, 59.5, 28.5, 26.3, 23.9; MS *m*/*z* 312/314/316 (10/19/10), 57 (100); $[\alpha]^{20}_D = +18$ (*c* 0.94, $CHCl_3$). Anal. Calcd for $C_{12}H_{19}NO_3Br_2$: C, 37.43; H, 4.97; N, 3.64. Found: C, 37.87; H, 5.04; N, 3.67.

(*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(2,2-dibromoethenyl)oxazolidine (5). (*R*)-**4** (123 mg, 0.5 mmol) was reacted to afford 154 mg (83%) of (*S*)-**5**: $[\alpha]^{20}_D = -19$ (*c* 0.92, $CHCl_3$).

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine (2). A solution of **5** (1.03 g, 2.7 mmol) in THF (20 mL) was cooled at −78 °C, and BuLi (3.4 mL, 5.4 mmol) was added dropwise. After 30 min the mixture was heated to −15 °C, stirred for a further 15 min, and then quenched with NaOH (0.01 M). After extraction, drying, and evaporation of the solvent, 614 mg of crude material was obtained which, after flash chromatography (CH_2Cl_2), afforded 482 mg (79%) of **2** as a colorless oil and 26 mg (5%) of **6a**. (*R*)-**2**:[10] $[\alpha]^{20}_D = -73.5$ (*c* = 1.01, $CHCl_3$) [lit.[17] $[\alpha]^{20}_D = -96.5$ (*c* 1.23, $CHCl_3$)]. **6a**: ^{1}H-NMR (200 MHz) δ 6.00 (bs, 1H), 5.78 (s, 1H), 5.01 (s, 1H), 2.85 (s, 1H), 1.45 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 152.2, 123.0, 106.3, 80.8, 80.2, 75.4, 28.2; MS *m*/*z* 167 (2), 57 (100); IR (film) 3310.

(*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine (2). (*R*)-Dibromide **5** (97 mg, 0.25 mmol) was reacted to afford 47 mg (58%) of (*S*)-**2**: $[\alpha]^{20}_D = +75$ (*c* 1.03, $CHCl_3$).

Synthesis of the Mosher's Esters of Deprotected 2. Compound **2** (104 mg, 0.5 mmol) was dissolved in MeOH/H_2O (10/1, 3 mL) together with 600 mg of Amberlist IR-120 (PLUS) and stirred at rt for 20 h. After filtration the resin was washed several times with MeOH. Evaporation of MeOH afforded 79 mg of crude material. After chromatography (petroleum ether/ethyl acetate: 3/1) 56 mg (65%) of (*R*)-**2a**[10,17] was recovered: $[\alpha]^{22}_D = -32.5$ (*c* 1.20, $CHCl_3$) [lit.[17] $[\alpha]^{20}_D = -43$ (*c* 1.08, $CHCl_3$)].

Anhydrous pyridine (0.300 mL), CCl_4 (0.500 mL), and (*S*)-MTPA chloride (50 mg, 0.20 mmol) were mixed together and reacted at rt for 1 h with 25 mg (0.1 mmol) of (*R*)-**2a**. After workup the residue was analyzed by ^{1}H-NMR and showed the presence of the 1*S*,2*R*-derivative with ee > 95%. The reaction was repeated with (*R*)-MTPA chloride affording the 1*R*,2*R*-diastereomer with ee > 95%. The two diastereoisomers were purified by chromatography (petroleum ether/ethyl acetate: 3/1).

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(1*S*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]but-3-ynyl 1-methoxy-1-(trifluoromethyl)phenylacetate: ^{1}H-NMR (200 MHz) δ 3.59 (q, *J* = 1.6 Hz, 3H); MS *m*/*z* 189 (100), 57 (63); ee > 95%.

(1*R*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]but-3-ynyl 1-methoxy-1-(trifluoromethyl)phenylacetate: ^{1}H-NMR (200 MHz) δ 3.56 (q, *J* = 1.4 Hz, 3H); MS *m*/*z* 189 (100), 57 (98); ee > 95%.

