Reaction of Tributyltin Hydride with α,β-Unsaturated *N*-Acyloxazolidinones

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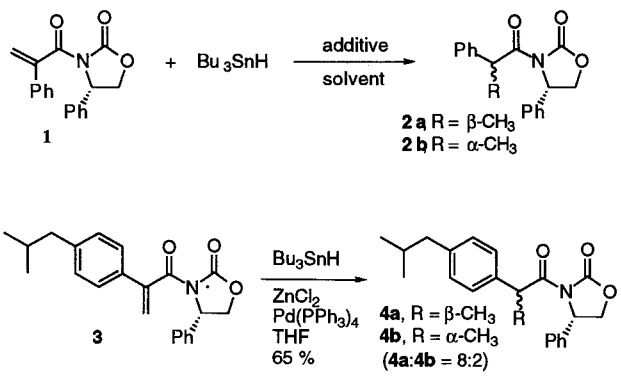
The treatment of tributyltin hydride with α-substituted propenoyl oxazolidinones in the presence of a catalytic amount of AIBN gave the tributyltin radical addition adduct when the substituent is an alkyl group. However, when the substituent is an aryl group, the reduction adduct was obtained in modest diastereoselectivity. The yield of this reduction process was improved by using $Pd(PPh_3)_4$ as a catalyst. The application of this stereoselective hydrogenation reaction to the synthesis of α-alkyl arylacetic acids is described.

The creation of new stereogenic centers at the α, β, or both positions via enantioselective addition reactions of α,β-unsaturated *N*-acyloxazolidinones or *N*-enoylsultams has been studied widely in recent years. Represented examples are Diels–Alder reactions,[1] ene reactions,[2] and addition reaction with organocuprates,[3] dialkylaluminum chlorides,[4] allylsilanes,[5] thiols,[6] and iodine azide.[7] Tributyltin hydride has been reported to effect 1,4-selective reduction of α,β-unsaturated carbonyl compounds[8] or undergo radical addition to the β-carbon of α,β-unsaturated esters.[9] We thought that the reaction of tributyltin hydride with α,β-unsaturated *N*-acyloxazolidinones by either reductive or addition processes would provide useful synthetic methods to prepare α-alkyl arylacetic acids, a group of biologically interesting compounds[10] or β-stannyl *N*-acyloxazolidinones, a precursor of chiral titanium homoenolates.[11]

Initially, we investigated the palladium catalyzed selective hydrogenation of *N*-(α-arylacryloxy)oxazolidinones with Bu_3SnH.[12] Thus, *N*-(α-phenylacryloyl)oxazolidinone **1** was prepared from the corresponding acid[13] according to literature procedure.[1] Treatment of a THF solution of **1** and Bu_3SnH with $ZnCl_2$ in the presence of catalytic amount of $Pd(PPh_3)_4$ at 25 °C for 2 hours provided *N*-(α-phenylpropanoyl)oxazolidinones **2a** and **2b** in a ratio of 70:30 and a yield of 54%. The absolute configuration of C(α) of the minor stereoisomer **2b** was determined to be *R* by comparison of its ^1H NMR spectrum with that of the authentic sample prepared from commercially available (*R*)-2-phenylpropionic acid.[14] We have also found that $TiCl_4$ and $BF_3 \cdot OEt_2$ were efficient catalysts for this reaction and the results are summarized in the Table. (4*S*)-*N*-[2-(4-Isobutylphenyl)acryloyl]-4-phenyloxazolidin-2-one **(3)** was prepared in the same manner and reacted with Bu_3SnH under the same reaction conditions to give **4a** and **4b** in a ratio of 80:20 and a yield of 65% (Scheme 1).

