Tandem Addition/Cyclization of Alkynylzinc Reagents to Enantiopure 2-*tert*-Butyl-3,5-dimethyl-2,3-dihydroimidazol-4-one *N*-Oxide: Potential Precursors of Quaternary α-Amino Acids

Frédéric Cantagrel,[a] Sandra Pinet,[a] Yves Gimbert,[a] and Pierre Y. Chavant*[a]

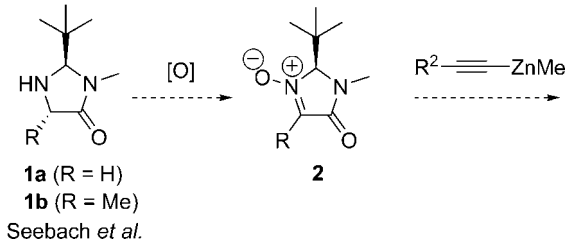
Keywords: Nitrones / Alkynylzinc / Amino acids / Imidazolidinone / Dihydroisoxazole / Cyclization

A new enantiopure cyclic nitrone, a potential electrophilic alanine synthon, has been prepared. Its reaction with alkynylzinc reagents led to a tandem addition/cyclization reaction with complete regio- and stereoselectivity. The adducts are potential precursors of quaternary α-amino acids.

Introduction

As part of a program involving the use of modified peptides featuring some hydroxamic linkages, we were interested in the preparation of *N*-hydroxy-α-amino acid derivatives.[1] For this purpose, we sought to add organometallic reagents onto properly designed, enantiopure nitrones. Nitrones are activated imine derivatives that are easily accessible through the oxidation of secondary amines.[2–11] Thus, we planned to choose our starting material from among the secondary amines that have been proposed as precursors of α-amino acids so that our nitrone precursor would be produced in a single oxidation step. The imidazolidinones **1** designed by Seebach et al.[12] were particularly attractive as starting materials. Enantiopure imidazolidinones **1** are easily accessible from simple α-amino acids. After *N*-benzoylation, these molecules were used in the most famous application of the self-reproduction of stereochemistry (SRS) principle.[12] It was easy to imagine that imidazolidinones **1** could be oxidized to cyclic nitrones **2** (Scheme 1), which could then be used as electrophiles, in another variant of the SRS principle.

Analogous cyclic nitrones already exist. Altenbach and co-workers[13,14] have prepared a menthone-derived spiro compound in both enantiopure forms. This nitrone was treated with simple Grignard reagents to produce *N*-hydroxylamines. Other enantiopure cyclic α-acyl nitrones[15–18] have also been proposed for use as substrates in 1,3-dipolar cycloaddition reactions. Very recently, Baldwin and Long[19] reported the first synthesis of **2a** (R = H) and its use in the preparation of nonproteinogenic amino acids by 1,3-dipolar cycloaddition reactions. All these studies dealt only with unsubstituted nitrones (R = H, from glycine).



Scheme 1. Nitrone **2** as an electrophilic precursor of amino acids.

We were mainly interested in reactions of such nitrones with organometallic reagents. In particular, we treated nitrones **2** with the alkynylzinc intermediates that we had developed previously[20,21] (Scheme 1).

In this article we describe the reaction of the new nitrone **2b** with 1-alkynes and dimethylzinc. Instead of yielding propargylic *N*-hydroxylamines as in the former work, under mild conditions this reaction proceeded further to 2,3-dihydroisoxazoles in high yields and diastereoselectivities.

Results and Discussion

Preparation of Nitrones 2a,b

We prepared imidazolidinones **1a**[22] and **1b**[23] according to the published procedures: the enantiomers of **1a** were obtained from mandelic salts. In the original article,[24] amines **1** were not purified, but directly *N*-benzoylated. However a single recrystallization of the hydrochloride **1b·HCl** in ethanol allowed the isolation of **1b** in the pure *trans* form.[24]

[a] LEDSS, UMR CNRS/UJF 5616, Institut de Chimie Moléculaire de Grenoble, Université Joseph Fourier,
BP 53, 38041 Grenoble Cedex 9, France
Fax: +33-4-76-63-59-83
E-mail: Pierre-Yves.Chavant@ujf-grenoble.fr

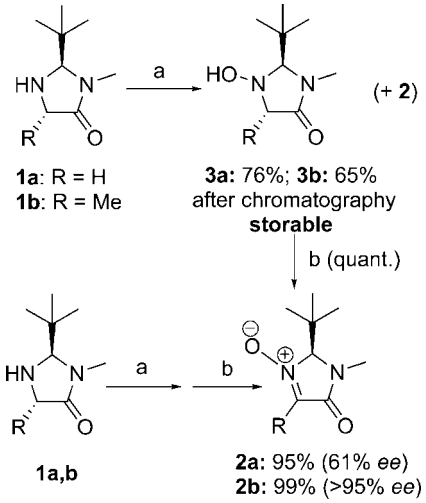
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

 DOI: 10.1002/ejoc.200400861

In a first attempt to oxidize **1a** with 2.1 equiv. of MCPBA,[25] we found that nitrone **2a** was contaminated with small amounts of a more oxidized product.[26] With less MCPBA, the contaminant was found to be *N*-hydroxylamine **3a**. In both cases, chromatography led to a low (<25%) isolated yield since **2a** is unstable on silica gel.[19] Note that Baldwin and Long[19] successfully oxidized **1a** to **2a** with urea/hydrogen peroxide (UHP) using methyltrioxorhenium (MTO) in methanol as a catalyst.[8]

We observed that our samples of **2a** decomposed on storage. Moreover, an enantiopure solid sample of **2b** stored at 20 °C for 3 months lost optical activity (without decomposition). To overcome these problems, we carried out the oxidation in two separate steps: the imidazolidinones **1a**,**b** were first treated with 1.2 equiv. of UHP and MTO.[7,8,27] Simple filtration through a pad of silica produced the corresponding *N*-hydroxylamines **3**; the sole impurity was nitrone **2**. At this stage, *N*-hydroxylamines **3** could be isolated by chromatography (yields **3a**: 76%; **3b**: 65%) and stored for months without any loss of optical activity.[28] The second oxidation step, from *N*-hydroxylamine **3** to nitrone **2**, could be performed quantitatively in very mild conditions with MnO_2[29] in DCM without any side reaction. After filtration, nitrones **2a**,**b** were pure enough to be used as such in further reactions. Thus, it was very easy to prepare **2** just before use.

Alternatively, since the impurity in the first step was nitrone **2**, crude **3** could be oxidized at once with MnO_2. Almost quantitative yields were produced from **1** (Scheme 2). However, although the oxidation of **3a** with MnO_2 produced **2a** in an enantiomerically impure form (61% *ee* in DCM, 40% *ee* in MeOH),[30] the more stable **2b** was obtained from **3b** in an enantiopure form.



