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Diastereoselective Allylstannane Additions to (*S*)-5,6-Dihydro-2 *H*-5-phenyloxazin-2-one. A Concise Synthesis of (*S*)-β-Methylisoleucine

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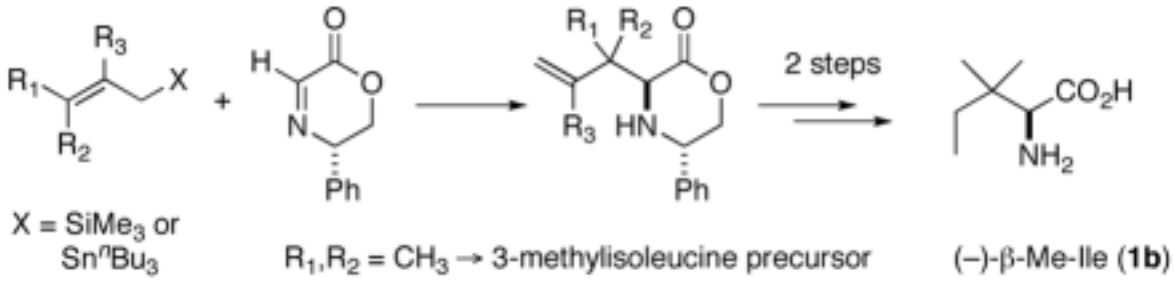
Abstract



The addition of allyl stannanes to (*S*)-4,5-dihydro-5-phenyl-2 *H*-oxazinone (3) was achieved under Brønsted acid catalysistogive 2-allylmorpholinones with high diastereoselectivity (up to *dr*14.2:1).The product of dimethylallyltributylstannane addition to 3 was converted to L-β-methylisoleucine, an α-amino acid residue found in the complex, biologically-active marine-derived peptides polytheonamides A and B and polydiscamides A–C.

Marine peptides often contain highly modified amino acids, including chlorinated amino acids,[1] β-amino acids[2] and highly-substituted β,β-dimethyl-α-amino acids.[3] L-*tert*-Leucine (**1a**) and L-*tert*-amylglycine (β-methylisoleucine, **1b**) occur in the 48-mers polytheonamides A and B; two highly cytotoxic β-helix, membrane-pore forming peptides from the marine sponge, *Theonella swinhoei*.[4] The peptides polydiscamide A from *Discodermia*[5a] (**2**, Figure 1), and the polydiscamides B–C from the sponge *Ircinia*,[5b] which are the first non-endogenous inhibitors of sensory neuron-specific G-protein coupled receptors (SNSRs), also contain **1a** and **1b**.[6] The amino acid γ-hydroxy-*tert*-leucine (L-pantonine, **1c**) was proposed as an intermediate in the biosynthesis of pantoic acid.[7] With an eye to the synthesis of highly biologically active, cyclic peptides, we sought to fulfill a need for a general synthesis of highly-β-branched α-amino acids.

Racemic syntheses of *tert*-alkyl-α-amino acids have been reported.[8] Asymmetric preparation of L-**1a** and L-**1b** was achieved by tandem-enzyme coupled reductive amination of the

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Supporting Information Available. Experimental procedures, full spectroscopic data and ^{1}H, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

corresponding α-ketoacids.[9] However, this biotechnology is not amenable to preparation of the D-antipode due to the enantiospecificity of the enzymes. In this report, we demonstrate a concise *asymmetric* synthesis of L-**1b** which exploits an efficient allylstannane addition to highly electrophilic 2*H*-oxazinone, **3**, a chiral glycine equivalent, and is amenable to preparation of D-**1** or other highly branched amino acids.

SeO_2-promoted oxidative rearrangement of 2-substituted oxazolines ***ii*** (Figure 2) to 5,6-dihydro-2*H*-1,4-oxazin-2-ones (e.g. **3**, hereafter, referred to as 'oxazinones'),[10] followed by hydrogenation-hydrogenolysis,[11] allows convenient access to a wide variety of α-amino acids, ***iii***.[12] Thus, the conversion of carboxylic acid ***i*** to ***iii***, constitutes a highly useful transformation; formal preparation of amino acids by oxidative insertion of NH_2 to the α-carbon of a carboxylic acid[12] of either configuration by choice of an appropriate chiral auxillary,[13] *R*- or *S*-phenylglycinol, obtained readily from the corresponding commercially available phenylglycines.