When the reaction of **1** with Bu_3SnH is catalyzed by AIBN in refluxing benzene, reduction products **2a** and **2b** are produced in 45% yield and 40% de. Normally, under these reaction conditions, tributyltin hydride was thought to undergo the reaction via a radical mechanism to give a tributyltin radical addition product. The absence of adducts could be due to the stability of the benzylic radical **5**. Since the rate of hydrogen abstraction of benzylic radicals is slow,[15] an alternative pathway of tributyltin radical addition to the carbonyl oxygen of **1** will take place, followed by fast hydrogen abstraction to generate stannyl enolate **7**. Upon aqueous workup, protonation takes place favoring the *re*-face to give **2a** as the major product. We then examined the reaction of Bu_3SnH with *N*-methacryloyloxazolidinone **8** in the presence of a catalytic amount of AIBN, this reaction indeed gave **9a** and **9b** in 72% yield as a 18:82 mixture of diastereomers. Pure **9b**, the major product, was obtained by flash column chromatography in 46% yield. The absolute configuration of C(α) of **9b** was determined to be *R* by conversion of **9b** to the corresponding methyl ester **10** and comparison of the optical rotation of **10** to literature values.[16] The formation of **9b** as the major product is due to the hydrogen abstraction favoring the less hindered *si*-face of enolate radical **A**.[17] Reaction of methyl α-phenylacrylate **(11)** with Bu_3SnH and a catalytic amount of AIBN under refluxing benzene for 24 hours gave the addition adduct **12** in 20% yield along with recovered starting material (30%). The additional stabilization of the α-radical by *N*-carbonyloxazolidinone to slow down the hydrogen abstraction seems to be essential to attain the reduction product.



Scheme 1

Table. 1,4-Selective Reduction of α,β-Unsaturated *N*-Acycloxazolidone **1**

Reagents	Solvent	Reaction Temp (°C)/ Time (h)	Ratio of **2a** and **2b**[a]	Yield (%) of **2a** and **2b**[b]
AIBN	benzene	80/24	70:30	45
$Pd(PPh_3)_4$, $ZnCl_2$	THF	25/2	70:30	54
$Pd(PPh_3)_4$, $TiCl_4$	THF	25/96	70:30	50
$Pd(PPh_3)_4$, $TiCl_4$	CH_2Cl_2	25/96	70:30	47
$Pd(PPh_3)_4$, $BF_3 \cdot OEt_2$	THF	25/96	55:45	57

[a] Diastereomeric ratios were determined by 200 MHz ^1H NMR spectroscopy of the crude products.
[b] Isolated yield.

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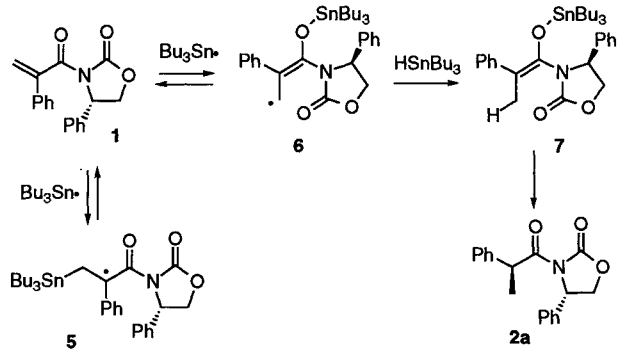
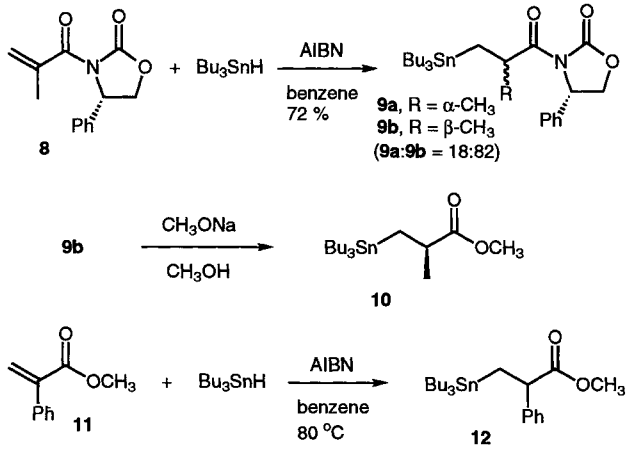


Scheme 2



Scheme 3

In conclusion, the stereoselective hydrogenation of α-arylpropenoyloxazolidinones with tributyltin hydride has provided a new synthetic method for the preparation of α-alkyl arylacetic acids. The tributyltin radical addition products have also been demonstrated to be precursors of chiral titanium homoenolates which will be published in the due course.