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(bromoethynyl)oxazolidine (7a). A solution of **5** (387 mg, 1.0 mmol) in THF (10 mL) was cooled at −100 °C. A THF solution (1 M) of NaHMDS (1.00 mL, 1.00 mmol) was added dropwise. The mixture was stirred for 45 min and then hydrolyzed at low temperature with aqueous NaOH (0.01 M). The organic layer was extracted with ether, washed with brine, and dried. After evaporation of the solvent 313 mg of crude material was obtained; 100 mg of the residue was purified by bulb-to-bulb distillation (90 °C, 0.75 mBar) to afford 87 mg (87%) of pure **7a** as a colorless oil: ^{1}H-NMR (300 MHz) δ 4.64−4.42 (m, 1H), 4.01−3.99 (m, 2H), 1.61 (s, 3H), 1.48 (s, 9H + 3H); ^{13}C-NMR (75.45 MHz) δ 151.5, 94.5, 80.5, 78.8, 68.4, 67.3, 49.4, 28.5, 25.7, 24.4; MS *m*/*z* 288/290 (3/3), 57 (100); $[\alpha]^{20}_D$ = −103 (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}NO_3Br$: C, 47.38; H, 5.96; N, 4.60. Found: C, 47.23; H, 6.01; N, 4.64.

Metalation of 2 and Reaction with Electrophiles: General Procedure. A THF solution of **2** was cooled at −78 °C. BuLi (1 equiv) was added, and the mixture was stirred for 30 min. The appropriate electrophile was then added and the reaction progress monitored by TLC. After the reaction was complete, the reaction mixture was diluted with ether, hydrolyzed with NaOH (0.01 M), then extracted, washed with brine, and dried.

(*R*)-Methyl [(2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidin-4-yl]propynoate (7c). Freshly distilled ClCOOMe (61 mg, 0.6 mmol) was reacted with **2** (108 mg, 0.5 mmol) in THF (5 mL) and stirred at −78 °C for 1 h. The reaction mixture was allowed to warm up to rt and then stirred for 1 h. After workup 153 mg of crude material was obtained. ^{1}H-NMR analysis showed the presence of compounds **7c** and **6c** in a 80/20 ratio. Flash chromatography (petroleum ether/ethyl acetate: 3/1) afforded 61 mg (46%) of **7c** and 12 mg (8%) of **6c**. **7c**: ^{1}H-NMR (300 MHz, 50 °C) δ 4.67−4.58 (m, 1H), 4.14−3.99 (m, 2H), 3.79 (s, 3H), 1.61 (s, 3H), 1.49 (s, 3H + 9H); ^{13}C-NMR (75.45 MHz) δ 153.7, 151.0, 94.8, 86.0, 80.9, 73.7, 67.7, 52.7, 48.3, 28.3, 25.8, 24.2; MS *m*/*z* 268 (3), 57 (100); IR (KBr) 1709; $[\alpha]^{20}_D$ = −105 (*c* 1.10, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.26; H, 7.40; N, 4.97. **6c**: ^{1}H-NMR (200 MHz) δ 5.94 (d, *J* = 0.6 Hz, 1H), 5.70 (d, *J* = 0.6 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.51 (s, 9H); ^{13}C-NMR (75.45 MHz) δ 153.6, 152.3, 149.5, 129.0, 124.6, 84.3, 81.8, 78.4, 54.1, 52.9, 27.8; MS *m*/*z* 268 (0.5), 57 (100).

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(3-methoxy-1-propynyl)oxazolidine (7d). Chloromethyl methyl ether (23 mg, 0.3 mmol) was reacted with **2** (52 mg, 0.2 mmol) in THF (3 mL). The reaction mixture was warmed up to −15 °C and stirred for 3 h. After workup 89 mg of crude material was obtained. ^{1}H-NMR analysis showed the presence of compounds **7d** and **6d** in a 70/30 ratio. **7d** and **6d** were not separable by chromatography. **7d**: ^{1}H-NMR (200 MHz) δ 4.68−4.50 (m, 1H), 4.13−4.08 (m, 2H), 4.05−3.97 (m, 2H), 3.36 (s, 3H), 1.62 (s, 3H), 1.48 (s, 9H + 3H); ^{13}C-NMR (50.3 MHz) δ 151.5, 94.3, 85.4, 80.3, 68.7, 59.9, 57.3, 55.8, 48.5, 28.4, 25.9, 24.3; MS *m*/*z* 254 (8), 57 (100). **6d**: ^{1}H-NMR (200 MHz) δ 5.48 (s, 1H), 5.43 (s, 1H), 4.87 (s, 2H), 4.21 (s, 2H), 3.38 (s, 3H), 3.35 (s, 3H), 1.48 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 153.7, 128.6, 119.4, 83.9, 83.2, 81.5, 79.6, 60.1, 57.7, 55.8, 28.1; MS *m*/*z* 199 (5), 57 (100).