The highly-electrophilic 2-*unsubstituted* oxazinone **3**[14] is particularly attractive as a chiral glycine equivalent that can add a variety of carbon-centered nucleophiles at the C=N bond to give morpholinone amino acid precursors, however, the diastereoselectivity and yield of these additions can be variable. For example, addition of MeMgBr or *t*-BuMgBr to **3** in the presence of BF_3•Et_2O gave one detectable diastereomer in poor yield (34% and 33%, respectively).[15] We now describe synthesis of 3-allylmorpholinones by highly diastereoselective allyl stannane additions to **3** promoted by Brønsted acid to give **4**, and subsequent conversion to β-methylisoleucine (**1b**).

Oxazoline (***ii***, R = H, Figure 2) was prepared in two steps from *S*-phenylglycinol[16,17] in 80%.[10,18] The original procedure for SeO_2-promoted rearrangement of the oxazoline to (*S*)-oxazinone **3**[10] required refluxing 1,4-dioxane for 2 h. Instead, short-exposure of the substrate (~1 mmole scale) to SeO_2 in a microwave reactor (10 min, 300 W, 110 °C), adapted from Snider's procedure for SeO_2-promoted allylic oxidations,[19] improved the yield of **3** (74%) and reduced byproducts.

As reported earlier,[20] BF_3•Et_2O-promoted additions of allyltrimethylsilane, methallyltrimethylsilane and dimethylallyltrimethylsilane to (*S*)-**3** (entries 1–3, Table 1) gave only modest diastereoselectivity and/or low yields of **4**. The diastereoselectivity of BF_3•Et_2O-promoted allyltrimethylsilane addition to **3** was 8:1 to give **4a** (entry 1, 60% yield), but with the more hindered nucleophiles, dimethylallyltrimethylsilane and methallyltrimethylsilane the diastereoselectivity diminished to 5:1 (entry 2, 25% yield) and 2:1 (entry 3, 60%), respectively.[21] Addition of allyltributylstannane in the presence of either BF_3•Et_2O or TFA also gave **4a** with low diastereoselectivities (dr 2.6:1 and 3.2:1, respectively, entries 5, 6),[22] as did use of methallyltributylstannane23 to give **4c** (37%, dr 1.4:1, entry 11). Gratifyingly, addition of dimethylallyltributylstannane to **3** *in the presence of TFA* (−78 °C, CH_2Cl_2, 1 h, entry 9) gave a *dramatic increase* in both the yield and diastereoselectivity for **4b** (dr 14.8:1, 80% yield). The major diastereomer (3*S*,5*S*)-**4b** was purified from the diastereomeric mixture by selective recrystallization from Et_2O/pentane (dr >20:1 Scheme 1).[24] A similar outcome was observed when the addition was carried out in acetonitrile at −30 °C (dr 12.5:1, 62% yield, entry 10), but diastereoselectivity eroded when the reaction was conducted with TFA in CH_2Cl_2 at higher temperatures (−20 °C, dr 6.2:1, 68% yield, entry 8).

The surprising difference in the outcome of additions of the two dimethylallyltrialkyl silane (entry 2) and stannanes (entries 9, 10) to oxazinone **3** deserves some comment. The role of the Brønsted or Lewis acid is activation of the imine to an iminium ion (Figure 3). For electronic reasons, both dimethylallyltrialkyl-silane and the corresponding stannane add at their more substituted sp^2 olefinic carbon. Consequently, the higher diastereoselectivity in formation of

(3*S*,5*S*)-**4b** from the stannane in the presence of TFA may be due to relaxed steric congestion with the ion pair **3**•H^+ TFA^- compared to the corresponding bulkier **3**•BF_3 complex. Under these conditions, tighter association of the vinyl bond to the C=N bond is allowed, serving to amplify differences in energies between top and bottom facial additions (Figure 3(a) and (b), respectively) in the respective transition states and favoring approach of the nucleophilic allyl equivalent from the side opposite the Ph group.

