A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

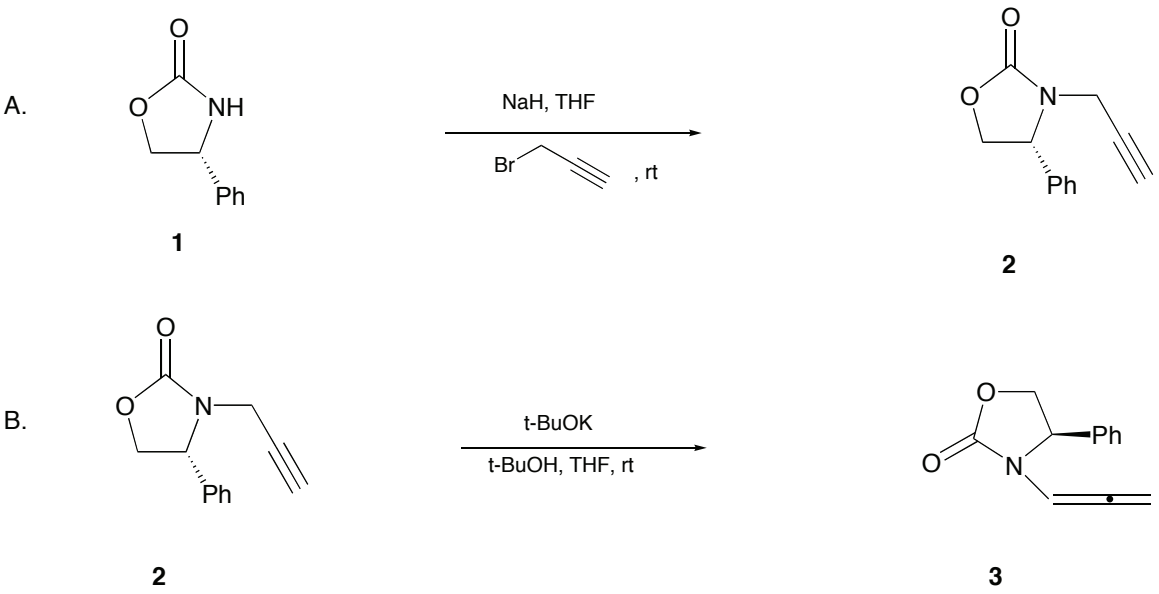
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.081.0147
Organic Syntheses, Vol. 81, p. 147-156 (2005); Coll. Vol. 11, p. 726-732 (2009).

PRACTICAL SYNTHESIS OF NOVEL CHIRAL ALLENAMIDES: (*R*)-4-PHENYL-3-(1,2-PROPADIENYL)OXAZOLIDIN-2-ONE (2-Oxazolidinone, 4-phenyl-3-(1,2-propadienyl)–, (4*R*)–)



Submitted by H. Xiong, M. R. Tracey, T. Grebe, J. A. Mulder, and R. P. Hsung.[1]
Checked by Peter Wipf and Jennifer Smotryski.
Discussion Addendum *Org. Synth.* **2014**, *91*, 12

1. Procedure

A. (R)-4-Phenyl-3-(2-propynyl)oxazolidin-2-one (2). A flame-dried, 500-mL, round-bottomed flask equipped with a magnetic stirbar and a rubber septum fitted with a nitrogen inlet is charged with 9.90 g (61 mmol) of (*R*)-4-phenyl-2-oxazolidinone (Note 1) and 200 mL of anhydrous tetrahydrofuran (THF) under a nitrogen atmosphere (Note 2). Sodium hydride (NaH) (2.90 g, 60% w/w in mineral oil, 1.20 equiv, 73 mmol) is added in small portions (Note 3), and the resulting white slush is stirred for 1 h at room temperature before carefully adding 8.00 mL of a solution of propargyl bromide in toluene (80% w/w in toluene, 72 mmol, 1.18 equiv) (Note 4) dropwise over ca. 10 min via syringe. Precipitation of sodium bromide is observed and does not affect the progress of the reaction. The reaction mixture is stirred at room temperature for 24 h and then

concentrated by rotary evaporation under reduced pressure. The residue is dissolved in 100 mL of anhydrous ether and filtered through a small bed of Celite washing with 1:1 ethyl acetate-hexane. The filtrate is concentrated by rotary evaporation, and the resulting residue is purified using silica gel column chromatography (gradient eluent with 0-33% ethyl acetate-hexane) to give 5.71-6.09 g (47-50%) of the desired propargyl amide **2** as a lightly yellow-colored oil (Note 5).

