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Chiral auxiliary mediated stereoselective allylation of electron deficient radicals

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Abstract

Electron deficient radicals bearing oxazolidine chiral auxiliaries undergo efficient addition to allyltributyltin with moderate to excellent stereoselectivities.

Keywords: Radicals and radical reactions; Addition reactions; Diastereoselection; Oxazolidines/oxazolidinones

The use of chiral auxiliaries for controlling the stereochemistry of free radical reactions has been well established [1,2]. For example, Porter has shown that radicals α to an amide which contain an oxazolidine chiral auxiliary undergo stereoselective addition to alkenes [3]. These radicals are believed to exist primarily in one conformation (central conformation, Figure 1), as controlled by steric factors. Attack of these radicals onto olefins occurs preferentially from the face opposite the chiral directing group, R.

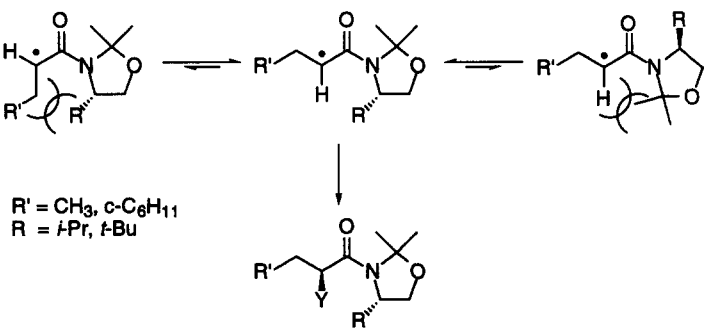

Figure 1

While this and many other examples have been detailed in the literature, all reports of stereoselective intermolecular free radical addition reactions have involved radicals which are either electron rich, electronically neutral or weakly electron deficient. We were interested in determining whether suitably substituted strongly electron deficient radicals would undergo stereoselective addition reactions [4]. In order to make direct comparisons to previously studied radicals, we chose to use β-ketoamidyl radicals **1a-c** (Figure 2) bearing oxazolidine

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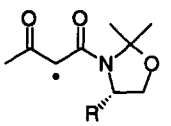
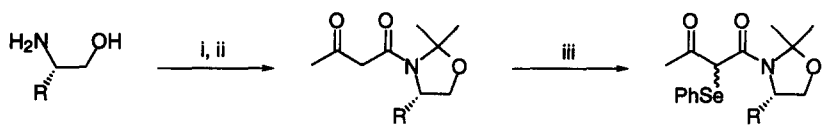
chiral auxiliaries. We postulated that the conformations of these electron deficient radicals, which are α to a pair of carbonyls, would be controlled in a fashion similar to that of Porter's α-amide radicals, affording high levels of diastereoselectivity.



1a R = *i*-Pr
1b R = CH_2Ph
1c R = *t*-Bu

Figure 2

A phenylselenyl group was chosen as the precursor to radicals **1a-c** for carrying out the allylation reactions [5]. The requisite precursors were prepared in three steps from the appropriate, commercially available aminoalcohols (Scheme 1). Aminoalcohols **2a-c** were first converted to oxazolidines under standard conditions [6] then acylated with diketene and a catalytic amount of DMAP [7,8]. Two step yields of amides **3a-c** from the aminoalcohols ranged from 54-60%. Radical precursors **4a-c** were prepared in 40-56% yield by quenching the enolates of the β-ketoamides with phenylselenenyl bromide. In all cases, the phenylselenides were isolated and used as unseparated mixtures of diastereomers. All new compounds reported gave satisfactory IR, ^1H and ^{13}C NMR and high resolution mass spectral data.



2a-c — **a** R = *i*-Pr; **b** R = CH_2Ph; **c** R = *t*-Bu — **3a-c** — **4a-c**

Reagents: i) acetone, $MgSO_4$; ii) diketene, DMAP; iii) NaH, DMSO then PhSeBr

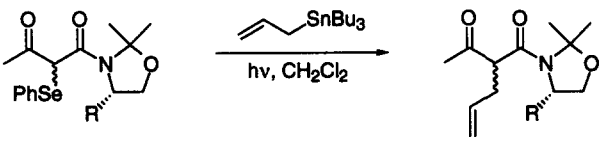
Scheme 1

Free radical allylation with allyltributyltin was used as a convenient method of assessing the effects of the chiral auxiliaries upon electron deficient radicals **1a-c** [9]. Reactions were carried out at room temperature and below by photolyzing a methylene chloride solution of the selenide (0.1 M in selenide) with two equivalents of allyltributyltin using a 450W medium pressure mercury arc lamp. Reactions at 80 °C were performed by refluxing a benzene solution of selenide (0.1 M in selenide) and two equivalents of allyltributyltin in the presence of a catalytic amount of AIBN. In each reaction, the only products detected were the two diastereomers of the allylated compounds, **5a-c**, and tin- and selenium-containing byproducts. Isolated yields for reactions at 0 °C and above were all 90-100%. Reactions done at -78 °C gave yields greater than 75% with recovered starting material making up the rest. Table 1 presents the ratio of the diastereomers of **5a-c** formed in each reaction as determined by the average of quadruplicate gas chromatographic analyses of duplicate reactions.