The synthesis of (−)-β-methylisoleucine (**1b**) was accomplished by conversion of the dimethylallylated morpholinone (3*S*,5*S*)-**4b** as follows (Scheme 1). Hydrogenation of (3*S*, 5*S*)-**4b** under acidic conditions (6 atm, $Pd(OH)_2$, MeOH, 1M HCl) followed by exhaustive acid hydrolysis (refluxing HCl) provided the optically pure amino acid salt (L-**1b**•HCl, Scheme 1) which was converted to the free amino acid by ion-exchange chromatography (elution with 2M NH_4OH) to neutral L-**1b** (96% yield, two steps).

Additions of dimethylallyl anion equivalent to **3** should find wider applicability in synthesis of other β,β-dimethyl-substituted amino acids. The versatile vinyl 'handle' in intermediate (3*S*,5*S*)-**4b** may find uses for preparation of amino acid derivatives related to **1b**. For example, selective hydrogenation of the terminal vinyl group of (3*S*,5*S*)-**4b** (Scheme 3, H_2, Pd-C, 96%) to give **5** models a potential route to preparation of specifically-labeled [^{2}H]- and [^{3}H]-(*S*)-**1b**. Oxidative or reductive modifications of the terminal vinyl group or olefin metathesis should provide access to other highly modified natural and non-natural amino acids including the γ-methysulfinyl-*tert*-leucine residue found in polytheonamide A.[4]

The optical rotation of L-**1b** ($[\alpha]_D^{22}$ +12.7 (*c* 0.48, 1M HCl), lit.**Error! Bookmark not defined.** +9.9 (*c* 1M, 1M HCl) and ^{1}H and ^{13}C NMR data[6,25] matched the literature values. Thus, L-**1b** was obtained in three steps from the chiral glycine equivalent (*S*)-**3** in an overall yield of 58%.

In summary, the versatility of chiral glycine synthon **3** for α-amino acid synthesis has been extended to highly diastereoselective additions dimethylallylstannane and a concise conversion of the product (3*S*,5*S*)-**4b** to the highly branched amino acid (−)-β-methylisoleucine (L-**1b**). The configurations of amino acids derived through allylstannane additions to **3** complement those from hydrogenation of oxazinones[10,11] (Figure 2, 3 R = alkyl). Consequently, antipodal amino acids can be obtained in high yield from oxazinones derived from a common phenylglycinol chiral auxilllary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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6. Curiously, the first identification of naturally occuring **1b** was from an extraterrestrial source; the Murchison meteorite, a carbonaceous chondrite. Cronin JR, Pizzarello S. Geochim Cosmochim Acta 1986;50:2419. [PubMed: 11542028]
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14. The 5,6-diphenylmorpholinone **3a** has been used both as a nucleophilic glycine equivalent and precursor for in situ prepartion of the electrophilic **3b**. (a) Williams RM. Aldrichimica Acta 1992;25:11. (b) Williams RM, Hendrix JA. Chem Rev 1992;92:889. and references, therein. (c) Williams RM, Sinclair PJ, Zhai D, Chen D. J Am Chem Soc 1988;110:1547.**3b** and **3c** have been converted to arylglycines by Mannich reaction with arenes. (d) Tohma S, Rikimaru K, Endo A, Shimamoto K, Kan T, Fukuyama T. Synthesis 2004:909. (e) Chen YJ, Lei F, Liu L, Wang D. Tetrahedron 2003;59:7609.**3b-c** were made in 5–6 steps from phenylglycine, and **3a** from benzoin
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21. Diastereomers of **4** were assigned by nOe measurements. Ref. [10, 12] and conversion of **4b** to (*S*)-**1b**.
22. Side-product formation lead to diminished yields of the desired **4a**.
23. Naruta Y, Nishigaichi Y, Maruyama K. Chem Lett 1986:1857.
24. Removal of Sn-containing byproducts was conveniently effected by chromatography over SiO_2 impregnated with KF. Harrowven DC, Guy IL. Chem Commun 2004:1968.
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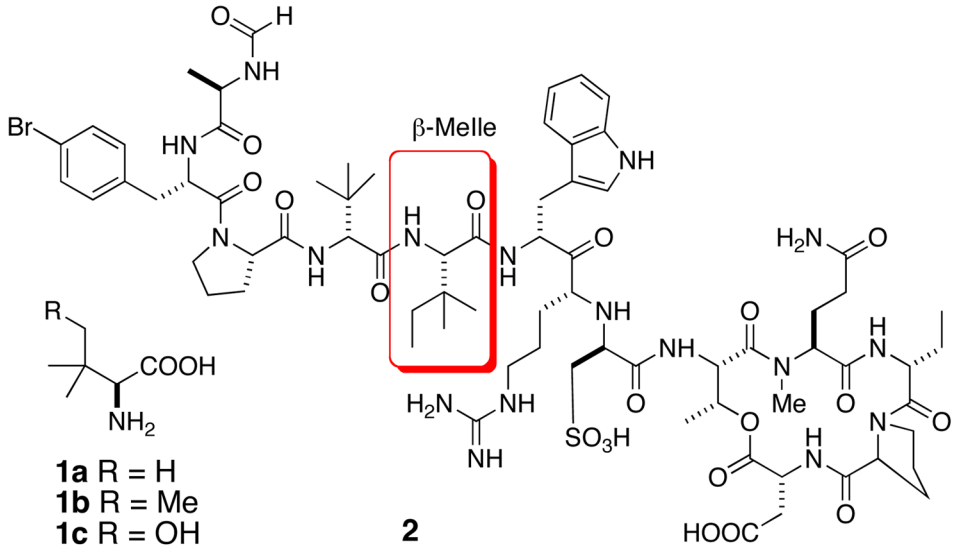