*B. (R)-4-Phenyl-3-(1,2–propadienyl)-2-oxazolidinone (**3**).* A flame-dried, 500-mL, round-bottomed flask equipped with a magnetic stirbar and a rubber septum fitted with a nitrogen inlet is charged with a solution of 6.67 g (33 mmol) of propargyl amide **2** in 300 mL of anhydrous THF (Note 2). Potassium *tert*-butoxide (1.26 g, 11 mmol, 0.33 equiv) (Notes 6, 7) is added in portions to the reaction mixture over ca. 10 min. The reaction mixture is stirred at room temperature for 24 h and the progress of the reaction is monitored by TLC (elution with 50% ethyl acetate-hexane) and ^{1}H NMR analysis. Upon completion of the reaction, the solvent is removed by rotary evaporation under reduced pressure. The resulting crude residue is dissolved in 50 mL of ethyl acetate and vacuum filtered through a small bed of silica gel. The solids are washed with two 40-mL portions of 25-50% ethyl acetate-hexane, and the filtrate is then concentrated by rotary evaporation. The residue is purified using silica gel column chromatography (gradient elution with 0% to 25% ethyl acetate-hexanes) to give 1.41-1.59 g (38-41%) of the desired allenamide **3** as a yellow brownish-red oil (Note 8).

2. Notes

1. (*R*)-4-Phenyl-2-oxazolidinone was purchased from Sigma-Aldrich or Urquima, S.A. Arnau de Vilanove, Barcelona, Spain and used as received.

2. Anhydrous THF was freshly distilled from sodium/ benzophenone under nitrogen.

3. *Caution: evolution of large amount of H_2 gas.* NaH was obtained from Sigma-Aldrich and used as received. NaH free of oil can also be used with no difference in yield and was prepared via four cycles of washing and decanting (via pipette) with anhydrous pentane.

4. Propargyl bromide was obtained as an 80% w/w solution in toluene from Sigma-Aldrich.

5. The submitters report obtaining the product in 66% yield prior to purification at 0.050 mole-scale and suggest that the purification step is not necessary because in most cases simple filtration through a small bed of Celite or silica gel provided the desired propargyl amide with high purity as determined by GC analysis. Specifically, GC analysis of propargyl amide **2** shows its purify to be 98.2% prior to column chromatography, and 98.5% after chromatography. After column chromatography, the submitters obtained 6.40 g (52%) of the desired amide. The amide displays the following physical properties: R_f = 0.49 (50% EtOAc in hexane); $[\alpha]_D^{20}$ 148.8 (c 10.2, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.25 (t, 1H, *J* = 2.4 Hz), 3.35 (dd, 1H, *J* = 2.4, 17.7), 4.12 (dd, 1H, *J* = 7.8, 8.7), 4.36 (dd, 1H, *J* = 2.4, 17.7), 4.65 (t, 1H, *J* = 8.7), 4.95 (dd, 1H, *J* = 7.8, 8.7), 7.32-7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.0, 59.0, 70.0, 73.4, 76.6, 127.3, 129.3, 129.4, 136.6, 157.8; IR (neat) cm^{-1}: 3285, 2913, 2100, 1733, 1494, 1177, 860; mass spectrum (EI): *m/e* (%relative intensity) 201 (20) M^+, 156 (51), 143 (24), 124 (30), 116 (66), 104 (100), 91 (22), 77 (21); *m/e* calcd for $C_{12}H_{12}NO_2$: 202.086; found 202.0871.

6. Potassium *tert*-butoxide was obtained from Sigma-Aldrich and used as received. Alternatively, equivalent results were obtained using *t*-BuOK that was prepared from potassium metal and anhydrous *tert*-butyl alcohol (*t*-BuOH) followed by removal of excess *t*-BuOH. In this case, the molecular weight of *t*-BuOK was calculated based on a 1:1 ratio of *t*-BuOK to *t*-BuOH (i.e., 186.34 for $C_8H_{19}O_2K$).

