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Tandem Enantioselective Conjugate Addition: Electrophile Trapping Reactions. Application in the Formation of Syn or Anti Aldols

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The 1,4 addition of organometallic reagents to α,β unsaturated ketones is a powerful method for carbon−carbon bond formation.[1] Recent years have seen tremendous advances in the asymmetric variant of this reaction with ee values greater than 90%, using as little as 1 mol % of chiral ligand, not uncommon.[2]

Following on from work within our own group[3] we became interested in trapping the enolate formed during the copper-catalyzed addition of organozincs to cyclic enones in a subsequent carbon−carbon bond forming reaction. Herein we outline our initial findings on the reactivity of these intermediates.

Early work carried out by Noyori indicated that aldehydes are suitable electrophilic traps for zinc enolates, giving predominately trans substitution.[4] Using the phosphoramidate ligand **1** developed by Feringa one can generate a homochiral (ee >98%) zinc enolate following the copper-catalyzed addition of diethyl zinc to cyclohexenone.[5] We decided to study the reactivity of this enolate, as outlined in Scheme 1, and the results are summarized in Table 1.

In addition to aldehydes, it was found that, with Lewis acid activation, acetals also gave aldol-type products. $BF_3{\cdot}OEt_2$ and TMSOTf were found to be suitable Lewis acids for the activation of benzaldehyde dimethyl acetal with TMSOTf giving a 2:1 excess of one diastereomer of **3a** albeit in lower yield. No reactivity was observed in the absence of Lewis acid. Alkyl acetals are found to be equally reactive with **3b** formed in good yield.

Ketones fail to react in the absence of Lewis acid although acetone/$BF_3{\cdot}OEt_2$ gave the enone that would arise following dehydration of the expected aldol product. However, the ketal 2,2-dimethoxypropane in conjunction with $BF_3{\cdot}OEt_2$ proved successful giving the dimethyl-substituted methyl ether product **3c** as a single diastereomer. In a similar fashion, methylorthoformate reacted in good overall yield providing a route to the differentially protected 1,3 dicarbonyl compound **3d**. Again, Lewis acid activation was found to be essential. The enolate **2b** formed from cycloheptenone gave similar results to **2a** with **3e** and **3f** formed in good overall yield. To the best of our knowledge, this is the first time zinc enolates have been used in the cleavage of acetals.

Scheme 1

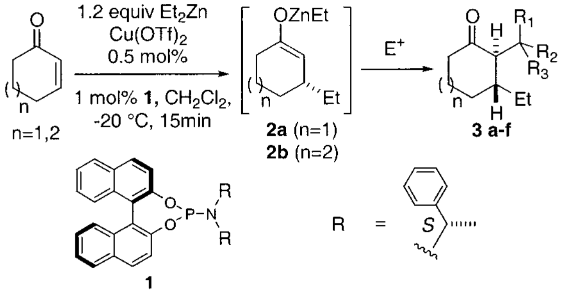


Table 1. Trapping of **2a**/**b** with a Variety of Electrophiles[a]

product	n	electrophile	R_1	R_2	R_3	%[b]
3a	1	$PhCH(OMe)_2$	OMe	H	Ph	62[c]
3b	1	$MeCH(OEt)_2$	OEt	H	Me	62[d]
3c	1	$Me_2C(OMe)_2$	OMe	Me	Me	54
3d	1	$(MeO)_3CH$	OMe	OMe	H	66
3e	2	$PhCH(OMe)_2$	OMe	H	Ph	58[d]
3f	2	$(Me)_3CH$	OMe	OMe	H	59

[a] Reagents and conditions: 1.5 equiv of electrophile, 1.5 equiv of Lewis acid, 0.5 M in dichloromethane, −20 to 0 °C, 2 h. [b] Isolated yield after column chromatography. [c] 1:1 ratio of diastereomers formed. [d] 2:1 ratio of diastereomers formed.

While we had succeeded in extending the scope of the reactivity of zinc enolates formed from conjugate addition, we also observed poor diastereocontrol in cases where a third stereocenter was generated. On the basis of our findings and those of Noyori,[4] it would appear that electrophiles will react to give trans-substituted products and it is the center β to the carbonyl group that is formed in a stereorandom manner. We therefore decided to use a chiral auxiliary approach to give stereocontrol in the second stage of the reaction.

Acetals **4a** (R = Ph) and **4b** (R = propenyl) are readily accessible and known to react with nucleophiles with high diastereocontrol.[6] We were delighted to find that treating **2a** with **4a** in the presence of TMSOTf gave alcohol **5a** as a single diastereomer, following cleavage of the TMS ether (Table 2). $BF_3{\cdot}OEt_2$ gave **5a** directly although in slightly lower overall yield.

Scheme 2

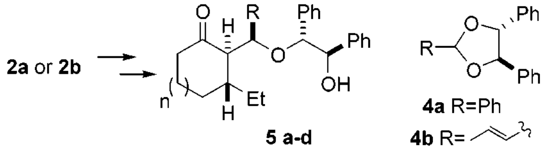
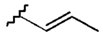
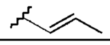


Table 2. Enolate Trappings with Chiral Acetals[a]

Substrate	n	Acetal	Product	R	%[b]
2a	1	**4a**	**5a**	Ph	66
2a	1	**4b**	**5b**		73
2b	2	**4a**	**5c**	Ph	61
2b	2	**4b**	**5d**		63

[a] Reagents and conditions: (i) **4a**/**4b** (1.5−2.0 equiv), TMSOTf (1.5−2.0 equiv), −20 to 0 °C, 0.5−2 h; (ii) MeOH, Amberlyst-15, 1 h. [b] Isolated yield after column chromatography.