Figure 1.
Structures of L-*tert*-leucine (**1a**), L-β-methylisoleucine (*tert*-amylglycine, **1b**), pantonine (**1c**) and polydiscamide A (**2**), a marine-derived peptide containing β,β-dimethyl-substituted α-amino acids.

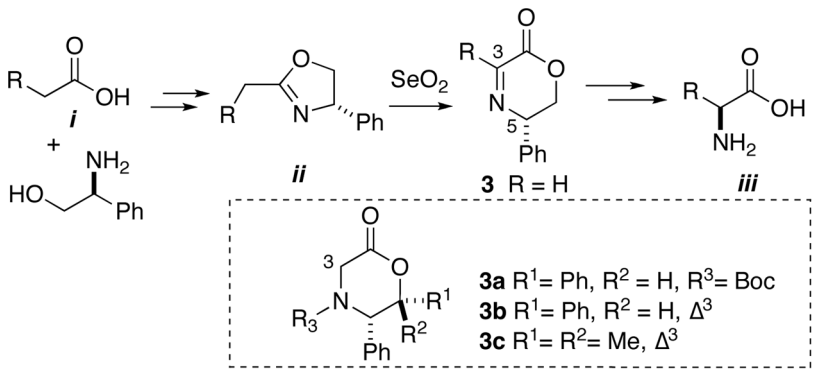


Figure 2.
Oxazoline-oxazinone oxidative rearrangement.