While the stereoselectivities afforded by the isopropyl and benzyl substituted oxazolidines were disappointing, the *t*-butyl substituted oxazolidine gave excellent stereoselectivities

(greater than 100:1 at -78 °C). By examining the temperature dependence of the selectivity data, it is possible to obtain information about the competing transition states leading to the two diastereomeric products. For the additions of radical **1c**, a plot of the natural logarithm of the diastereomer ratio versus 1/T gives a straight line with a correlation coefficient of 0.98. Using the attributes of this line, $\Delta\Delta H^{\ddagger}$ was calculated to be 2.0 kcal/mol and $\Delta\Delta S^{\ddagger}$ was found to be 0.4 eu. These values indicate that selectivity is due primarily to enthalpic factors, consistent with findings for radicals α to a single carbonyl [10].

Table 1
Results of diastereoselective allylation reactions



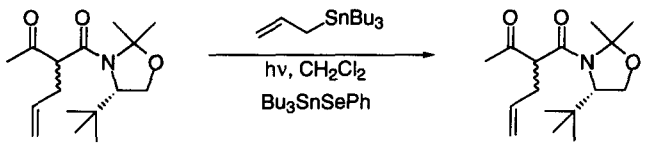
4a-c **5a-c**

Selenide	Temperature	Diastereomer Ratio
4a (R = *i*-Pr)	0 °C	2.6:1
4b (R = CH_2Ph)	0 °C	2.5:1
	-78 °C	3.1:1
4c (R = *t*-Bu)	80 °C	13:1
	25 °C	24:1
	0 °C	32:1
	-78 °C	>100:1

Selectivities obtained with electron deficient radicals **1a** and **1c** were slightly lower than selectivities for the corresponding radicals α to a single amide carbonyl. To make a direct comparison, Porter reports that allylation of an α-amide radical bearing a *t*-butyl oxazolidine gave 25:1 selectivity at 80 °C, as compared to 13:1 at 80 °C reported here for *t*-butyl substituted radical **1c** [3]. The selectivity of the addition of isopropyl substituted radical **1a** at 0 °C (2.6:1) was lower than Porter's reported selectivity for the isopropyl derivative at 80 °C (5:1). It is somewhat surprising that the benzyl substituted compound **1b** performed so poorly. Benzyl substituted oxazolidines have not been used previously in radical addition reactions. However, Sibi has shown that a benzyl substituted oxazolidinone gives excellent control of stereochemistry in addition reactions done in the presence of a chelating Lewis acid [11].

The poorer selectivity observed for the electron deficient radicals in comparison to the corresponding radicals which are α to a single carbonyl was unexpected. Houk and Giese have shown through calculations that the extent of bond formation in the transition state for radical addition to alkenes increases with increasing electrophilicity of the attacking radical [12,13]. The smaller distance between the reactants in the transition state should increase steric effects, giving greater stereoselectivities. Instead, the reduced stereoselectivities may indicate that rotation around the bond between the radical carbon and the carbonyl carbon is not as well controlled in the electrophilic radicals as it is in their more electron-rich counterparts, perhaps because of repulsive interactions between the carbonyl dipoles in the sterically favored conformation (Figure 1).

A concern in these reactions is the potential susceptibility of β-ketoamides to enolization. Evans has shown that similar β-ketoamides are resistant to epimerization in the presence of weak acids and bases [14]. However, we worried that products **5a-c** might equilibrate via their enols under the conditions of the radical addition reaction, giving false diastereomer ratios. To test for this possibility, a 1:2 mixture of diastereomers **5c** (favoring the minor isomer of the addition reactions) was photolyzed with one equivalent of allyltributyltin and one equivalent of tributyltin phenylselenide, the major byproduct of the radical addition reactions. This process resulted in no change in the ratio of the diastereomers (Scheme 2), showing that the allylation products do not enolize under the reaction conditions.



5c
1:2 mix of diastereomers

5c
1:2 mix of diastereomers (no change)

Scheme 2

In conclusion, free radical allylation of electron deficient radicals bearing oxazolidine chiral auxiliaries can occur with excellent stereoselectivity and chemical yields We assume that the model proposed to explain the stereoselectivity of similar reactions of radicals which are α to a single amide carbonyl is also operative in these electron deficient radicals. Unfortunately, the major diastereomer of product **5c** is not crystalline and attempts to convert it to a crystalline derivative are hampered by its enolizability in the presence of acid or base. Alternate approaches to determine the configuration of the major diastereomer in selective additions are currently being pursued.

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