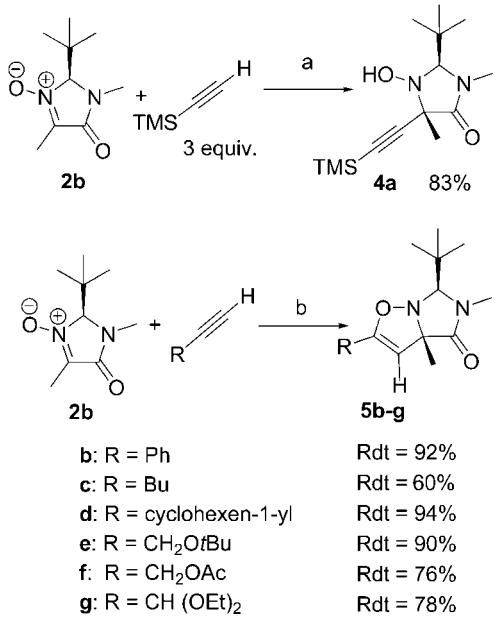
Scheme 2. Preparation of *N*-hydroxylamines **3a**,**b** and nitrones **2a**,**b**: a) UHP (1.2 equiv.), MTO (2–5%), DCM, 20 °C, 10 h; b) MnO_2, DCM, 20 °C, 2 h.

Reaction of Nitrone 2b with 1-Alkynes and Dimethylzinc

We have previously shown[20,21] that 1-alkynes react with nitrones in the presence of diethylzinc in toluene or DCM to produce propargylic *N*-hydroxylamines **4**.[31–38] With simple nitrones in toluene, 0.2 equiv. of diethylzinc is sufficient to allow complete conversion of the nitrone.

However the reaction of nitrone **2b** failed under the same conditions; only traces of the product could be detected. Nevertheless, it was possible to achieve a complete transformation of **2b** if more than 1 equiv. of dimethylzinc was used.[39] The reaction of trimethylsilylacetylene (3 equiv.), dimethylzinc (1.5 equiv.), and **2b** led to the propargylic *N*-hydroxylamine **4a** in 83% yield (toluene, 20 °C, 6 h).

However, it rapidly became apparent that the reaction with trimethylsilylacetylene was an exception. With all the other alkynes tested, the nucleophilic addition reaction was followed in situ by a slow cyclization reaction to form the 2,3-dihydroisoxazoles **5**.[40] When the reaction mixture was left at room temperature for 18 h, the intermediate **4** was totally consumed and high yields of **5** were achieved (Scheme 3).[41]

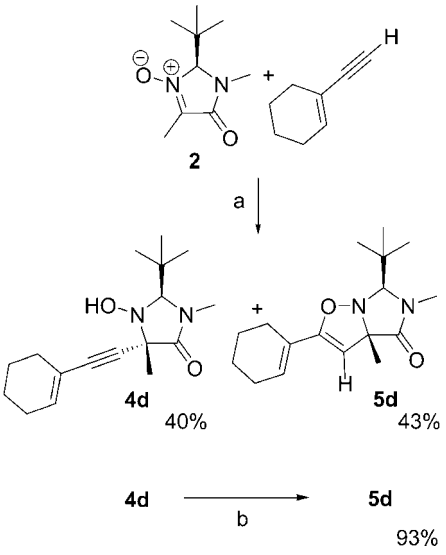


Scheme 3. Tandem addition/cyclization reaction of **2b** with alkynes: a) Me_2Zn (1.3 equiv.), toluene, 20 °C, 6 h, then NH_4Cl; b) Me_2Zn (1.3 equiv.), toluene, 20 °C, 18 h, then NH_4Cl.

This reaction was compatible with various functional groups on the alkyne, even in the propargylic position. In all cases, a single diastereoisomer was detected by NMR spectroscopy. The relative stereochemistry of the new stereogenic center was proven by NOE experiments in the case of **5e**.[42]

Although the global outcome was identical to that of a 1,3-dipolar cycloaddition reaction (with the same regiochemistry), the reaction clearly followed a two-step pathway. TLC analysis of hydrolyzed aliquots of the reaction mixture showed the formation and disappearance of the intermediate **4**. The second step was relatively slow with 1-ethynylcyclohexene (Scheme 4) and the reaction could be stopped when **4d** had accumulated (**4d**/**5d** ≈ 50:50). Chromatography gave pure **4d** in 40% yield. A sample of **4d** was then

treated in toluene with fresh dimethylzinc to regenerate the Zn–O bond. After 18 h at 20 °C and hydrolysis, conversion into **5d** was complete (Scheme 4).

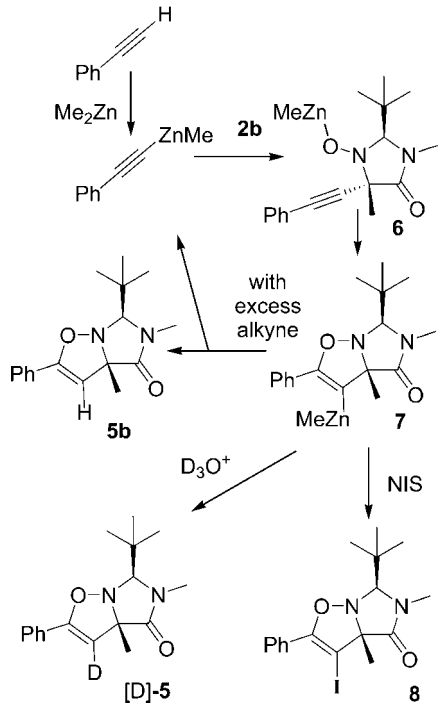


Scheme 4. Cyclization of the intermediate *N*-hydroxylamine **4**. a) Me_2Zn (1.5 equiv.), toluene, 20 °C, 6 h, then H_2O; b) Me_2Zn (1.5 equiv.), toluene, 20 °C, 18 h, then H_2O.

An efficient cyclization of propargylic *N*-hydroxylamines in the presence of zinc iodide and DMAP (both in catalytic amounts) has been published.[43] The mechanism proposed by the authors involves the formation of RR′N–O–ZnI (and DMAP iodohydrate). This intermediate adds to the triple bond to form a vinylzinc species, which is immediately protolyzed by the amine iodohydrate.

We repeated one of our reactions of Scheme 3 (reaction b) in [D_6]benzene [**2b** (1 equiv.), phenylacetylene (3 equiv.), and dimethylzinc (1.5 equiv.)]. NMR signals for **2b**, **5b**, the adduct **6** (Scheme 5), acetylenic hydrogen, and Me–ZnY could be distinguished.[44] We observed again that the first alkyne addition was faster than the cyclization reaction (50% of **2b** was consumed after approx. 40 min, 50% of **5b** was formed after approx. 4 h). Noticeably, after 60 min, the methylzinc signals had shifted from –0.59 to –0.10 ppm. From then on, the intensities of this methylzinc signal and those of **6** decreased synchronously, in agreement with the structure proposed below for **6**. The bicyclic vinylzinc intermediate **7** was not observed in this experiment: the vinylic proton of **5** was present in quantitative amounts. We concluded that **7** was rapidly protonated by the excess alkyne.

Nevertheless, we could accumulate the vinylzinc species **7** by changing the reaction protocol. Phenylacetylene (2 equiv.) was treated with excess dimethylzinc (4 equiv.) for 1 h at 20 °C and then **2b** was added to the preformed alkynylzinc. After 12 h at 20 °C, the reaction mixture was treated with DCl in D_2O. NMR analysis of **5b** indicated 87% deuterium incorporation.[45] This reaction was repeated and iodolysis (NIS, 20 °C) produced the vinyl iodide **8** in 62% yield.