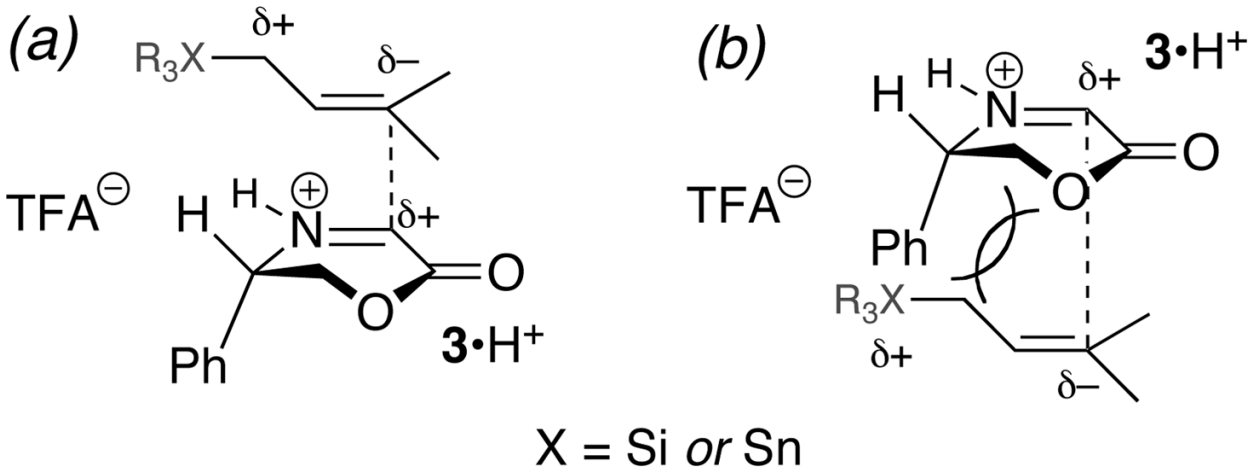
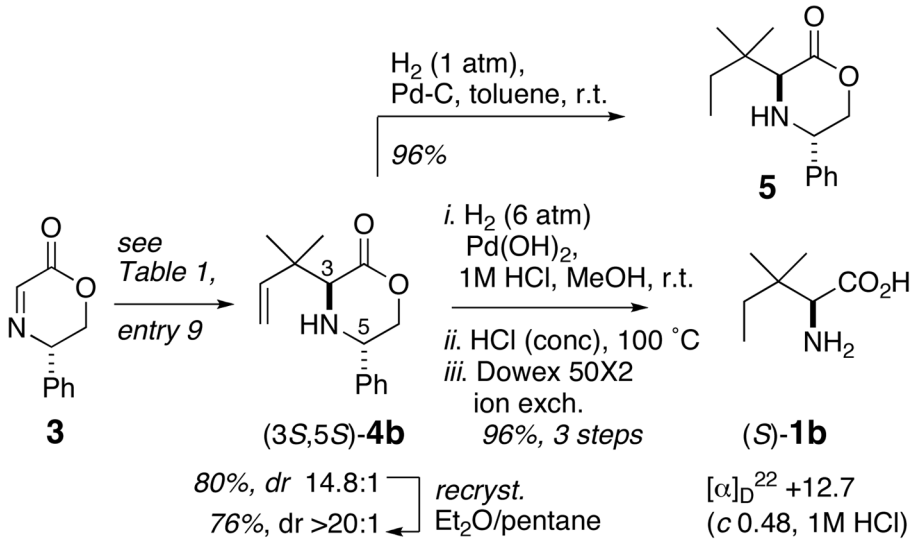


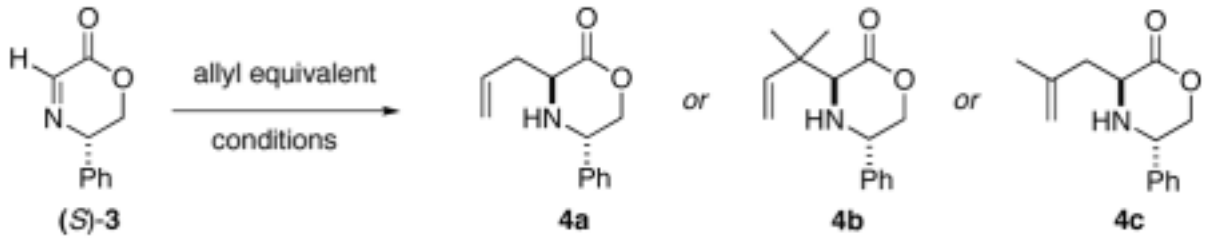
Figure 3.
Possible transition states for reaction of $3•H^+$ with dimethylallyl-silane or -stannane



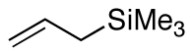
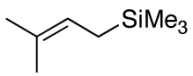
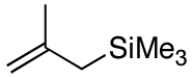
Scheme 1.
Conversion of morpholinone (3*S*,5*S*)-**4b** to L-β-methylisoleucine **1b**.

Table 1

promoted Allylsilane and Allylstannane Additions to Oxazinone (*S*)-**3**.