Coupling with Electrophiles under Sonogashira[21] Conditions: General Procedure. Compound **2** (0.2 mmol) was dissolved in the appropriate amine (2 mL). The electrophile (0.2 mmol) was then added together with CuI (10%) and $(Ph_3P)_2PdCl_2$ (10%) and left to react as specified case by case. The amine was evaporated. The residue was dissolved with ether, filtered over SiO_2, and, after evaporation of the solvent, purified by flash chromatography.

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-[(*p*-nitrophenyl)ethynyl]oxazolidine (8a). 4-Nitroiodobenzene (44 mg, 0.2 mmol) was stirred with a solution of **2** (46 mg, 0.2 mmol) in Et_2NH (2 mL) at rt for 4 h. After workup 76 mg of crude material was obtained. Purification (petroleum ether/ethyl acetate: 5/1) afforded 41 mg (67%) of **8a** as a yellow, low-melting solid: ^{1}H-NMR (200 MHz) δ 8.16 (bd, *J* = 8.6 Hz, 2H), 7.54 (bd, *J* = 8.6 Hz, 2H), 4.93−4.73 (m, 1H), 4.14−4.09 (m, 2H), 1.66 (s, 3H), 1.53 (s, 3H), 1.50 (s, 9H); ^{13}C-NMR δ (50.3 MHz) δ 151.3, 147.1, 132.4, 129.7, 123.5, 94.6, 93.6, 80.3, 77.2, 68.5, 49.1, 28.4, 26.0, 24.3; MS *m*/*z* 290 (4), 57 (100); $[\alpha]^{20}_D$ = −149 (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.47; H, 6.38; N, 8.17.

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-[(*p*-formylphenyl)ethynyl]oxazolidine (8b). 4-Bromobenzaldehyde (54 mg, 0.3 mmol) was stirred with a solution of **2** (67 mg, 0.3 mmol) in Et_3N (2 mL) for 2 h at 50 °C. After workup 108 mg of crude material was obtained. Purification (petroleum ether/ethyl acetate: 5/1) afforded 56 mg (59%) of **8b**: ^{1}H-NMR (200 MHz) δ 9.99 (s, 1H), 7.81 (bd, *J* = 8.0 Hz, 2H), 7.57 (bd, *J* = 8.0 Hz, 2H), 4.91−4.69 (m, 1H), 4.14−4.07 (m, 2H), 1.66 (s, 3H), 1.53 (s, 3H), 1.50 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 191.4, 151.5, 135.4, 132.2, 129.4, 129.1, 94.1, 92.3, 81.2, 80.3, 68.6, 49.1, 28.4, 25.9, 24.4; MS *m*/*z* 273 (7), 57 (100); $[\alpha]^{22}_D$ = −185 (*c* 1.44, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.37; H, 7.08; N, 4.29.

(*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(benzoylethynyl)oxazolidine (8c). Benzoyl chloride (34 mg, 0.2 mmol) was stirred with a solution of **2** (46 mg, 0.2 mmol) in Et_3N (1 mL) for 17 h at rt. After workup 76 mg of crude material was obtained. Purification (petroleum ether/ethyl acetate: 4/1) afforded 47 mg (70%) of **8c**: ^{1}H-NMR (200 MHz) δ 8.20−8.08 (m, 2H), 7.75−7.38 (m, 3H), 4.93−4.75 (m, 1H), 4.20−4.11 (m, 2H), 1.69 (s, 3H), 1.50 (s, 9H + 3H); ^{13}C-NMR (50.3 MHz) δ 177.5, 151.1, 136.5, 134.5, 130.5, 128.8, 94.8, 92.7, 81.0, 79.8, 68.0, 48.7, 28.3, 26.0, 24.2; MS *m*/*z* 314 (2), 105 (100); $[\alpha]^{23}_D$ = −111 (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.21; H, 6.95; N, 4.30.