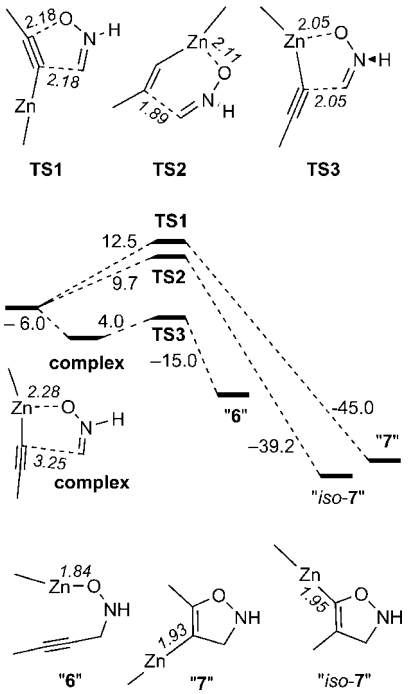


Scheme 5. Accumulation of the vinylzinc intermediate **7**.

Thus, the latter process (with dimethylzinc in excess over alkyne) opens the way to a three-component reaction between a nitrone, a 1-alkyne, and an organozinc reagent to yield a new organozinc reagent. We are currently investigating the reactivity of **7**.

The exact mechanism of such a *trans* oxyzincation of a triple bond (from **6** to **7**) is not obvious, and any explanation should involve the intervention of a second zinc atom that would both activate the alkyne and take part in the final C–Zn bond. One could alternatively consider a 1,3-dipolar cycloaddition of the nitrone to the alkynylzinc triple bond (from **2** to **7** direct; an analogous concerted cycloaddition of a nitrone and an alkynylcopper species has been postulated in the mechanism for the β-lactam synthesis described by Miura et al.[46]). In this hypothesis, the nucleophilic addition (from **2** to **6**) should be reversible (since in the experiment **7** is formed from **6**). To address this point we used DFT calculations[47] to compare the postulated nucleophilic addition reaction (from **2** to **6**) with the hypothetical concerted 1,3-dipolar cycloaddition of the alkynylzinc reagent to **2**. In the latter reaction, both orientations of the cycloaddition were checked. Our results are summarized in Scheme 6.

Two transition states (**TS1** and **TS2**) were located with activation barriers of 9.7 and 12.5 kcal mol^{-1}, respectively. The transition state with the higher energy led to **7** with the experimentally observed regiochemistry. The pathway to the addition product **6** is much more favorable. The nitrone and the alkynylzinc first form a complex (–6 kcal mol^{-1}). The energy barrier from this complex to adduct **6**, via **TS3**, is very low (4 kcal mol^{-1}). Unfortunately, we have so far been unable to find a solution, in this model, for the reaction pathway of the second cyclization step (**6** to **7**).



Scheme 6. Optimized structures at the B3LYP/6-31+G* level of theory. Distances (in *italics*) in Å, energies in kcal mol^{-1}.

Finally, we undertook a series of tests (Scheme 7 and Table 1) in order to explain the changes in reactivity (stoichiometric vs. catalytic Zn^{II}) and in the outcome (cyclic dihydroisoxazole vs. open-chain propargylic *N*-hydroxylamine) when **2b** was used instead of other nitrones.[20]

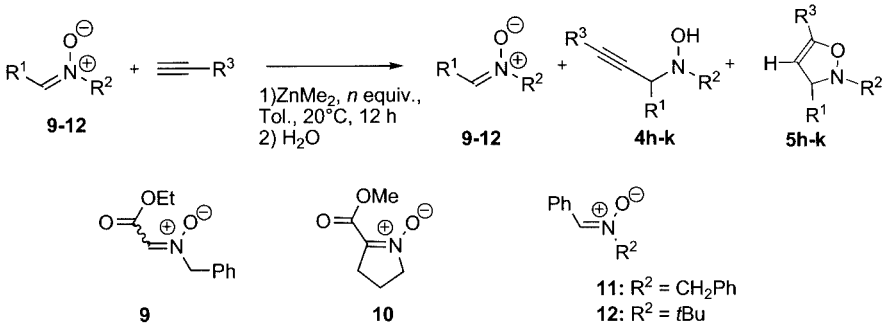
It is evident that the catalytic cycle was effective with reactive nitrones like **11**[48] (Scheme 7), but was blocked if the nitrone carried a carboxy group (nitrones **9**[49] and **10**[50]). If a 0.2:1 ratio of dimethylzinc to nitrone was used, approximately 20% conversion of the nitrone was achieved; the adducts (approximately 20% yields) were recovered as dihydroisoxazoles **5h** or **5i** after 12 h.

The presence of an ester in the reaction mixture is not the cause of the cyclization: in the presence of 1.5 equiv. of Me_2Zn, the nitrone **11** was totally consumed in less than 15 min producing only **4j**. When this reaction was repeated in the presence of 10 equiv. of ethyl acetate, complete conversion of **11** required 5 h and also yielded **4j**.

The cyclization reaction took place whenever the nitrone carried an ester (**9** and **10**) or amide (**2b**) group. It never took place with the simple nitrone **11** (or with other examples reported in ref.[20]), except when the alkyne contained an acetyl group (entries **k** and **l**). It appears that the driving force for the cyclization reaction is the presence of a carbonyl group that can intramolecularly bind with the vinylic zinc atom. NMR evidence for analogous intramolecular chelations between an organozinc and a neighbouring carboxylic oxygen atom have been published.[51,52]

Conclusions

We have shown that the self-regenerating stereocenter principle[12] can be applied to the preparation of enantiopure nitrones **2a**,**b** from natural α-amino acids. We have also found that **2b** and other α-carboxy-nitrones react with 1-



Scheme 7. Factors influencing the cyclization reaction.

Table 1. Factors influencing the cyclization reaction.

Entry	Nitrone	R^3	Me_2Zn [equiv.]	Nitrone[a] [%]	**4**[a][b] [%]	**5**[a][b] [%]
h	**9**	Ph	0.2	82	0	18
h	**9**	Ph	1.5	0	0	100 (91)
i	**10**	CH_2OtBu	0.2	75	0	25
i	**10**	CH_2OtBu	1.5	0	0	100 (95)
j	**11**	CH_2OtBu	0.2	0	100 (82)[20]	0
j	**11**	CH_2OtBu	1.5	0	100 (88–92)	0
k	**11**	CH_2OAc	0.2	0	100 (70)[20]	0
k	**11**	CH_2OAc	1.5	0	0	100 (82)
l	**12**	CH_2OAc	0.2[c]	0	0	100[20]

[a] Ratio of products in the crude hydrolyzed material. [b] The yields of the isolated pure materials are given in parentheses. [c] Diethylzinc (0.2 equiv.), 19 h, see ref.[20].

alkynylzinc derivatives in a tandem addition/cyclization process, leading regio- and diastereoselectively to a series of highly functionalized bicyclic imidazoisoxazoles **5** in excellent yields. α,α-Disubstituted α-amino acids are masked in **5**. We are currently studying further transformations of these molecules into new quaternary amino acids that feature complex side-chains.