(*S*)-**3** **4a** **4b** **4c**

allyl equivalent	product	Brønsted or Lewis acid	solvent	temp, time	yield (%)[a]	*dr*[b]	ref.
	**4a**	BF_3•Et_2O	CH_2Cl_2	−78 °C, 0.5 h	73[c]	8:1	20
	**4b**	BF_3•Et_2O	CH_2Cl_2	−78 °C, 0.5 h	25[c,d,e]	5:1	20
	**4c**	BF_3•Et_2O	CH_2Cl_2	−78 °C, 1 h	60[c]	2:1	20

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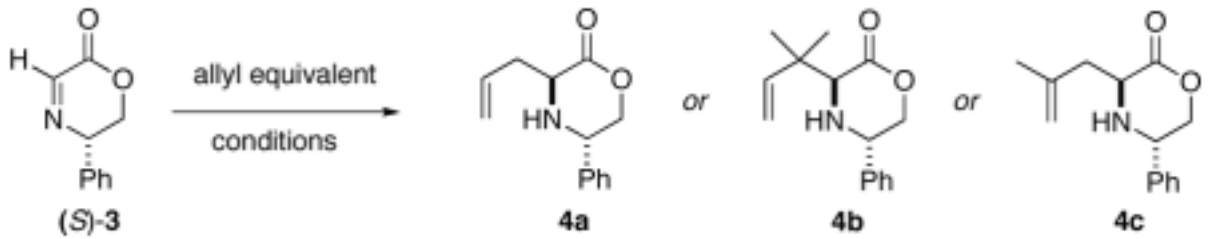
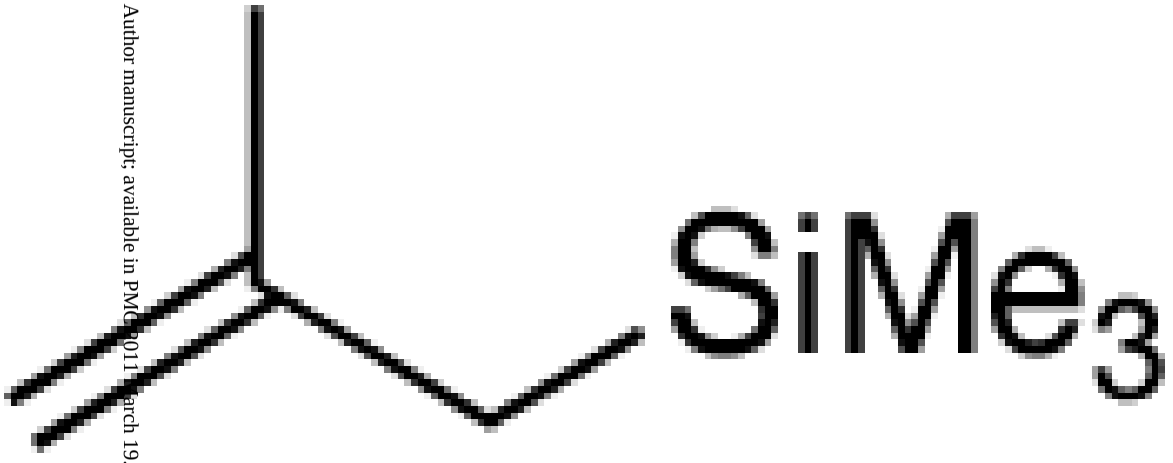
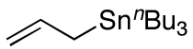


allyl equivalent	product	Brønsted or Lewis acid	solvent	temp, time	yield (%)[a]	*dr*[b]	ref.
	**4c**	TFA	CH_2Cl_2	−78 °C, 1 h	54[c]	2.6:1	*g*
	**4a**	BF_3•Et_2O	CH_2Cl_2	−78 °C, 1 h	35[c,e]	3.2:1	*g*