(*R*,*E*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-[(2-tributylstannyl)ethen-1-yl]oxazolidine (3). (Tributylstannyl)cuprate was prepared according to the literature.[1] A solution of **2** (794 mg, 3.5 mmol) in THF (10 mL) was added, and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was diluted with ether and hydrolyzed with ammonium buffer. Evaporation of the solvent afforded 2.863 g of crude material which was purified by flash chromatography (petroleum ether/ethyl acetate: 15/1); 1.342 g (74%) of **3** was obtained as a colorless oil: ^{1}H-NMR (200 MHz) δ 6.06 (bd, *J* = 19.4 Hz, 1H), 5.90 (dd, *J* = 19.4, 5.4 Hz, 1H), 4.41−4.28 (m, 1H), 4.02 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.76 (dd, *J* = 8.4, 2.4 Hz, 1H), 1.62−1.18 (m, 12H + 6H + 9H), 0.88 (t, *J* = 7.4 Hz, 15H); ^{13}C-NMR (50.3 MHz) δ 151.9, 146.7, 128.9, 93.9, 79.4, 68.3, 62.3, 29.1, 28.4, 27.2, 26.5, 23.8, 13.7, 9.4; MS *m*/*z* 460 (9), 57 (100); $[\alpha]^{19}_D$ = −44 (*c* 1.19, $CHCl_3$).

(*R*,*E*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(2-iodoethen-1-yl)oxazolidine (9a). A solution of **3** (302 mg, 0.6 mmol) in $CHCl_3$ (2 mL) was reacted with I_2 (150 mg, 0.6 mmol) for 3 h at rt. After solvent evaporation, 193 mg of crude product was obtained. Purification by flash chromatography (petroleum ether/ethyl acetate: 8/1) afforded 112 mg (54%) of **9a**: ^{1}H-NMR (300 MHz, 50 °C) δ 6.50 (dd, *J* = 14.4, 7.6 Hz, 1H), 6.75 (bd, *J* = 14.4 Hz, 1H), 4.38−4.21 (m, 1H), 3.99 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.75 (dd, *J* = 8.8, 2.1 Hz, 1H), 1.59 (s, 3H), 1.49 (s, 3H), 1.45 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 151.7, 144.3, 94.1, 80.1, 78.1, 67.1, 61.3, 28.4, 26.5, 23.6; MS *m*/*z* 338 (2), 282 (19), 57 (100); $[\alpha]^{22}_D$ = −75.3 (*c* 1.9, $CHCl_3$).

(*R*,*E*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(2-phenylethen-1-yl)oxazolidine (9b). A solution of **3** (148 mg, 0.3 mmol) and bromobenzene (65 mg, 0.4 mmol) in toluene (2 mL) was refluxed for 24 h in the presence of $Pd(Ph_3)_4$ (10%). After this time bromobenzene (30 mg, 0.15 mmol) was readded and the reaction mixture kept under reflux for a further 24 h. The mixture was filtered through a SiO_2 plug, diluted with ether, and then stirred for 2 h with a saturated KF solution (10% NH_4OH). The organic layer was separated and evapo-

rated to afford 138 mg of crude material; 31 mg of the mixture was purified by TLC (petroleum ether/ethyl acetate: 10/1) and gave 16 mg (78%) of **9b**: ^{1}H-NMR (200 MHz) δ 7.42−7.21 (m, 5H), 6.50 (bd, J = 15.6 Hz, 1H), 6.16 (dd, J = 15.6, 8.2 Hz, 1H), 4.62−4.38 (m, 1H), 4.12 (dd, J = 9.2, 5.8 Hz, 1H), 3.83 (dd, J = 9.2, 2.2 Hz, 1H), 1.66 (s, 3H), 1.55 (s, 3H), 1.44 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 152.5, 137.2, 132.1, 129.0, 128.1, 126.9, 94.2, 80.1, 68.8, 60.0, 28.9, 27.1, 24.2; MS *m*/*z* 303 (1), 247 (59), 189 (100), 57 (97); $[\alpha]^{24}_D = -71.3$ (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.97; H, 8.28; N, 4.53.