7. The submitters report that equivalent results were obtained using between 0.20-0.35 equiv of *t*-BuOK.

8. The submitters report obtaining the allenamide in 63% yield on this scale with its purity determined by GC analysis to be between 94%-96% in different runs. The lower yield obtained by the checkers may be explained by partial decomposition of product during the chromatographic purification on standard (40-60 nm) silica gel. The physical properties of 3 are as follows: R_f = 0.59 (50% ethyl acetate-hexane); $[\alpha]_D^{20}$ –156.4 (c 0.225, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)) δ: 4.14 (dd, 1H, *J* = 5.9, 9.8), 4.69 (t, 1H, *J* = 9.0), 4.87 (dd, 1H, *J* = 6.4, 9.5), 4.88 (dd, 1H, *J* = 6.4, 9.5), 5.16 (dd,

1H, J = 5.9, 9.8), 6.79 (t, 1H, J = 6.4), 7.23 – 7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 59.0, 70.6, 87.7, 95.6, 126.5, 128.7. 129.0, 138.4, 155.5, 201.9; IR (neat) cm^{-1} 3063, 3035, 2979, 1963, 1767, 1494, 1462, 1216, 966, 911, 881; mass spectrum (EI): *m/e* (%relative intensity) 201 (17) M^+, 156 (100), 129 (17), 115 (20), 104 (54), 91 (17), 77 (17); *m/e* calcd for $C_{12}H_{11}NO_2$ 201.0790, found 201.0784.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Praactices in the Laboratory"; National Academy Press; Washington, DC, 1995.

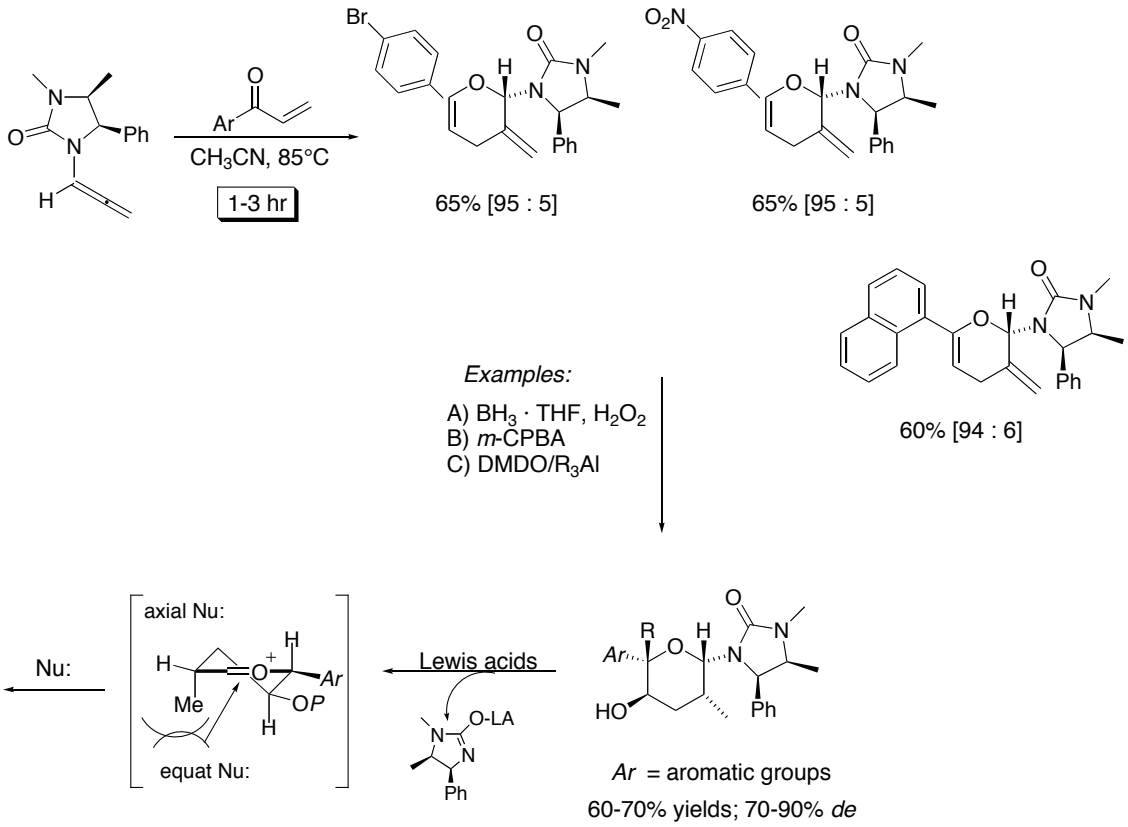
3. Discussion

A. Preparation. The level of purity during preparations of allenamides was unambiguously established using GC analysis for both the propargyl amide intermediates and the allenamides. The level of optical purity was established based on optical purity of the chiral auxiliaries from commercial sources. The $[\alpha]_D^{20}$ values for the commercial (*R*)-2-phenyloxazolidinone and (*S*)-2-phenyloxazolidinone that were used for this preparation are –52.33 (c 2.0, $CHCl_3$) and +52.95 (2.0, $CHCl_3$), respectively. Based on the known $[\alpha]_D^{20}$ values for (*R*)-2-phenyloxazolidinone and (*S*)-2-phenyloxazolidinone from Aldrich (-48.0 (c 2.0, $CHCl_3$) and + 48.0 (c 2.0, $CHCl_3$), respectively), the *ee* or optical integrity of these two enantiomeric auxiliaries should be very high. Since it is not likely to severely erode the *ee* of the auxiliary under the rather mild reaction conditions described in these two procedures, the level of *ee* for propargyl amide (*R*)-2 and allenamide (*R*)-3 should be comparable to that of the starting (*R*)-2-phenyloxazolidinone.

