Stereoselectivity in Aldol Reactions of Chiral N-Acyl Selones

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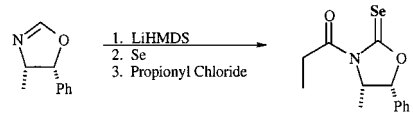
Aldol reactions have played a central role in many stereoselective constructions of carbon−carbon bonds. Evans reported in 1981 that a boron based enolate of an N-acylated 2-oxazolidinone underwent stereoselective carbon−carbon bond formation with aldehydes to give a syn aldol product.[1] Prompted by that landmark work, intensive efforts began which have given rise to a large number of chiral auxiliaries,[2] achiral and chiral-based Lewis acids,[3] and catalytic processes[4] for aldol reactions. During the past several years we have been exploiting the selenocarbonyl group both as a chiral interrogation tool (using ^{77}Se NMR spectroscopy) and as a platform for the development of new chemical methods associated with selone based chiral derivatizing agents (CDA's).[5] During the course of these studies we have uncovered a new type of aldol reaction using chiral selone reagents in which the selenocarbonyl plays a pivotal role in determining the stereoselectivity of these reactions. We report here the results of our studies involving the use of titanium(IV) enolates of *N*-acyloxazolidin-2-selones with a variety of aldehydes.

As these investigations proceeded, it was clear that large quantities of N-acylated selones needed to be constructed. Based on previous NMR results using the [2-^{13}C] labeled valine derived selone in the study of the acylation reaction,[6] we were confident that a one-pot process for the conversion of the oxazoline to the N-acylated selone could be accomplished. Treatment of the 4(*S*)-methyl-5(*R*)-phenyloxazoline with lithium bis(trimethylsilyl)amide at −78 °C gave rise to selective deprotonation at C2 (Scheme 1). Addition of elemental selenium, followed by slow warming to 0 °C, allows for the selenium insertion into the C2 carbon−lithium bond. As soon as the reaction is shown to be complete by TLC, the anion is quenched with the appropriate acid chloride. Use of propanoyl chloride in this one-pot process has afforded a 95% yield of the N-acyl selone **2**.

During the initial phase of these investigations we observed that reaction of benzaldehyde with the titanium-based enolate of

Scheme 1



1 **2**

2 gave one predominant product in good yield. Not only did the product appear to be stable, but the reaction also gave the opposite syn isomer observed for an Evans-type process. Although rare, "non-Evans" aldol reactions have been reported. The Crimmins[7] and Yan[8] groups recently reported on "non-Evans" aldols that employ thiocarbonyl-based CDA's. Table 1 illustrates the range of products that can be obtained using our selenium-based CDA's. The scope of the aldol process was evaluated using the propanoyl and glycolate selone adducts with α-aryl, α-alkyl, α-alkenyl, and −*n*-butyloxy and −benzyloxy aldehydes. The reaction of the *N*-propanoyl selone enolates with uncomplexed aldehydes gives rise to the syn ("non-Evans") products in yields ranging from 85 to 92% and with good selectivity (>98%).[9] For aldol **10** the more sterically demanding 2-methyl-2-pentenal required higher temperatures for the reaction to proceed to completion. We were especially pleased to observe that the glycolate selone adducts enolized quite readily and presumably with chelation of the α-benzyloxy group, giving rise to the Z-enolate.[10] Addition of α-aryl, α-alkyl, and α-alkenyl aldehydes to this enolate solution gave rise to the "non-Evans" aldols (Table 1, compounds **5**, **7**, and **11**). Lower yields and selectivities were observed for the glycolate enolates when 2-methylpropionaldehyde and 2-methyl-2-pentenal were used (Table 1, compounds **3** and **9**). Again, this was attributed to the increased steric demand of these aldehydes. Interestingly, the use of benzyloxyacetaldehyde with the glycolate selone has given rise to an anti selective aldol (Table 1, compounds **13** and **14**). If the benzyloxyacetaldehyde was not precomplexed with $TiCl_4$, the reaction gave little or no diastereoselectivity. However, precomplexation of the benzyloxyacetaldehyde with 1.05 equiv of $TiCl_4$ gave rise to excellent diastereoselectivity (>99% by ^{1}H and ^{77}Se NMR spectroscopy). The anti relationship between the two new chiral centers that are generated in this carbon−carbon bond forming reaction is supported by the measured proton−proton coupling ($J = 8.3$ Hz) and the ORTEP (Figure 1).[11] Especially in aldol reactions, this type of anti relationship is one of the more difficult to access with high levels of diastereoselectivity.[12] In an effort to establish the generality of the anti selective aldol process, an additional four anti aldol products were constructed using this method (Table 1, compounds **15**, **16**, **17**, and **18**).