(*R*,*E*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(*p*-anisoylethen-1-yl)oxazolidine (9c). A solution of **3** (86 mg, 0.2 mmol) and anisoyl chloride (34 mg, 0.2 mmol) in $CHCl_3$ (2 mL) was refluxed for 10 h in the presence of $Pd(Ph_3)ClBz$ (10%). After this time the reaction mixture was filtered through a SiO_2 plug. Evaporation of the solvent afforded 98 mg of crude material. Purification by TLC (petroleum ether/ethyl acetate: 4/1) yielded 36 mg (53%) of **9c**: ^{1}H-NMR (300 MHz, 60 °C) δ 7.94 (dt, J = 8.7, 1.8 Hz, 2H), 7.02−6.80 (bd + m, 2H + 2H), 4.59−4.47 (m, 1H), 4.13 (dd, J = 6.4, 9.0 Hz, 1H), 3.90−3.82 (m, 1H), 3.88 (s, 3H), 1.65 (s, 3H), 1.56 (s, 3H), 1.46 (s, 9H); MS *m*/*z* 305 (19), 246 (36), 202 (20), 135 (51), 77 (21), 57 (100); $[\alpha]^{22}_D = +33$ (*c* 0.9, $CHCl_3$).

(*R*,*E*,*E*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(5-phenyl-1,4-pentadien-1-yl)oxazolidine (9d). A solution of **3** (208 mg, 0.4 mmol) and cinnamyl acetate (73 mg, 0.4 mmol) in DMF (2 mL) was stirred in the presence of $Pd_2(dba)_3$ (10%) and LiCl (52 mg) for 24 h at rt. The reaction mixture was diluted with ether and then stirred with a saturated KF solution (10% NH_4OH). The organic layer was separated and washed with brine. Evaporation of the solvent afforded 233 mg of crude material which was purified by flash chromatography (petroleum ether/ethyl acetate: 5/1) to give 77 mg (56%) of **9d**: ^{1}H-NMR (300 MHz) δ 7.36−7.13 (m, 5H), 6.38 (d, J = 15.9 Hz, 1H), 6.16 (dt, J = 15.9, 6.6 Hz, 1H), 5.77−5.52 (m, 1H), 5.48 (dd, J = 7.6, 15.5 Hz, 1H), 4.42−4.18 (m, 1H), 4.00 (dd, J = 8.7, 6.6 Hz, 1H), 3.71 (dd, J = 8.7, 2.3 Hz, 1H), 2.95−2.88 (m, 2H), 1.58 (s, 3H), 1.48 (s, 3H), 1.41 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 152.0, 137.6, 130.9, 130.4, 130.0, 128.5, 128.2, 127.0, 126.0, 93.7, 79.6, 68.4, 59.1, 35.4, 28.5, 26.9, 23.9; MS *m*/*z* 287 (2), 144 (77), 57 (100); $[\alpha]^{18}_D = -11.5$ (*c* 0.8, $CHCl_3$).

(*R*,*E*,*E*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(4-phenyl-1,3-butadien-1-yl)oxazolidine (9e). A solution of **3** (77 mg, 0.15 mmol) and *trans*-β-iodostyrene (47 mg, 0.2 mmol) in DMF (2 mL) was stirred in the presence of $Pd_2(CH_3CN)_2$ (10%) for 15 h at rt. DMF was removed under vacuum; 103 mg of crude material was obtained which was purified by TLC (petroleum ether/ethyl acetate: 10/1) to give 31 mg (62%) of **9e**: ^{1}H-NMR (200 MHz) δ 7.42−7.18 (m, 5H), 6.75 (dd, J = 15.6, 10.2 Hz, 1H), 6.50 (d, J = 15.6 Hz, 1H), 6.42−6.18 (m, 1H), 5.83−4.62 (bdd, J = 15.8, 8.1 Hz, 1H), 4.51−4.24 (m, 1H), 4.06 (dd, J = 5.8, 8.8 Hz, 1H), 3.76 (dd, J = 8.8, 2.6 Hz, 1H), 1.62 (s, 3H), 1.51 (s, 3H), 1.45 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 151.9, 137.2, 132.6, 132.5, 132.0, 128.6, 128.2, 127.5, 126.3, 93.9, 79.7, 68.3, 59.2, 28.5, 26.6, 23.8; MS *m*/*z* 273 (21), 91 (50), 57 (100); $[\alpha]^{19}_D = -15$ (*c* 0.6, $CHCl_3$).