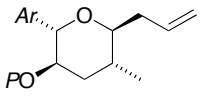
Furthermore, using (*S*)-2-phenyloxazolidinone led to the propargyl amide (*S*)-**2a** that has an opposite optical rotation of + 157.97 (c 10.0, EtOH). After based-induced isomerization, the allenamide (*S*)-**3a** also possesses an opposite optical rotation of + 157.13 (c 10.0, CH_2Cl_2).

B. Applications. Stereoselective inverse-demand hetero (4 + 2) cycloadditions. A Chiral Template for *C*-Aryl Glycoside Synthesis. Chiral allenamides[2,3,4] had been used in highly stereoselective inverse-demand hetero (4 + 2) cycloaddition reactions with heterodienes.[5] These reactions lead to stereoselective synthesis of highly functionalized pyranyl heterocycles. Further elaboration of these cycloadducts provides a unique entry to C-aryl-glycosides and pyranyl structures that are common in other natural products (**Scheme 1**).

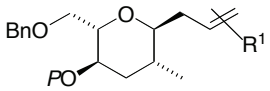
Scheme 1



C-aryl glycosides



Building Blocks



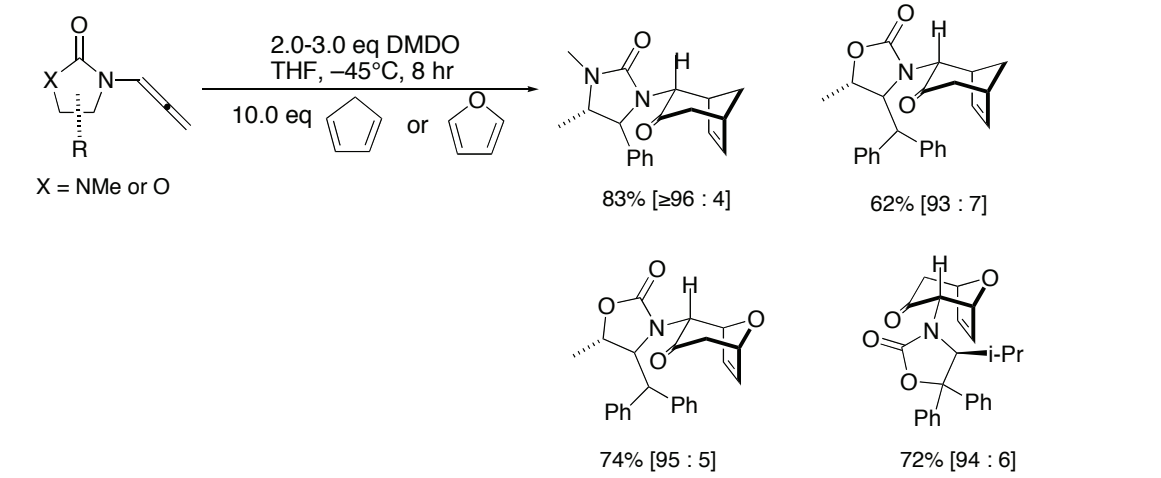
P = protecting groups

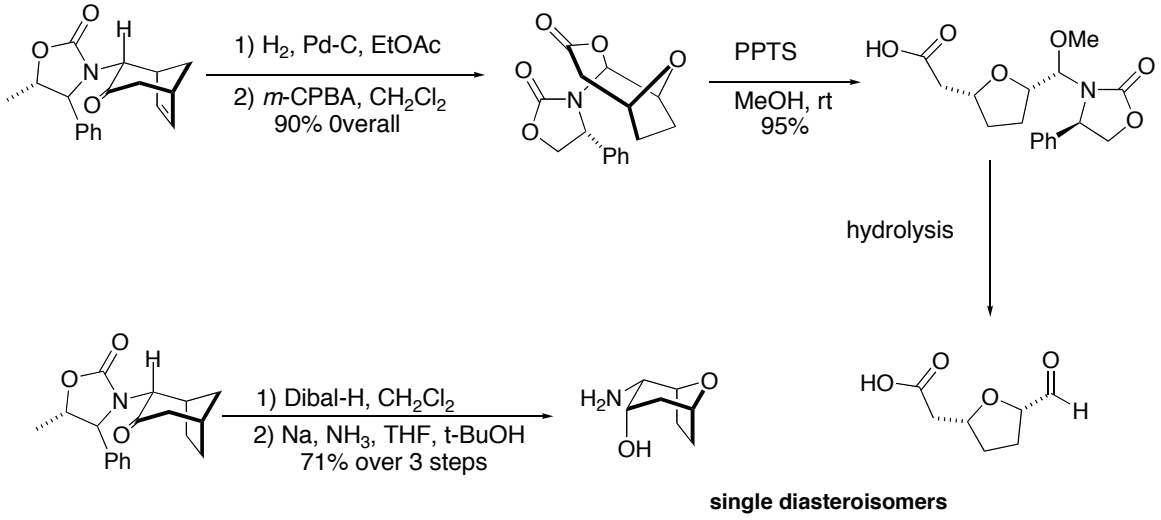
Lewis Acid: 1.5 equiv $SnBr_4$; **Nu**: = allylsilanes
56-75% yields; up to 55% to 80% *de*

2. *Highly stereoselective [4 + 3] oxyallyl cycloadditions*. An *endo*-Selective Sequential Epoxidation-Oxyallyl Cycloaddition and the First Nitrogen-Stabilized Oxyallyl Cations.

Epoxidations of chiral allenamides lead to chiral nitrogen-stabilized oxyallyl catioins that undergo highly stereoselective (4 + 3) cycloaddition reactions with electron-rich dienes.[6] These are the first examples of epoxidations of allenes, and the first examples of chiral nitrogen-stabilized oxyallyl cations. Further elaboration of the cycloadducts leads to interesting chiral amino alcohols that can be useful as ligands in asymmetric catalysis (**Scheme 2**).

Scheme 2


2.0-3.0 eq DMDO
THF, –45°C, 8 hr
10.0 eq
or
X = NMe or O
83% [≥96 : 4]
62% [93 : 7]
74% [95 : 5]
72% [94 : 6]


1) H2, Pd-C, EtOAc
2) m-CPBA, CH2Cl2
90% 0verall
PPTS
MeOH, rt
95%
hydrolysis
1) Dibal-H, CH2Cl2
2) Na, NH3, THF, t-BuOH