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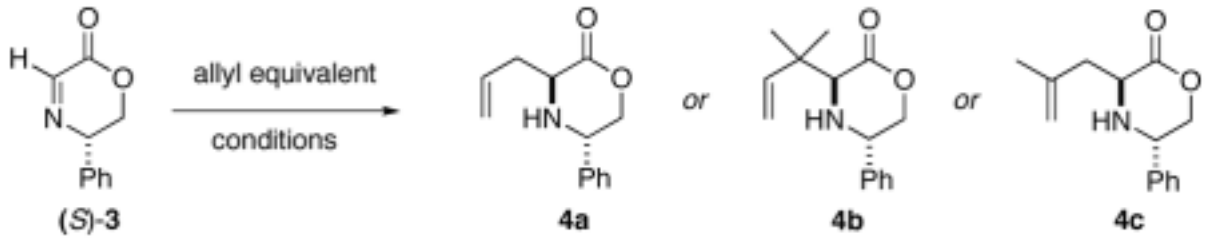
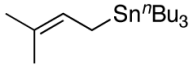
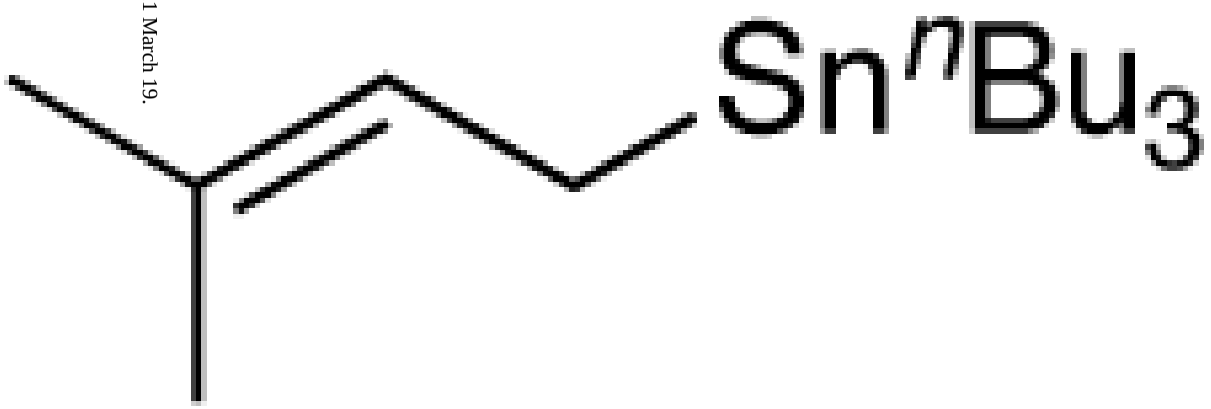
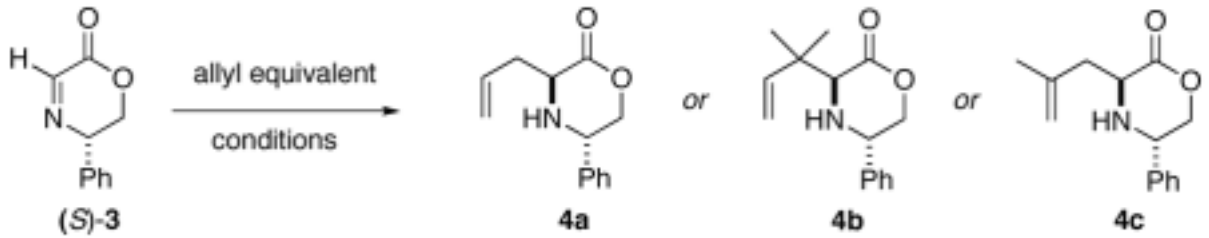
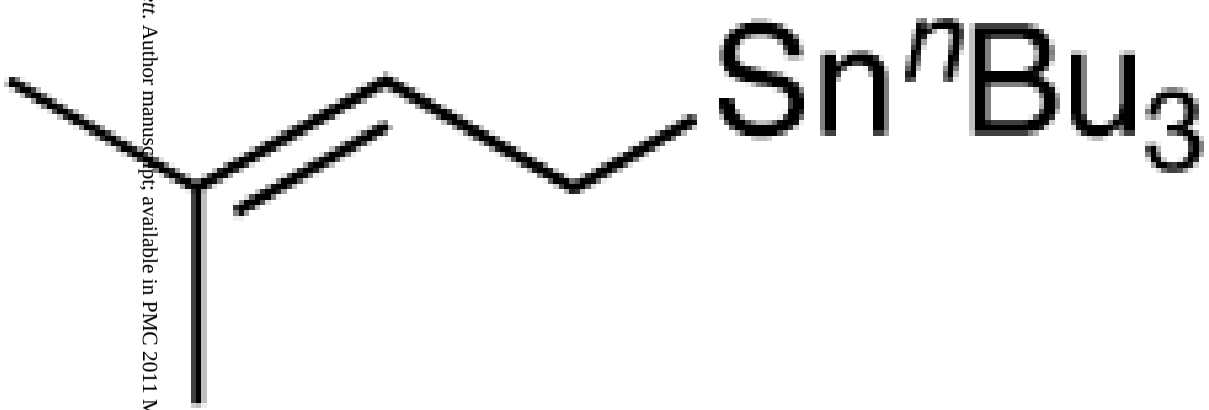
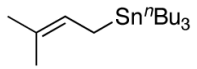
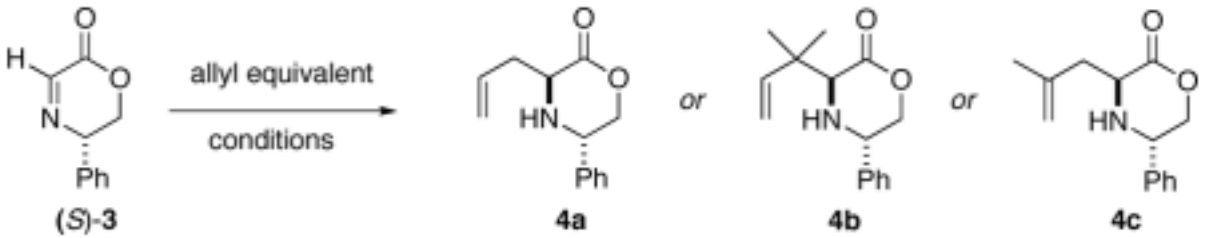