(*R*,*E*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenylbut-3-en-1-ol (12b). The crude material (103 mg) obtained from reaction of **3** with bromobenzene (see above) was dissolved in MeOH/H_2O (90/10, 4 mL) and stirred with a catalytic amount of PTSA at rt for 48 h. MeOH was evaporated; the residue was dissolved with ether and washed with brine. After evaporation of the solvent and chromatography (petroleum ether/ethyl acetate: 2/1) 41 mg (71% from **3**) of **12b** was obtained: ^{1}H-NMR (200 MHz) δ 7.37−7.18 (m, 5H), 6.57 (d, J = 16.2 Hz, 1H), 6.12 (dd, J = 16.2, 6.2 Hz, 1H), 5.03 (bd, J = 7.4 Hz, 1H), 4.42−4.27 (m, 1H), 3.77−3.64 (m, 2H), 2.56 (bs, 1H), 1.44 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 156.0, 136.3, 131.8, 128.5, 127.7, 126.7, 126.4, 79.9, 65.4, 54.6, 28.3; MS *m*/*z* 248 (11), 232 (15), 84 (100), 57 (97); $[\alpha]^{22}_D = -33$ (*c* 1.25, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 68.42; H, 8.42; N, 5.32. Found: C, 69.17; H, 8.19; N, 5.19.

(*R*,*E*,*E*)-2-[(*tert*-Butoxycarbonyl)amino]-7-phenyl-3,6-heptadien-1-ol (12d). A solution of **9d** (40 mg, 0.1 mmol) in MeOH/H_2O (90/10, 4 mL) was stirred with a catalytic amount of PTSA at rt for 72 h. After the workup 33 mg of crude material was obtained. Purification by TLC (petroleum ether/ethyl acetate: 5/1) afforded 22 mg (62%) of **12d**: ^{1}H-NMR (300 MHz) δ 7.33−7.20 (m, 5H), 6.40 (d, J = 16.2 Hz, 1H), 6.18 (dt, J = 16.2, 6.2 Hz, 1H), 5.79 (dtd, J = 15.2, 6.2, 1.4 Hz, 1H), 5.46 (dtd, J = 15.2, 1.0, 1.4 Hz, 1H), 3.77−3.64 (m, 2H), 2.56 (bs, 1H), 1.44 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 156.0, 136.3, 131.8, 128.5, 127.7, 126.7, 126.4, 79.9, 65.4, 54.6, 28.3; MS *m*/*z* 272 (19), 144 (77), 57 (100); $[\alpha]^{23}_D = -8.22$ (*c* 0.9, $CHCl_3$).

(*R*,*E*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenylbutan-1-ol (13). 12b (35 mg, 0.1 mmol) was dissolved in ethanol (95%, 1 mL) and hydrogenated (H_2, 1 atm) overnight over catalytical Pd on carbon. After filtration over SiO_2 and evaporation of the solvent, 32 mg (91%) of pure **13** was obtained: ^{1}H-NMR (200 MHz) δ 7.33−7.15 (m, 5H), 4.66 (bs, 1H), 3.72−3.54 (m, 2H + 1H), 2.81−2.58 (m, 2H), 2.35 (bs, 1H), 1.88−1.55 (m, 2H), 1.46 (s, 9H); ^{13}C-NMR (50.3 MHz) δ 156.5, 141.5, 128.4, 128.3, 126.0, 79.7, 65.9, 52.6, 33.3, 32.4, 28.4; MS *m*/*z* 234 (6), 91 (88), 57 (100); $[\alpha]^{19}_D = +4.5$ (*c* 1.1, $CHCl_3$).

Acknowledgment. We are grateful to Prof. Maurizio Taddei for helpful discussions and critical reading of the paper. Financial support by the Consiglio Nazionale delle Ricerche, Rome, is much appreciated.

Supporting Information Available: ^{1}H-NMR spectra of compounds **3**, **9a**,**d**,**e**, **12d**, and **13** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. See any current masthead page for ordering information.

JO970619S