71% over 3 steps
single diasteroisomers

1. School of Pharmacy, University of Wisconsin, 777 Highland Ave., Madison, Wisconsin 53705-2222 USA.

2. (a) Saalfrank, R. W.; Lurz, C. J., in *Methoden Der Organischen Chemie* (*Houben-Weyl*), Kropf, H. and Schaumann, E., Eds. Georg thieme Verlag: Stuttgart, **1993**, 3093. (b) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*, John Wiley and Sons: New York, 1984.

3. First preparations of allenamides or electron deficient allenamines: (a) Dickinson, W. B.; Lang, P. C. *Tetrahedron Lett.* **1967**, *8*, 3035. (b) Overman, L. E.; Marlowe, C. K.; Clizbe, L. A. *Tetrahedron Lett.* **1979**, *20*, 599.

4. (a) Gardiner, M.; Grigg, R.; Sridharan, V.; Vicker, N. *Tetrahedron Lett*. **1998**, *39*, 435, and references cited therein. (b) Noguchi, M.; Okada, H.; Watanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581. (c) Farina, V.; Kant, J. *Tetrahedron Lett*. **1992**, *33*, 3559 and 3563. (d) Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc.* **1997**, *119*, 10869.

5. (a) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903. (b) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Organic Lett.* **1999**, *1*, 2145. (c) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Organic Lett*. **2000**, *2*, 2869.

6. (a) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (b) Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem.* **2002**, *67*, 1339.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*R*)-4-Phenyl-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-, (4*R*)-; (90319-52-1).

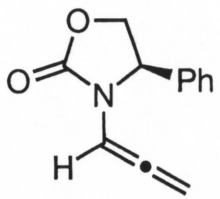
Sodium hydride: Sodium hydride (NaH); (7646-69-7).

Propargyl bromide: 1-Propyne, 3-bromo-; (106-96-7).

R-4-Phenyl-3-(2-propynyl)-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-3-(2- propynyl); (4*R*)-; (256382-74-8).

R-4-Phenyl-3-(1,2-propadieny)-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-3-(1,2-propadienyl)-, (4*R*)-; (256382-50-0).

Potassium *tert*-butoxide: 2-Propanol, 2-methyl-, potassium salt; (865-47-4).



3f