Experimental Section

General Remarks: ^{1}H (200 or 300 MHz) and ^{13}C NMR (50 or 75 MHz) spectra were recorded with Bruker AC200 or Advance300 spectrometers in $CDCl_3$ with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The number of hydrogen atoms on each carbon atom was obtained from DEPT experiments. IR spectra were recorded with a Nicolet Impact-400 FTIR spectrometer from neat films or sintered KBr discs. HRMS (chemical ionisation) and elemental analyses were performed at the Service Central d′Analyse du CNRS, Vernaison, France. Thin-layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-254 plates. Spots were visualized with UV light or by dipping the TLC plate into a basic potassium permanganate solution and heating, or by dipping the plate in a 1% triphenyl tetrazolium chloride (TTC) solution and then in a 5% NaOH solution of ethanol/water and heating; a strong permanent red colour is characteristic of *N*-hydroxylamines. Forced-flow column chromatography was performed by using Macherey–Nagel silica gel 60, 230–400 mesh. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. All reactions were performed by using conventional Schlenk techniques under dry nitrogen in oven-dried glassware and with magnetic stirring. All reagents were purchased from Aldrich, Acros, or Fluka and used as received. Dimethylzinc was used as a commercial (Aldrich) 2 M solution in toluene. Dichloromethane (DCM) was distilled from CaH_2. Toluene was distilled from sodium. Dimethylformamide (DMF) and *N*-methylpyrrolidin-2-one were distilled and stored on 4- molecular sieves.

DFT calculations were carried out using the Gaussian 98[53,54] system of programs. Critical points (reactants, transition structures, precomplexes, and products) were fully characterized as minima or first-order saddle points by diagonalizing the Hessian matrices of the optimized structures at the B3LYP/6-31+G* level of theory.[47] All critical points were further characterized by analytic computation of the harmonic frequencies at the same level of calculation. Transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C and C–O bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all optimized structures and used to compute both ZPVE and activation energies. The intrinsic reaction coordinates[55,56] were also calculated in order to analyze in detail the mechanism for all transition structures obtained.

Preparation of Imidazolidinones 1a,b: Imidazolidinone **1a** was prepared as its mandelic salt[22] on a 50-mmol scale. Imidazolidinone **1b**, obtained following the procedure described in ref.[23], was recrystallized once in ethanol to yield the pure *trans* isomer.

Preparation of *N*-Hydroxylamines 3: Urea/hydrogen peroxide (UHP, 1.13 g, 12 mmol) followed by methyltrioxorhenium (MTO, 50 mg, 0.2 mmol) were added to a solution of imidazolidinone (*S*)-**1a** or (*S,S*)-**1b** (10 mmol) in dichloromethane (20 mL). The reaction was monitored by TLC (silica, eluent cyclohexane/ethyl acetate, 1:1) until the conversion of **1a** was complete (in some runs it was necessary to add another 50 mg of MTO after several hours). After filtration through Celite and concentration, the crude *N*-hydroxylamine **3** (contaminated with nitrone **2**) was either directly oxidized with MnO_2 (see below) or purified by chromatography on silica.

(*R*)-(+)-2-*tert*-Butyl-1-hydroxy-3-methylimidazolidin-4-one (3a): Chromatography (cyclohexane/ethyl acetate, 1:1, R_f = 0.18) yielded 76% (1.48 g) of **3a**, m.p. 68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.22 (s, 1 H), 3.73, (d, J = 17.8 Hz, 1 H), 3.52 (d, J = 17.8 Hz, 1 H), 3.01 (s, 3 H), 0.97 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 (C), 97.7 (CH), 61.8 (CH_2), 37.2 (C), 31.8 (CH_3), 26.2 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3302, 2961, 2874, 1677, 1484, 1476, 1453, 1414, 1293, 1262, 1247, 1205, 1124, 1084, 907, 826 cm^{-1}. HRMS: found: m/z = 195.1107 [M + Na]; calculated: m/z = 195.1109 [M + Na]. $[\alpha]_D^{25}$ = +40.6 (c = 2.4, CH_2Cl_2).

NMR measurement of enantiomeric purity: A sample of enantioenriched **3a** and approximately 2 mol-equiv. of (*S*)-*O*-acetylmandelic acid were mixed in $CDCl_3$. Lines for (*S*)-**3a** in this solution are 4.25 (s, 1 H), 3.73 (d, J = 18 Hz, 1 H), 3.50 (d, J = 18 Hz, 1 H), 2.99 (s, 1 H), 0.95 (s, 1 H) ppm; for (*R*)-**3a** 4.24 (s, 1 H), 3.76 (d, J = 18 Hz, 1 H), 3.53 (d, J = 18 Hz, 1 H), 2.99 (s, 1 H), 0.91 (s, 1 H) ppm.

(*2S,5S*)-(–)-2-*tert*-Butyl-1-hydroxy-3,5-dimethylimidazolidin-4-one (3b): Chromatography (cyclohexane/ethyl acetate, 1:1, R_f = 0.56) yielded 65% (1.21 g) of **3b**, m.p. 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 4.17 (s, 1 H), 3.65 (q_4, J = 7.2 Hz, 1 H), 3.00 (s, 3 H), 1.36 (d, J = 7.2 Hz, 3 H), 1.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5 (C), 96.4 (CH), 62.5 (CH), 36.9 (C), 32.3 (CH_3), 26.8 (CH_3), 10.8 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3349, 3317, 2960, 2872, 1680 cm^{-1}. HRMS: found: m/z = 209.1266; calculated: m/z = 209.1266 [M + Na]. $[\alpha]_D^{25}$ = –32 (c = 2.0, CH_2Cl_2).

Oxidation of *N*-Hydroxylamines 3 to Nitrones 2: Crude **3a**,**b** from the preceding preparation was added to DCM (20 mL) and stirred with activated MnO_2 (Fluka, ref. 63548, 1.74 g, 20 mmol) for 2 h at 20 °C. Filtration of the slurry through Celite and repeated washing with EtOAc yielded nitrone **2a**,**b** in sufficient purity for direct use. When crude **3a**,**b** were oxidized, the yields of **2a**,**b** from **1a**,**b** were 95 and 99% respectively. When the same MnO_2 oxidation reaction was performed with purified samples of **3a** and **3b**, quantitative yields were obtained.

The *ee* values of **2a** and **2b** were determined by reversed-phase HPLC on a Daicel CHIRALPAK AD-RH column (length: 150 mm, flow rate: 0.3 mL min^{-1}, mobile phase: acetonitrile/water (40:60) for **3a**, 25:75 for **3b**. Retention times: (*R*)-**2a** 20.4 min, (*S*)-**2a** 24.8 min, (*S*)-**3a** 17.4 min, and (*R*)-**3a** 18.6 min.

(*R*)-2-*tert*-Butyl-3-methyl-2,3-dihydroimidazol-4-one *N*-Oxide (2a): Yield = 95% from **3a** (crude material, oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (s, 1 H), 4.64 (s, 1 H), 3.10 (s, 3 H), 1.14 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9 (C), 126.4 (CH), 94.9 (CH), 37.3 (C), 32.3 (CH_3), 25.5 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3080, 2967, 2936, 2869, 1717, 1574, 1559, 1288, 647, 557 cm^{-1}. HRMS: found: m/z = 171.1137; calculated: m/z = 171.1134 [M + H]. The crude sample had 61% *ee*. $[\alpha]_D^{25}$ = –73.3 (c = 1.34, $CHCl_3$) [lit.[19] +218 (c = 0.15, $CHCl_3$ for (*S*)-**2a**)].

