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Tandem Chain Extension–Aldol Reaction: Syn Selectivity with a Zinc Enolate

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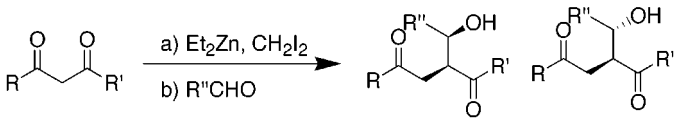
ABSTRACT



A tandem chain extension–aldol reaction was developed in which *β*-keto esters are transformed to α-substituted-*γ*-keto esters in an efficient zinc-mediated, one-pot reaction. The diastereoselectivity of the reaction ranged from good to excellent with syn stereochemistry observed for *β*-keto ester and amide substrates and anti-stereochemistry observed for a *β*-keto imide.

Preparation of nucleophilic zinc ester enolates used in mixed aldol reactions through the action of zinc metal on α-bromoesters is known as the Reformatsky reaction.[1] Reactions of zinc enolates generated in this fashion from esters and amides have been studied under kinetically and thermodynamically controlled reaction conditions with mixed, often confusing, results. Furthermore, diastereoselection of the traditional ester-based Reformatsky reactions has rarely exceeded 50% de. Similarly, a general method for performing highly stereoselective zinc-mediated aldol reactions on ester or amide enolates has not been reported,[2] although incorporation of chiral imide-based auxiliaries has provided beneficial stereochemical influences in traditional Reformatsky reactions.[3]

An underlying assumption of the Zimmerman−Traxler model[4] is that the enolate is an oxygen-bound species, yet a preponderance of evidence has demonstrated that the Reformatsky intermediate (zinc ester enolate) exists in nonpolar solvents as a dimeric species with significant covalent interaction between the zinc and the α-carbon.[5] While isomerization from the carbon-bonded zinc intermediate to a zinc enolate has been proposed,[6] the lack of enolate structural knowledge has hindered development of diastereoselective zinc enolate reactions.

We have been investigating a zinc-mediated reaction in which a *β*-keto ester is transformed to a *γ*-keto ester[7] through

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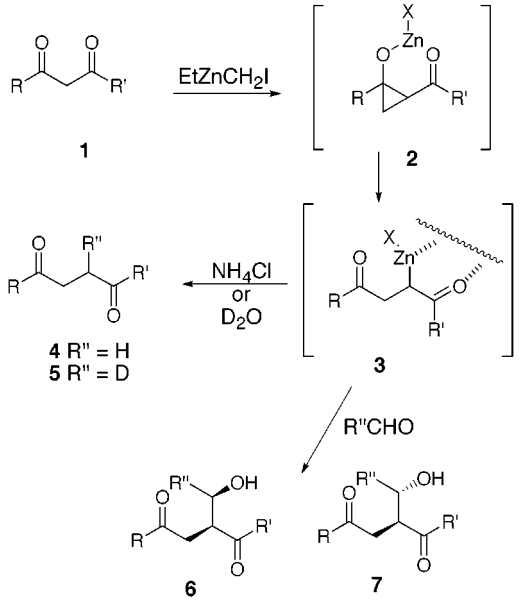
Scheme 1. Chain Extension−Reformatsky Reaction



the influence of the Furukawa reagent, ethyl(iodomethyl)-zinc[8] (Scheme 1). The reaction mechanism is believed to involve intermediacy of a donor−acceptor cyclopropane **2**, which upon fragmentation and protonation provides the chain-extended ester **4**. NMR investigations of similar chain extension reactions have suggested that the cyclopropane is not a persistent intermediate and that a ring-opened species is formed rapidly.[7b] Deuterium quenching of the chain extension reaction suggested that a zinc enolate (**3**) similar to a Reformatsky intermediate may be present in the reaction.

We report herein the development of a tandem chain extension−aldol reaction that facilitates the diastereoselective formation of α-substituted-γ-keto esters, products that were not accessible through the chain extension of α-substituted-β-keto esters.[7a] The tandem chain extension−aldol reaction proceeds efficiently with β-keto ester and amide starting materials (Table 1). For example, treatment of methyl pivaloylacetate **1a** with diethylzinc and methylene iodide, followed by addition of benzaldehyde, resulted in an isolated 95% yield of two aldol products **6a** and **7a** in a syn:anti ratio of 12:1. The appearance of multiple hemiacetal isomeric forms, in addition to open chain aldols, serves to complicate analysis of the reactions. For example, the syn isomer **6a** appears in $CDCl_3$ as a 1:1:1 mixture of open chain and two hemiacetal forms. It was noteworthy that hemiacetal forms are generally more prevalent for the syn isomers **6** than for the anti isomers **7**, thereby making the appearance of hemiacetal forms a useful predictor for stereochemical assignment.