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(9) For example, to a CH_2Cl_2 solution containing the N-acylated selone, the $TiCl_4$ (1.1 equiv) was added dropwise at −15 °C. This mixture was stirred for 5 min, followed by the dropwise addition of DIPEA (1.15 equiv). The solution was stirred for an additional 30 min then cooled to −78 °C, and 1.2 equiv of the aldehyde was added. The reaction mixture was stirred for the appropriate amount of time (Table 1). The reaction was quenched with 2 mL of methanol. Filtration through a pad of silica gel, followed by washing with a 40% ethyl acetate/toluene mixture (v/v), afforded a bright yellow solution. The ethyl acetate/toluene mixture effects the azeotropic removal of methanol. Carrying out the concentration step without toluene gives rise to a solution highly enriched with methanol, which causes decomposition of the selone adducts (red precipitate forms). Flash silica gel chromatography can be visually monitored because all of the aldol selone adducts prepared to date are bright yellow.
(10) We are currently performing ^{1}H−^{1}H DQF-COSY NMR solution experiments to help ascertain the enolate geometry.
(11) Assignment of the aldol configuration is based on the well-established fact that J_{threo}(7−9 Hz) > $J_{erythro}$(3−6 Hz). See: Wang, Y.-C.; Su, D.-W.; Lin, C.-M.; Tseng, H.-L.; Li, C−L.; Yan, T.-H. *J. Org. Chem.* **1999**, *64*, 6495 and references therein.

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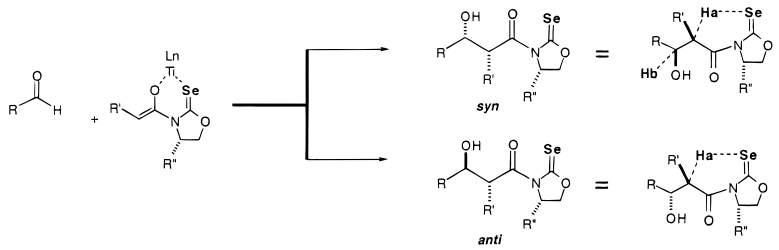
Table 1. $TiCl_4$-Mediated Stereoselective Aldols



compd	R	R′	R″	*T* (°C)	*t*	yield (%)	syn:anti[a]	δ_H[b]	*J*[c]	δ^{77}_{Se}[d]
3	Me_2CH	BnO	Me_2CH	−78	2.0 h	72.0	75:12.5,12.5	6.6[e]	2.0[e]	412.6[e]
								6.9[g]	8.7[g]	423.6[g]
								6.6[g]	9.3[g]	422.4[g]
4	Me_2CH	CH_3	Bn	−78	15 m	86.0	>99:1	5.3	2.7	451.2
5	Pr	BnO	Me_2CH	−78	2.0 h	90.0	98:1,1	6.5	2.1	428.5
6	Pr	CH_3	Bn	−78	15 m	85.6	>99:1	5.2	2.8	451.6
7	MeCH═CH	BnO	Me_2CH	−78	2.0 h	85.0	99:1	6.6	3.6	441.0
8	MeCH═CH	CH_3	Bn	−78	15 m	85.6	>99:1	5.3	4.2	444.3
9	EtCH═CCH_3	BnO	Me_2CH	−78 to rt	2.0 h	63.0[h]	61:39	6.8[e]	3.2[e]	419.0[e]
								6.9[g]	7.2[g]	428.0[g]
10	EtCH═CCH_3	CH_3	Bn	−78	15 m	17.6	>99:1	5.4	3.4	440.0
	EtCH═CCH_3	CH_3	Bn	−78 to −15	10 m	87.0	>99:1	5.4	3.4	440.0
11	Ph	BnO	Me_2CH	−78	2.0 h	97.0	99:1	6.9	3.2	432.8
12	Ph	CH_3	Bn	−78	15 m	90.6	>99:1	5.6	4.5	449.3
13	$BnOCH_2$	BnO	Me_2CH	−78 to −15	2.0 h	91.0	43:26	6.6[e]	2.4[e]	431.9[e]
	$BnOCH_2$[f]	BnO	Me_2CH	−78 to −15	2.0 h	90.0	<0.1:99.9	6.8	8.3	440.0
14	$BnOCH_2$	CH_3	Bn	−78 to −15	10 m	91.8	50:50	5.3[e]	4.3[e]	447.2[e]
	$BnOCH_2$[f]	CH_3	Bn	−78 to −15	10 m	99.4	<0.1:99.9	5.5	7.0	441.1
15	$BuOCH_2$[f]	CH_3	Bn	−78	1.0 h	81	<0.1:99.9	5.4	7.9	439.1
16	$BuOCH_2$[f]	BnO	Me_2CH	−78	1.0 h	86	1:99	6.6	8.5	440.6
17	$BnOCH(CH_3)$[f,i]	CH_3	Me_2CH	−78	1.0 h	85	<0.1:99.9	5.6	9.1	424.2
18	$BnOCH(CH_3)$[f,i]	BnO	Me_2CH	−78 to −30	2.0 h	95	1:97,2	6.7	9.3	440.1