Oxidation with UHP/MTO: UHP (77 mg, 0.82 mmol) and then MTO (5 mg, 0.03 mmol) were added to enantiopure (*R*)-**3a** (54 mg, 0.35 mmol) in methanol (1 mL) at 0 °C . The reaction was stirred for 18 h at 20 °C. Work up according to ref.[19] led to **2a** (quant.) in 95% *ee*. This crude sample had $[\alpha]_D^{25}$ = –142.6 (c = 2.06, $CHCl_3$).

(*2S*)-2-*tert*-Butyl-3,5-dimethyl-2,3-dihydroimidazol-4-one *N*-Oxide (2b): Yield 99% from **2b** (crude material, solid), m.p. 67 °C. ^{1}H

NMR (300 MHz, $CDCl_3$): δ = 4.57 (s, 1 H), 3.11 (s, 3 H), 2.08 (s, 3 H), 1.12 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (C), 135.9 (C), 93.0 (CH), 37.5 (C), 32.4 (CH_3), 25.5 (CH_3), 7.6 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 2964, 2925, 2874, 1692, 1594, 1468, 1448, 1380, 1335, 1268, 1228, 1197, 1056, 1003, 734, 577, 545 cm^{-1}. HRMS: found: *m*/*z* = 185.1282; calculated: *m*/*z* = 185.1290 [M + H]. $[\alpha]_D^{25}$ = +158.5 (*c* = 4.46, CH_2Cl_2). Chiral HPLC: one enantiomer was detected. A sample was prepared according to ref.[19]: $[\alpha]_D^{25}$ = +152.1 (*c* = 1.46, CH_2Cl_2); one enantiomer was detected by HPLC.

General Procedure: Reaction of Nitrone 2b with Excess Alkyne and Dimethylzinc: Nitrone **2b** (184 mg, 1 mmol) and the alkyne (3 mmol) in toluene (2 mL) were introduced into a 30 mL Schlenk vessel under N_2. A 2 M solution of dimethylzinc in toluene (1.5 mmol) was added at 20 °C, and the reaction mixture was stirred at 20 °C overnight. Hydrolysis was performed with saturated aqueous NH_4Cl (2 mL) at 20 °C for 30 min. After extraction with EtOAc, the organic phase was washed with brine, dried with Na_2SO_4, and concentrated to give a crude oil which was purified by chromatography.

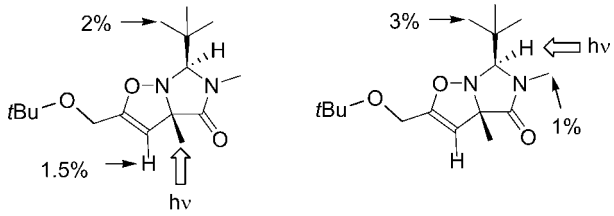
(2*S*,5*S*)-2-*tert*-Butyl-1-hydroxy-3,5-dimethyl-5-(trimethylsilylethynyl)imidazolidin-4-one (4a): Prepared according to general procedure from **2b** (173 mg, 0.94 mmol), trimethylsilylacetylene (0.45 mL, 3.0 mmol), and dimethylzinc (0.75 mL, 1.5 mmol). Chromatography (EtOAc/cyclohexane, 4:6) yielded 220 mg (83%) of **4a** (R_f = 0.75 in EtOAc/cyclohexane, 1:1), m.p. 113 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.67 (s, 1 H), 3.75 (s, 1 H), 2.94 (s, 3 H), 1.52 (s, 3 H), 1.01 (s, 9 H), 0.14 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3 (C), 98.0 (C), 95.2 (C), 88.3 (CH), 65.5 (C), 35.2 (C), 30.9 (CH_3), 26.5 (CH_3), 23.3 (CH_3), 0.1 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3370, 2996, 2962, 2900, 2871, 2174, 1706, 1404, 1396, 1345, 1254, 1176, 1094, 1086, 896, 848, 767 cm^{-1}. HRMS: found: *m*/*z* = 305.1682; calculated: *m*/*z* = 305.1661 [M + Na]. $[\alpha]_D^{25}$ = –64 (*c* = 2.4, CH_2Cl_2).

(6*S*,3a*S*)-6-*tert*-Butyl-3a,5-dimethyl-2-phenyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (5b): Prepared according to the general procedure from **2b** (346 mg, 1.88 mmol), phenylacetylene (602 mg, 6.0 mmol), and dimethylzinc (1.5 mL, 3 mmol). Chromatography (EtOAc/cyclohexane, 4:6) yielded 495 mg (92%) of **5b** as an oil (R_f = 0.55 in EtOAc/cyclohexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.45 (m. 2 H), 7.34–7.29 (m. 3 H), 5.30 (s. 1 H), 4.13 (s. 1 H), 2.93 (s. 3 H), 1.51 (s. 3 H), 1.08 (s. 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (C), 153.8 (C), 129.8 (CH), 128.8 (CH), 128.1 (C), 126.1 (CH), 97.4 (CH), 92.9 (CH), 75.8 (C), 36.0 (C), 31.3 (CH_3), 26.2 (CH_3), 23.5 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3107, 3061, 2961, 2925, 2869, 2851, 1707, 1495, 1481, 1449, 1396, 1282, 1241, 1071, 1004, 997, 765, 740, 716, 691 cm^{-1}. HRMS: found: *m*/*z* = 287.1755; calculated: *m*/*z* = 287.1760 [M + H]. $[\alpha]_D^{25}$ = +28 (*c* = 3.1, MeOH).

(6*S*,3a*S*)-2-Butyl-6-*tert*-butyl-3a,5-dimethyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (5c): Prepared according to the general procedure from **2b** (364 mg, 1.98 mmol), hex-1-yne (0.91 mL, 8 mmol), and dimethylzinc (1.5 mL, 3 mmol). Chromatography (EtOAc/cyclohexane, 3:7) yielded 318 mg (60%) of **5c** as an oil (R_f = 0.70 in EtOAc/cyclohexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.53 (s, 1 H), 3.93 (s, 1 H), 2.86 (s, 3 H), 2.05 (t, *J* = 8.2 Hz, 2 H), 1.33 (s, 3 H), 1.34 (m, 4 H), 0.97 (s, 9 H), 0.83 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C), 155.4 (C), 95.6 (CH), 91.7 (CH), 73.6 (C), 34.6 (C), 29.9 (CH_3), 27.8 (CH_2), 24.8 (CH_3), 24.2 (CH_2), 22.3 (CH_3), 21.2 (CH_2), 12.7 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 2957, 2926, 2855, 1712, 1482, 1467, 1425, 1396, 1365, 1071 cm^{-1}. HRMS: found: *m*/*z* = 267.2066; calculated: *m*/*z* = 267.2073 [M + H]. $[\alpha]_D^{25}$ = –27 (*c* = 2.9, CH_2Cl_2).