Stereochemical assignments were made by comparison to literature compounds or by X-ray crystal structure. The presence of a hydrogen bond acceptor (ketone) on the C2 side chain makes stereochemical assignment through a

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Table 1. Chain Extension−Reformatsky Reactions

SM	R	R′	R″	yield, %[a]	**6**:**7**[b]
1a	tBu	OMe	Ph	97 (57)	12:1 (17:1)
1b	tBu	OMe	Ar[c]	61[d]	9:1
1c	Ar[c]	OEt	Ar[c]	57	7:1
1d	Me	OMe	tBu	85[d]	>20:1
1e	Me	OMe	Ph	61[e]	15:1
1f	Me	NPhMe	Me	46[f]	3:1[g]

[a] Total isolated yield of purified isomers. [b] Syn:anti ratio of aldols determined by integration of the ^{1}H NMR of the crude reaction material. [c] Ar = 3,4-$(OMe)_2C_6H_3$. [d] Only the syn isomer was isolated. [e] The O-methylated syn isomer **9** (7%) was not included in the total. [f] The O-methylated syn isomer **10** (40%) was not included in the total. [g] If the O-methylated syn isomer **10** is included, syn:anti selectivity is >5:1.

reliance on ^{1}H NMR coupling constants ($^3J_{HH}$) a risky proposition. However, a trend consistent with the literature[9] was observed in which the anti isomer possesses a larger $^3J_{HH}$ than the syn isomer.

Yields for the reaction range from 60% to 95%, and in all cases the diastereocontrol is greater than 75% de. Enhanced diastereoselectivity (entry b), with modest diminishment of yield, is observed when the aldol portion of the reaction is performed at −78 °C. The reaction appears to be operating under kinetic control, since no evidence of reversibility has been observed and diastereoselectivity is independent of reaction time.

In two instances small amounts (7%) of O-methylated aldol products **8** and **9** were isolated from the reaction mixture. Treatment of the syn-aldol product **6c** with the Furukawa reagent confirmed the structure and stereochemistry of **8** and suggested that **8** is generated during the tandem reaction by reaction of the hydroxide with the electrophilic carbenoid. The syn stereochemistry of compound **9** was confirmed in a similar fashion.

An effort to apply this tandem reaction methodology to a β-keto imide resulted in a complete reversal of stereochemical consequences. The anti-aldol isomer **10** was isolated as the sole product (60%) of the reaction, a result consistent with the proposal of Heathcock that excess metal counterions can influence stereochemical control through an open transition state.[10] Since the tandem chain extension−aldol reaction is performed with at least 4 equiv of zinc, effective syn-aldol generation with control of absolute stereochemistry is unlikely using imide auxiliaries.

Uncommon syn diastereocontrol in the ester and amide zinc enolate reactions may be due to an inherent bias for *Z*-enolate (**11**, Figure 1) formation via complexation with the ketone carbonyl.[11] A comparison between the tandem chain extension−aldol reaction and kinetically controlled

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(11) Generation of the proposed zinc enolate through traditional Reformatsky chemistry on an α-bromo-γ-keto ester would be informative. We have attempted to make this starting material, but have been hindered by the predictable elimination reaction.

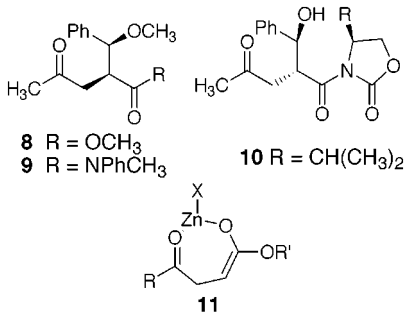

Figure 1.

Reformatsky reactions[12] with similar steric influences and solvent polarities suggests that the ketone is vital to the diastereocontrol. An alternate explanation for the aldol reaction would be nucleophilic attack of the donor−acceptor cyclopropane **2** on the aldehyde. However, the anti-selectivity observed in the titanium(IV)-mediated reaction of a donor−acceptor cyclopropane[13] suggests the syn-selective zinc-mediated reactivity reported herein is the result of an alternate pathway.

In conclusion, a zinc enolate, which has been generated in a zinc-mediated chain extension reaction, has provided modest to excellent syn selectivity in a variety of aldol reactions. Although the presence of a ketone provides homoenolate character to the zinc nucleophile,[14] the involvement of this ketone appears limited to stereoselective enolate formation.

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Supporting Information Available: Characterization data for all compounds and experimental procedures. Crystal structure data for **6b**, **6d**, **6e**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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