[a] Measured by ^1H integration of Ha and/or by integration of the ^{77}Se signals. [b] δ_H of Ha in ppm. [c] Ha (J_{Ha-Hb}). [d] δ^{77}_{Se} in ppm (relative to diphenyldiselenide at 465 ppm). [e] Data for syn isomer. [f] The aldehyde was precomplexed with 1.05 equiv of $TiCl_4$ at −78 °C. [g] Data for anti isomer. [h] Crude yield from NMR. Aldol could not be purified. [i] Derived from ethyl (*S*)-(−)-lactate.

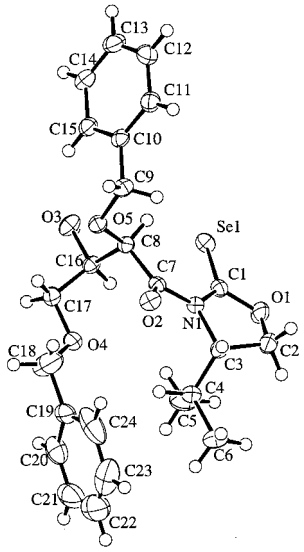


Figure 1. ORTEP of **13**.

The selone auxiliary can easily be removed using a variety of methods. We have reduced aldol amide **4** with $LiBH_4$ to give the corresponding 1,3 diol in 98% yield. The selone CDA was recovered in 95% yield. The optical rotation of the resulting diol indicated an ee that compares favorably with the ee of the parent chiral selone.[13] Hydrolysis to the β-hydroxy acid is effected within 5 min using LiOH. The end point is reached when the yellow aldol solution becomes nearly colorless. Direct conversion of the aldols to esters (81%) or the Weinreb amide was effected with DMAP using the mild Yan procedure.[14]

We are currently investigating the scope and limitations of these new aldol reactions using chiral N-acyl selones and these results will be reported in due course.[15]

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Supporting Information Available: ^1H, ^{13}C, ^{77}Se, IR, HRMS, and/or EA for compounds **3**−**8** and **10**−**14**, $^1H/^{77}Se$ HMQC for **13** and crystallographic data for **13**; ^1H, ^{13}C, ^{77}Se NMR spectra for **15**, **16**, **17**, and **18**; $^1H-^1H$ DQF-COSY NMR spectra for **15** and **17** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. JA992702Y

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(13) The rotation of the diol, $[\alpha]^{24}_D$ +10° (*c* 0.006, $CHCl_3$), compares favorably to its reported value ($[\alpha]^{24}_D$ +10.29° (*c* 0.91, $CHCl_3$)). Garcia, J.; Kim, B.-M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831. This value also compares favorably with that reported for its enantiomer ($[\alpha]^{24}_D$ −10.42° (*c* 0.96, $CHCl_3$)]. Rychnovsky, S. D.; Hoye, R. C. *J. Am Chem. Soc.* **1994**, *116*, 1753.

(14) Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197. Following this process and monitoring the reaction for completion by thin-layer chromatography, conversion of the selone adducts to the ester or Weinreb amide is effected. Reduction of the adductions with 2.0 equiv of $LiBH_4$ in THF at 0 °C gave rise to the 1,3 diol.

(15) Although it gives rise to poor anti selectivity the use of precomplexed aliphatic aldehyde solutions (varying amounts of $TiCl_4$ up to 2 equiv) with selone-based enolates has given good chemical yields of the aldols. We are currently investigating the use of other Lewis acids to effect *anti* selectivity when simple aldehydes are used. For an example of the exceptional chelating potential of Me_2AlCl and $MeAlCl_2$ with aldehydes, see: Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1990**, *40*, 4461. Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457.