(6*S*,3a*S*)-6-*tert*-Butyl-2-(cyclohex-1-enyl)-3a,5-dimethyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (5d): Prepared according to the general procedure from **2b** (172 mg, 0.93 mmol), 1-ethynylcyclohexene (300 mg, 2.84 mmol), and dimethylzinc (0.75 mL, 1.5 mmol). Chromatography (EtOAc/cyclohexane, 4:6) yielded 255 mg (94%) of **5d** as an oil (R_f = 0.55 in EtOAc/cyclohexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.13 (m, 1 H), 4.83 (s, 1 H), 4.05 (s, 1 H), 2.95 (s, 3 H), 2.14–2.12 (m, 4 H), 1.69–1.59 (m, 4 H), 1.44 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (C), 154.5 (C), 128.5 (C), 125.4 (C), 96.7 (CH), 92.5 (CH), 75.1 (C), 35.7 (C), 31.0 (CH_3), 27.1 (CH_2), 25.9 (CH_3), 25.4 (CH_2), 23.3 (CH_3), 22.3 (CH_2), 22.0 (CH_2) ppm. FTIR: $\tilde{\nu}$ = 2930, 2866, 1715, 1659, 1620, 1482, 1398, 1368, 1280, 1266, 1248, 1076, 998, 959, 926 cm^{-1}. HRMS: found: *m*/*z* = 291.2093; calculated: *m*/*z* = 291.2073 [M + H]. $[\alpha]_D^{25}$ = –146 (*c* = 2.1, CH_2Cl_2).

(6*S*,3a*S*)-2-*tert*-Butoxymethyl-6-*tert*-butyl-3a,5-dimethyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (5e): Prepared according to the general procedure from **2b** (213 mg, 1.15 mmol), 3-*tert*-butoxyprop-1-yne (390 mg, 3.5 mmol), and dimethylzinc (0.87 mL, 1.75 mmol). Chromatography (EtOAc/cyclohexane, 4:6) yielded 319 mg (90%) of **5e** as an oil (R_f = 0.66 in EtOAc/cyclohexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.90 (s, 1 H), 4.06 (s, 1 H), 3.95 (s, 1 H), 2.93 (s, 3 H), 1.43 (s, 3 H), 1.20 (s, 9 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C), 154.5 (C), 98.9 (CH), 92.6 (CH), 74.7 (C), 74.4 (C), 55.8 (CH_2), 35.8 (C), 31.8 (CH_3), 27.5 (CH_3), 25.9 (CH_3), 23.3 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3116, 2974, 2930, 2871, 1710, 1396, 1366, 1194, 1071 cm^{-1}. HRMS: found: *m*/*z* = 297.2184; calculated: *m*/*z* = 297.2178 [M + H]. $[\alpha]_D^{25}$ = –122 (*c* = 1.2, CH_2Cl_2). For details of the NOE experiment see Scheme 8.



Scheme 8.

(6*S*,3a*S*)-2-(Acetoxymethyl)-6-*tert*-butyl-3a,5-dimethyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (5f): Prepared according to the general procedure from **2b** (92 mg, 0.5 mmol), prop-2-ynyl acetate (150 mg, 1.5 mmol), and dimethylzinc (0.38 mL, 0.75 mmol). Chromatography (EtOAc/cyclohexane, 4:6) yielded 107 mg (76%) of **5f** as an oil (R_f = 0.50 in EtOAc/cyclohexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.99 (s, 1 H), 4.63 (s, 2 H), 4.08 (s, 1 H), 2.95 (s, 3 H), 2.10 (s, 3 H), 1.44 (s, 3 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (C), 169.9 (C), 150.4 (C), 101.0 (CH), 92.5 (CH), 74.6 (C), 56.4 (CH_2), 35.6 (CH_3), 30.9 (C), 25.6 (CH_3), 22.9 (CH_3), 20.6 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3115, 2963, 2873, 1752, 1706, 1482, 1450, 1429, 1397, 1367, 1232, 1062, 1032, 990 cm^{-1}. HRMS: found: *m*/*z* = 305.1464; calculated: *m*/*z* = 305.1477 [M + Na]. $[\alpha]_D^{25}$ = –34.4 (*c* = 1.7, CH_2Cl_2).

(6*S*,3a*S*)-6-*tert*-Butyl-2-(diethoxymethyl)-3a,5-dimethyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (5g): Prepared according to the general procedure from **2b** (296 mg, 1.61 mmol), 1,1-diethoxyprop-2-yne (0.69 mL, 4.8 mmol), and dimethylzinc (1.2 mL, 2.4 mmol). Chromatography (EtOAc/cyclohexane, 2:8) yielded 390 mg (78%) of **5g** as an oil (R_f = 0.82 in EtOAc/cyclohexane, 1:1). ^1H NMR

(300 MHz, $CDCl_3$): δ = 5.07 (d, J = 1.0 Hz, 1 H), 5.03 (d, J = 1.0 Hz, 1 H), 4.07 (s, 1 H), 3.70–3.49 (m, 4 H), 2.94 (s, 3 H), 1.45 (s, 3 H), 1.21 (t, J = 7.2 Hz, 6 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C), 152.8 (C), 101.1 (CH), 95.3 (CH), 93.0 (CH), 74.9 (C), 62.3 (CH_2), 61.8 (CH_2), 36.1 (C), 31.4 (CH_3), 15.5 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 2976, 2930, 2877, 1709, 1396, 1121, 1065 cm^{-1}. HRMS: found: m/z = 267.1716; calculated for $C_{14}H_{23}N_2O_3$: m/z = 267.1709. $[\alpha]_D^{25}$ = –4 (c = 2,3, CH_2Cl_2).

^{1}H NMR Observation of the Tandem Reaction: Signals observed in the reaction mixture ([D_8]toluene, 300 MHz, reference toluene 2.09 ppm, all singlets). Nitrone **2b**: 0.76 (9 H), 1.91 (3 H), 2.50 (3 H), 3.86 (1 H) ppm. Adduct **6**: 0.82 (9 H), 1.84 (3 H), 2.65 (3 H), 3.84 (1 H) ppm. Cycloadduct **5b**: 0.88 (9 H), 1.60 (3 H), 2.57 (3 H), 3.84 (1 H), 5.43 (1 H) ppm.

Preparation of (2*S*,5*S*)-2-*tert*-Butyl-5-(cyclohex-1-enylethynyl)-1-hydroxy-3,5-dimethylimidazolidin-4-one (4d): Nitrone **2b** (184 mg, 1 mmol) in toluene (2 mL), 1-ethynylcyclohexene (300 mg, 2.84 mmol), and dimethylzinc (1.5 mmol) in toluene (0.75 mL) were introduced into a 30 mL Schlenk vessel under N_2. The reaction mixture was stirred at 20 °C for 6 h. Hydrolysis was performed with saturated aqueous NH_4Cl (2 mL) at 20 °C for 30 min. After extraction of the reaction mixture with EtOAc, the organic phase was washed with brine, dried with Na_2SO_4, and concentred to give a crude oil which was purified chromatography (EtOAc/cyclohexane, 1:9 to 4:6). Compound **4d** was eluted first as an oil in 40% yield (116 mg). R_f = 0.76 in EtOAc/cyclohexane, 1:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.19–6.15 (m, 1 H), 4.72 (s, OH), 3.83 (s, 1 H), 2.98 (s, 3 H), 2.11–2.08 (m, 4 H), 1.61–1.57 (m, 4 H), 1.58 (s, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7 (C), 136.9 (CH), 119.6 (C), 91.6 (C), 88.2 (CH), 79.5 (C), 65.3 (C), 35.2 (C), 30.8 (CH_3), 29.3 (CH_2), 26.6 (CH_3), 25.8 (CH_2), 23.5 (CH_3), 22.3 (CH_2), 21.5 (CH_2) ppm. FTIR: $\tilde{\nu}$ = 3391, 2934, 2863, 2934, 2863, 2230 (w), 1705, 1488, 1402, 1365, 1260, 1204, 1137, 1068 cm^{-1}. HRMS: found: m/z = 313.1909; calculated: m/z = 313.1879 [M + Na]. $[\alpha]_D^{25}$ = –29 (c = 2.0, CH_2Cl_2).