Palladium Catalyzed Hydrogenation of *N*-(α-Arylacryloyl)oxazolidinones with Bu_3SnH; General Procedure:

Method A: To a stirred oxygen-free solution of *N*-(α-arylacryloyl)oxazolidinone (0.5 mmol), $Pd(PPh_3)_4$ (0.01 mmol), and Lewis acid (0.5 mmol) was added dropwise Bu_3SnH (0.6 mmol) over a period of few minutes at r.t. The resulting solution was stirred until the starting material was consumed, diluted with Et_2O, and washed with sat. KF solution. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash column chromatography.

AIBN Catalyzed Reaction of Unsaturated *N*-Acylamides with Bu_3SnH; General Procedure:

Method B: A solution of unsaturated *N*-acylamide (0.5 mmol) and Bu_3SnH (0.52 mmol) in benzene (10 mL) containing AIBN (5 mg) was refluxed under N_2 with stirring until the starting material was consumed. The solution was cooled to r.t. and evaporated in vacuo. The residue was purified by flash column chromatography.

(4S)-N-[(2S)-2-Phenylpropanoyl]-4-phenyloxazolidin-2-one (**2a**); yield: 38% (Method A, $ZnCl_2$), 32 (Method B); white solid; $[\alpha]_D^{25}$ −163.27 (*c* = 0.1, $CHCl_3$); mp 147–149°C.

^{1}H NMR ($CDCl_3$): δ = 7.21–7.44 (m, 10H), 5.33 (dd, 1H, *J* = 8.6, 3.2 Hz), 5.13 (q, 1H, *J* = 7.0 Hz), 4.53 (t, 1H, *J* = 8.6 Hz), 4.20 (dd, 1H, *J* = 8.6, 3.2 Hz), 1.41 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 174.05, 153.22, 140.14, 139.34, 129.24, 128.71, 128.60, 128.21, 127.25, 125.80, 69.71, 58.10, 43.20, 19.40.

(4S)-N-[(2R)-2-Phenylpropanoyl]-4-phenyloxazolidin-2-one (**2b**); yield: 16% (Method A, $ZnCl_2$); 13% (Method B); white solid; $[\alpha]_D^{25}$ +143.43 (*c* = 0.5, $CHCl_3$); mp 139–140°C.

^{1}H NMR ($CDCl_3$): δ = 6.90–7.39 (m, 10H), 5.46 (dd, 1H, *J* = 9.0, 5.2 Hz), 5.11 (q, 1H, *J* = 7.0 Hz), 4.64 (t, 1H, *J* = 9.0 Hz), 4.09 (dd, 1H, *J* = 9.0, 5.2 Hz), 1.40 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 173.99, 153.35, 139.96, 138.39, 129.02, 128.66, 128.33, 127.25, 125.98, 69.54, 57.75, 43.72, 18.43.

(4S)-N-[(2S)-2-(4-Isobutylphenyl)propanoyl]-4-phenyloxazolidin-2-one (**4a**); yield: 40% (Method A, $ZnCl_2$); white solid; $[\alpha]_D^{25}$ +165.93 (*c* = 0.9, $CHCl_3$); mp 163–164°C.

^{1}H NMR ($CDCl_3$): δ = 7.24–7.41 (m, 7H), 7.08 (d, 2H, *J* = 8.1 Hz), 5.34 (dd, 1H, *J* = 8.6, 3.2 Hz), 5.11 (q, 1H, *J* = 7.0 Hz), 4.56 (t, 1H, *J* = 8.6 Hz), 4.21 (dd, 1H, *J* = 8.6, 3.2 Hz), 2.44 (d, 2H, *J* = 7.2 Hz), 1.84 (m, 1H), 1.40 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 6H, *J* = 6.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 174.28, 153.23, 140.66, 139.37, 137.31, 129.28, 129.19, 128.64, 127.85, 125.77, 69.65, 58.06, 45.04, 42.69, 30.12, 22.39, 19.38.