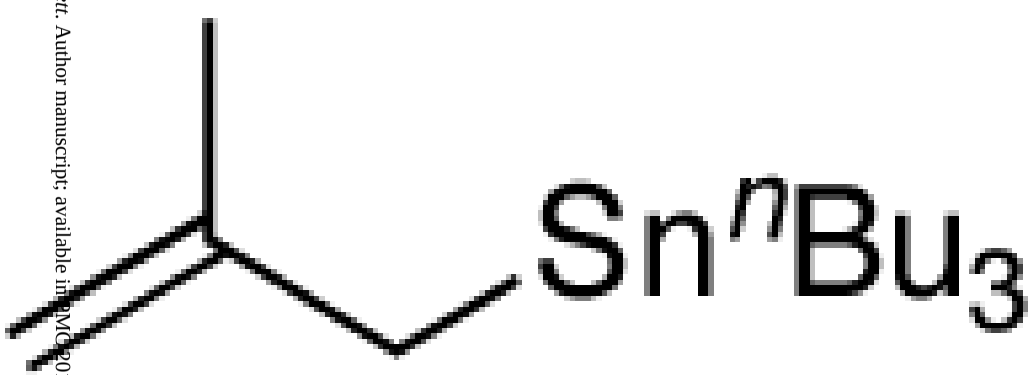
allyl equivalent	product	Brønsted or Lewis acid	solvent	temp, time	yield (%)[a]	*dr*[b]	ref.
	**4a**	TFA	CH_2Cl_2	−78 °C, 1 h	60[c]	5:1	*g*
	**4b**	BF_3•Et_2O	CH_2Cl_2	−78 °C, 0.5 h	64(75)[f]	7.1:1	*g*
	**4b**	TFA	CH_2Cl_2	−20 °C, 1 h	68[f]	6.2:1	*g*



allyl equivalent	product	Brønsted or Lewis acid	solvent	temp, time	yield (%)[a]	*dr*[b]	ref.
	**4b**	TFA	CH_2Cl_2	−78 °C, 1 h	**80**[f]	**14.8:1**	*g*
	**4b**	TFA	CH_3CN	−30 °C, 2 h	62[f]	12.5:1	*g*



(*S*)-**3** **4a** **4b** **4c**

allyl equivalent	product	Brønsted or Lewis acid	solvent	temp, time	yield (%)[a]	*dr*[b]	ref.
	**4c**	TFA	CH_2Cl_2	−78 °C, 1 h	37[c,e]	1.4:1	*g*

yield after SiO_2 column chromatography (yields in parentheses are based on recovered starting material).

^{1}H NMR integration.

omers not separated.

ized.

on to an unidentified byproduct (see Ref. [20] and footnote 23).

astereomer separated by crystallization.

ce = *this work*.