Cyclization of 4d: A 2 M solution of dimethylzinc (0.35 mmol) in toluene (0.17 mL) was added to pure **4d** (50 mg, 0.17 mmol) in toluene (0.5 mL). After 18 h at 20 °C, the reaction mixture was hydrolyzed with sat. NH_4Cl (1 mL). After the usual work up and filtration through silica, a 93% yield (47 mg) of **5d** was obtained. The reaction was repeated identically and deuterolysis was performed with a 1 M solution of DCl in D_2O (0.5 mL) for 30 min, followed by the usual EtOAc extraction. The ^{1}H NMR signal at δ = 4.83 ppm (vinylic) was less intense (intensity 0.13 H) in the deuteriated sample.

(*rac*)-6-*tert*-Butyl-3-iodo-3a,5-dimethyl-2-phenyl-5,6-dihydro-3a*H*-imidazo[1,5-*b*]isoxazol-4-one (8): Toluene (2 mL), phenylacetylene (0.25 mL, 2.2 mmol), and a 2 M solution of dimethylzinc (4.8 mmol) in toluene (2.4 mL) were introduced into a Schlenk tube under N_2. After stirring for 1.5 h at 20 °C, a solution of (*rac*)-**2b** (216 mg, 1.17 mmol) in toluene (2 mL) was added. The mixture was stirred at 20 °C for 12 h. Then, *N*-iodosuccinimide (2.5 g, 6 mmol) in THF (10 mL) was introduced. After 1 h, the usual aqueous work up and chromatography (EtOAc/cyclohexane, 1:9) yielded 299 mg (62%) of **8** as an oil (R_f = 0.82 in EtOAc/cyclohexane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.72 (m, 2 H), 7.30–7.28 (m, 3 H), 3.99 (s, 1 H), 2.87 (s, 3 H), 1.40 (s, 3 H), 0.99 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (C), 151.5 (C), 130.0 (CH), 128.2 (CH), 127.9 (CH), 127.3 (C), 91.3 (CH), 76.5 (C), 35.4 (C), 30.5 (CH_3), 25.7 (CH_3), 21.9 (CH_3) ppm; C–I was not detected. FTIR: $\tilde{\nu}$ = 2976, 2930, 2877, 1709, 1396, 1121, 1065 cm^{-1}. HRMS: found: m/z = 435.0520; calculated: m/z = 435.0545 [M + Na].

Treatment of a sample of **5b** with NIS in THF (20 °C, 2 h) did not produce **8**.

Ethyl 2-Benzyl-2,3-dihydro-5-phenylisoxazole-3-carboxylate (5h): Prepared according to the general procedure from nitrone **9** (52 mg, 0.25 mmol), phenylacetylene (77 mg, 0.75 mmol), and dimethylzinc (0.18 mL, 0.36 mmol). Chromatography (EtOAc/cyclohexane, 2:8) yielded 70 mg (91%) of **5h** as an oil (R_f = 0.82 in EtOAc/cyclohexane, 2:8). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.28 (m, 10 H), 5.28 (d, J = 3.0 Hz, 1 H), 4.62 (d, J = 3.0 Hz, 1 H), 4.40 (d, J = 12.8 Hz, 1 H), 4.17 (quad, J = 7.1 Hz, 2 H), 4.05 (d, J = 12.8 Hz, 1 H), 1.23 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 (C), 155.0 (C), 135.8 (C), 133.8 (C), 130.0 (CH), 129.8 (CH), 128.7 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 90.4 (CH), 72.0 (CH), 63.8 (CH_2), 61.7 (CH_2), 14.5 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3114, 3088, 3061, 3036, 2960, 2935, 2898, 2871, 1764, 1455, 1006, 763, 740, 701, 532 cm^{-1}. HRMS: found: m/z = 310.1451; calculated: m/z = 310.1443 [M + H].

Methyl 2-(*tert*-Butoxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]isoxazole-3a-carboxylate (5i): Prepared according to the general procedure from nitrone **10** (86 mg, 0.60 mmol), 3-*tert*-butoxyprop-1-yne (200 mg, 1.8 mmol), and dimethylzinc (0.45 mL, 0.9 mmol). Chromatography (EtOAc/cyclohexane, 2:8) yielded 145 mg (95%) of **5i** as an oil (R_f = 0.85 in AcOEt/cyclohexane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.79 (s, 1 H), 3.95 (s, 2 H), 3.75 (s, 3 H), 3.75–3.32 (m, 2 H), 2.25–2.14 (m, 1 H), 2.10–2.02 (m, 1 H), 1.95–1.79 (m, 2 H), 1.21 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (C), 155.6 (C), 96.5 (CH), 82.2 (C), 74.3 (C), 60.2 (CH_2), 56.0 (CH_2), 52.6 (CH_3), 36.8 (CH_2), 29.8 (C), 27.5 (CH_3), 23.2 (CH_2) ppm. FTIR: $\tilde{\nu}$ = 2954, 2950, 2860, 1747, 1561, 1458, 1388, 1259, 1182, 1112 cm^{-1}. HRMS: found: m/z = 256.1538; calculated: m/z = 256.1549 [M + H].

(2-Benzyl-2,3-dihydro-3-phenylisoxazol-5-yl)methyl Acetate (5k): Prepared according to the general procedure from nitrone **11** (106 mg, 0.50 mmol), 3-acetoxyprop-1-yne (147 mg, 1.5 mmol), and dimethylzinc (0.40 mL, 0.8 mmol). Chromatography (EtOAc/cyclohexane, 2:8) yielded 126 mg (82%) of **5i** as an oil (R_f = 0.75 in AcOEt/cyclohexane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 –7.10 (m, 10 H), 4.98 (d, J = 2.5 Hz, 1 H), 4.87 (d, J = 2.5 Hz, 1 H), 4.67 (d, J = 13.4 Hz, 1 H), 4.61 (d, J = 13.4 Hz, 1 H), 4.27 (d, J = 13.0 Hz, 1 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.35 (C), 149.78 (C), 141.53 (C), 136.11 (C), 129.50 (CH), 128.49 (CH), 128.34 (CH), 128.13 (CH), 127.62 (CH), 126.94 (CH), 99.91 (CH), 72.98 (CH), 63.34 (CH_2), 57.18 (CH_2), 20.75 (CH_3) ppm. FTIR: $\tilde{\nu}$ = 3090, 3062, 3030, 2927, 1746, 1669, 1230, 932, 761, 698 cm^{-1}. HRMS: found: m/z = 310.1455; calculated: m/z = 310.1443 [M + H].

Acknowledgments

F.C. thanks LEDSS (UMR, 5616) for financial support. We thank Dr. C. Philouze for carrying out the X-ray structure determination.