(4S)-N-[(2R)-2-(4-Isobutylphenyl)propanoyl]-4-phenyloxazolidin-2-one (**4b**); yield 10% (Method A, $ZnCl_2$); oil; $[\alpha]_D^{25}$ −106.57 (*c* = 1.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.21 (d, 2H, *J* = 8.2 Hz), 7.01 (s, 5H), 6.90 (d, 2H, *J* = 8.2 Hz), 5.46 (dd, 1H, *J* = 9.0, 5.2 Hz), 5.10 (q, 1H, *J* = 6.9 Hz), 4.64 (t, 1H, *J* = 9.0 Hz), 4.08 (dd, 1H, *J* = 9.0, 5.2 Hz), 2.45 (d, 2H, *J* = 7.3 Hz), 1.86 (m, 1H), 1.40 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 6H, *J* = 6.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 173.96, 153.19, 140.59, 138.27, 136.97, 129.23, 128.83, 128.48, 127.92, 125.79, 69.55, 57.77, 45.07, 43.33, 30.22, 22.35, 18.47.

(4S)-N-[(2R)-2-Methyl-3-tributylstannylpropanoyl]-4-phenyloxazolidin-2-one (**9b**); yield: 46% (Method B); oil; $[\alpha]_D^{25}$ +29.71 (*c* = 2.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.20–7.40 (m, 5H), 5.41 (dd, 1H, *J* = 8.5, 3.2 Hz), 4.65 (t, 1H, *J* = 8.5 Hz), 4.23 (dd, 1H, *J* = 8.5, 3.2 Hz), 3.89 (m, 1H), 0.75–1.70 [m, 32H, including 1.12 (d, 3H, *J* = 6.8 Hz)].

^{13}C NMR ($CDCl_3$): δ = 177.91, 153.29, 139.39, 129.16, 128.60, 125.75, 69.77, 57.82, 35.91, 29.08, 27.35, 20.66, 13.91, 13.69, 9.50.

MS (EI): *m/z* = 466 ($M^+ - C_4H_9$, 100).

HRMS: *m/z* calc. for $C_{25}H_{41}NO_3Sn$ 523.2109, found 523.2114.

Methyl (2*R*)-2-Methyl-3-tributylstannylpropanoate (10):

To a solution of NaH (24 mg, 1 mmol) in MeOH (2 mL) was added a solution of **9b** (0.26 g, 0.5 mmol) in MeOH (3 mL) at 25°C under N_2. The resulting reaction mixture was stirred for 2 h, quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), the solvent evaporated and the residue was purified by flash column chromatography to give **10** (0.17 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ +15.0 (*c* = 0.3, $CHCl_3$) [Lit.[16] $[\alpha]_D^{25}$ +17.0 (*c* = 1.0, $CHCl_3$)].

^{1}H NMR ($CDCl_3$): δ = 3.67 (s, 3H), 2.66 (m, 1H), 0.80–1.63 (m, 3H), 1.18 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 178.36, 51.57, 37.40, 29.12, 27.39, 20.99, 14.44, 13.67, 9.30.

Methyl 2-Phenyl-3-tributylstannylpropanoate (**12**); yield: 20% (Method B).

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^{1}H NMR ($CDCl_3$): δ = 7.25–7.32 (m, 5 H), 3.75 (dd, 1 H, J = 9.2, 7.5 Hz), 3.63 (s, 3 H), 1.15–1.65 (m, 16 H), 0.86 (t, 9 H, J = 6.8 Hz), 0.68 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 176.03, 141.82, 128.57, 127.61, 127.15, 52.00, 49.21, 29.03, 27.35, 13.66, 9.03.

MS (EI): m/z = 397 ($M^+ - C_4H_9$, 100).

HRMS: m/z calc. for $C_{18}H_{29}O_2Sn$ ($M^+ - C_4H_9$) 397.1206, found 397.1206.

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