X-ray crystallography revealed the stereochemistry of **5a** to be as shown in Figure 1.[7] This is in keeping with the expected stereochemical outcome for reaction with chiral acetals.[6]

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(1) Reviews: Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol 4, pp 69 and 139.

(2) For a recent reviews see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, New York, 2000; p 1105. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

(3) (a) Alexakis, A.; Frutos, J.; Mangeney P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427. (b) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745. (c) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869. (d) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000,** *2*, 2579. (e) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.-M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011.

(4) (a) Kitamura, M.; Miki T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141. (b) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999.

(5) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vires, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (c) For an alternative, highly stereoselective ligand system see: Knöbel, A. K. H.; Escher I. H.; Pfaltz, A. *Synlett* **1997**, 1429.

(6) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

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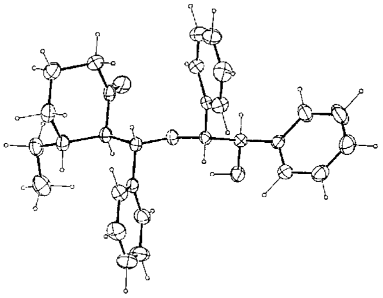
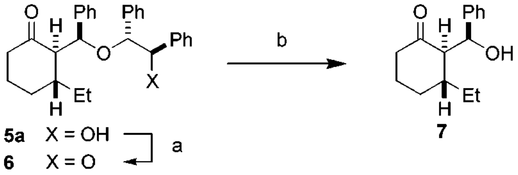


Figure 1. X-ray structure of **5a**.

To incorporate functionalities other than aryl,[8] we investigated the use of acetal **4b**. One can envisage using the double bond contained within the products of these reactions (**5b** and **5d**) as a chemical handle for a wide range of transformations, thus dramatically extending the synthetic potential. Reaction with **4b** could afford either the direct opening product or the conjugate addition adduct. Despite the presence of copper, the products of direct 1,2 opening were isolated in good yield (Table 2).[9]

After examining several unsuccessful methods, the chiral auxiliary was removed using a mild, highly efficient, two-step procedure as outlined in Scheme 3. Oxidation of the secondary alcohol **5a** gave ketone **6** which, when treated with excess zinc in aqueous acetic acid, resulted in the elimination of the trans-threo aldol product **7** in overall quantitative yield.

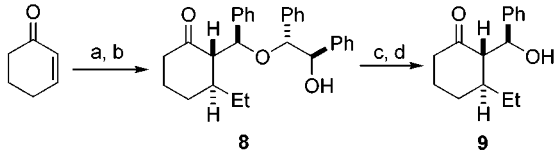
Scheme 3[a]



[a] Reagents and conditions: (a) PDC (2.0 equiv), 3 Å sieves, CH_2Cl_2, room temperature, 36 h; (b) Zn, AcOH/H_2O, 1 h; >99% overall yield.

By using the enantiomer of ligand **1** in the conjugate addition step, trans-erythro aldol **9** was formed as a single diastereomer after removal of the chiral auxiliary (Scheme 4) providing a method to selectively access *both* diastereomeric aldol products. Therefore, a chiral acetal overcomes the directing effect of the chiral enolate.[6] It should be noted that the nature of the Lewis acid is vital as the use of $BF_3{\cdot}OEt_2$ gave none of the desired product. As this was not found to be the case in the formation of the trans-threo isomer, this would seem to point to a mismatch effect between the enolate *ent*-**2a** and acetal **4a**.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) 0.5 mol % copper(II) triflate, 1.0 mol % *ent*-**1**, CH_2Cl_2, 0.5 M, −20 °C, 15 min; (ii) **4a** (1.5 equiv), TMSOTf (1.6 equiv), −20 to 0 °C, 2 h; (b) MeOH, Amberlyst-15, 1 h; (c) PDC (2.0 equiv), CH_2Cl_2, 3 Å sieves, room temperature, 36 h; (d) Zn, AcOH/H_2O, 1 h; 56% overall yield.

To verify that the chiral ligand plays no role in the reaction with the chiral acetal a control experiment with triphenylphosphine as ligand was carried out. This resulted in the formation of a racemic 3:2 mixture of **5a** and **8**, indicating that the stereocontrol at the aldol center arises purely as a result of the chiral auxiliary.

In summary we have extended the reactivity of homochiral zinc enolates to include trapping with acetals, ketals, and ortho esters. In the case of chiral acetals, three contiguous stereocenters and two carbon−carbon bonds can be generated in a tandem, one-pot reaction with complete control to give syn and anti aldol products with allyl and aryl substitution.

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Note Added after ASAP: There was a spelling error in the title in the version posted ASAP 04/17/2001. It has been corrected in the print version posted 05/09/2001.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C spectra are available for compounds **3a**−**f**, **5a**−**d**, and **6** to **9** plus tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic displacement parameters and figures for **5a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] Crystal data for **5a**: Orthorhombic, space group $P2_12_12_1$, colorless crystal, $a = 8.8471(6)$ Å, $b = 14.5780(7)$ Å, $c = 19.1945(10)$ Å, $Z = 4$, 200 K, GOF = 1.56, $R = 0.033$, $wR = 0.034$.

[8] For the 1,4 addition of cuprates to **4b** see: Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3143

[8] The acetal formed by condensation of acetaldehyde and (*S*,*S*)-2,4-pentanediol reacted with **2a** with lower selectivity.