[1] H. C. J. Ottenheijm, J. D. M. Herscheid, *Chem. Rev.* **1986**, *86*, 697–707.
[2] For oxidation with SeO_2/H_2O_2, see: S.-I. Murahashi, T. Shiota, *Tetrahedron Lett.* **1987**, *28*, 2383–2386.
[3] For oxidation with Na_2WO_4/H_2O_2, see: S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, S. Watanabe, *J. Org. Chem.* **1990**, *55*, 1736–1744.
[4] S.-I. Murahashi, T. Shiota, Y. Imada, *Org. Synth.* **1991**, *70*, 265–271.

[5] For oxidation with SeO_2 or Na_2WO_4/UHP, see: E. Marcantoni, M. Petrini, O. Polimanti, *Tetrahedron Lett.* **1995**, *36*, 3561–3562.
[6] For oxidation with MTO/H_2O_2, see: R. W. Murray, K. Iyanar, J. Chen, J. T. Wearing, *J. Org. Chem.* **1996**, *61*, 8099–8102.
[7] For oxidation with MTO/UHP, see: A. Goti, L. Nannelli, *Tetrahedron Lett.* **1996**, *37*, 6025–6028.
[8] A. Goti, F. Cardona, G. Soldaini, *Org. Synth.* **2004**, *81*, 204–212.
[9] S. Yamazaki, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 877–883.
[10] For *N*-phenylsulphonyl-*C*-phenyloxaziridine, see: W. W. Zajac, Jr., T. R. Walters, M. G. Darcy, *J. Org. Chem.* **1988**, *53*, 5856–5860.
[11] For dimethyldioxirane, see: R. W. Murray, M. Singh, *J. Org. Chem.* **1990**, *55*, 2954–2957.
[12] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708–2748.
[13] A. Vogt, H.-J. Altenbach, M. Kirschbaum, M. G. Hahn, M. S. P. Matthaeus, A. R. Hermann, *Eur. Pat. Appl*. 99-114037, **2000**.
[14] B. Westermann, A. Walter, U. Floerke, H.-J. Altenbach, *Org. Lett.* **2001**, *3*, 1375–1378.
[15] A. Long, S. W. Baldwin, *Tetrahedron Lett.* **2001**, *42*, 5343–5346.
[16] S. W. Baldwin, B. G. Young, A. T. McPhail, *Tetrahedron Lett.* **1998**, *39*, 6819–6822.
[17] O. Tamura, K. Gotanda, J. Yoshino, Y. Morita, R. Terashima, M. Kikuchi, T. Miyawaki, N. Mita, M. Yamashita, H. Ishibashi, M. Sakamoto, *J. Org. Chem.* **2000**, *65*, 8544–8551.
[18] N. Katagiri, M. Okada, Y. Morishita, C. Kaneko, *Tetrahedron* **1997**, *53*, 5725–5746.
[19] S. W. Baldwin, A. Long, *Org. Lett.* **2004**, *6*, 1653–1656.
[20] S. Pinet, S. U. Pandya, P. Y. Chavant, A. Ayling, Y. Vallee, *Org. Lett.* **2002**, *4*, 1463–1466.
[21] S. K. Patel, S. Py, S. U. Pandya, P. Y. Chavant, Y. Vallee, *Tetrahedron: Asymmetry* **2003**, *14*, 525–528.
[22] R. Fitzi, D. Seebach, *Tetrahedron* **1988**, *44*, 5277–5292.
[23] R. Naef, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 135–143.
[24] R. Fitzi, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 345–346; a corrigendum to this publication has been published in *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 766.
[25] R. W. Feenstra, E. H. M. Stokkingreef, A. M. Reichwein, W. B. H. Lousberg, H. C. J. Ottenheijm, *Tetrahedron* **1990**, *46*, 1745–1756.
[26] Not isolated. We propose the structure (2*S*)-2-*tert*-butyl-2-hydroxy-3-methyl-2,3-dihydroimidazol-4-one 1-oxide on the basis of NMR evidence.
[27] R. W. Murray, K. Iyanar, J. Chen, J. T. Wearing, *Tetrahedron Lett.* **1996**, *37*, 805–808.
[28] For the NMR determination with *O*-acetylmandelic acid as chiral shift reagent, see the Exp. Sect.
[29] S. Cicchi, M. Marradi, A. Goti, A. Brandi, *Tetrahedron Lett.* **2001**, *42*, 6503–6505.
[30] Determined by HPLC. In our hands Baldwin and Long's procedure (see ref.[19]) produced **2a** in 95% *ee* from enantiopure **3a** (see Exp. Sect.).
[31] For nitrone alkynylation, see: D. E. Frantz, R. Faessler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246.
[32] S. K. Patel, K. Murat, S. Py, Y. Vallee, *Org. Lett.* **2003**, *5*, 4081–4084.
[33] S. Hanessian, M. Bayrakdarian, X. Luo, *J. Am. Chem. Soc.* **2002**, *124*, 4716–4721.
[34] For recent examples of C=N bond alkynylation reactions, see: D. A. Black, B. A. Arndtsen, *Org. Lett.* **2004**, *6*, 1107–1110.
[35] C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639.
[36] C. Fischer, E. M. Carreira, *Org. Lett.* **2004**, *6*, 1497–1499.
[37] J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *Org. Lett.* **2003**, *5*, 3273–3275.
[38] N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2003**, *42*, 5763–5766.
[39] We observed that when stoichiometric amounts of diethylzinc were present in the reaction of nitrones, trace amounts of the ethyl adduct were sometimes observed. Replacing diethylzinc with dimethylzinc suppressed this side reaction.
[40] We previously observed one occurrence of this cyclization reaction (see ref.[20]): see the last entry of Table 1.
[41] Under the same conditions, the reaction of **2a** led mainly to decomposition products.
[42] See the Exp. Sect.
[43] P. Aschwanden, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 2331–2333.
[44] See the Exp. Sect.
[45] Nevertheless, mass spectrometry indicated only 22% deuterium.
[46] M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999–5004.
[47] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[48] M. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, S. Watanabe, *J. Org. Chem.* **1990**, *55*, 1736–1744.
[49] Y. Inouye, Y. Watanabe, S. Takahashi, H. Kakisawa, *Bull. Chem. Soc., Jpn.* **1979**, *52*, 3763–3764.
[50] A. Goti, L. Nannelli, *Tetrahedron Lett.* **1996**, *37*, 6025–6028.
[51] F. Lambert, B. Kirschleger, J. Villiéras, *J. Organomet. Chem.* **1991**, *405*, 273–286.
[52] R. F. W. Jackson, R. J. Moore, C. S. Dexter, *J. Org. Chem.* **1998**, *63*, 7875–7884.
[53] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R.Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Burant, J. C. Stratmann, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, P. Komaromi, I. Gomperts, R. R. Martin, R. L. Fox, D. J. Keith, T. Al Laham, M. A. Peng, C. Y. A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head Gordon, E. S. Replogle, J. A. Pople, Gaussian 98, Revision A6, Gaussian, Inc.: Pittsburgh PA, **1998**.
[54] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[55] For IRC analysis, see: K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363–368.
[56] M. Head-Gordon, J. A. Pople, *J. Chem. Phys.* **1988**, *89*, 5777–5786.

Received: December 3, 2004

