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The First Catalytic Enantioselective Aldol-Type Reaction of Ethyl Diazoacetate to Ketones

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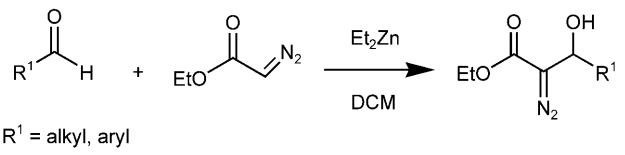
Abstract: The aldol-type addition to ketones still represents a great challenge in asymmetric catalysis. Recently, the direct aldol reaction between the commercially available ethyl diazoacetate and aldehydes has attracted increasing attention. Ethyl diazoacetate is economical and allows further transformation of the aldol adduct obtained. We present a solution for the arduous, and not previously described, addition of diazoacetate to ketones. Our procedure employs commercially available norephedrine-derived ligands and dialkylzinc reagents [R_2Zn: (diethylzinc, Et_2Zn; dimethylzinc, Me_2Zn)] as starting materials, therefore the active catalyst is prepared with a very straightforward methodology. Remarkably, the reaction gives good enantiomeric excesses with α-halo ketones, a class of compounds that has not been commonly used in enolate addition.

Keywords: diazoacetates; dimethylzinc; enolates; ketones; norephedrine

Enantioselective C–C bond formation under catalytic condition remains a challenging task in modern organic synthesis.[1] Recently, Feringa[2] and ourselves[3] have described highly enantioselective variants of the Reformatsky reaction[4] with ketones, affording high levels of enantiomeric excess.

However, these catalytic asymmetric processes rely on the use of iodoacetate to successfully promote the formation of the zinc enolate.[5] Considering the convenience of atom efficiency, it would be more desirable to employ nucleophiles directly in catalytic asymmetric aldol reactions with ketones.[6] Pioneering work developed by Shibasaki,[7] Trost,[8] and Kobayashi[9] was directed towards the development of catalytic asymmetric aldol reactions through the use of particularly acidic nucleophiles.[10] It is well known that the aldol reaction between commercially available α-diazo esters and aldehydes has a valuable synthetic utility and is also atom-economical. However, α-diazo carbonyl compounds, despite their usefulness in the preparation of amino alcohols and acids,[11] have only in recent years been employed in direct aldol reactions. Wang has recently developed a DBU-catalyzed aldol-type condensation of aldehydes with ethyl diazoacetate.[12,13] Interesting examples of catalytic asymmetric aldol condensation of ethyl diazoacetate as nucleophile with aldehydes and imines have been reported.[14,15] This year, a highly enantioselective method for the catalytic direct aldol reaction of ethyl diazoacetate with a broad range of aldehydes was described by Trost.[16] Among all the procedures accounted for in the literature, Et_2Zn was also used to deprotonate ethyl diazoacetate, and to promote the corresponding reaction with aldehydes (Scheme 1).[17]

As the formation of a zinc enolate was probably involved in these reactions, we conceived that the first catalytic enantioselective addition of ethyl diazoacetate to ketones might be developed using ligands active in catalytic enantioselective Reformatsky-type reactions.[2,3] Herein, we report a practical catalytic enantioselective addition of ethyl diazoacetate to ketones promoted by inexpensive amino alcohols as chiral ligands.



Scheme 1. Reaction of aldehydes in the presence of Et_2Zn as a base.

Many chiral amino alcohols were tested as ligands in the model reaction with acetophenone (see Supporting Information).

Remarkably, the corresponding aldol product was isolated with encouraging enantiomeric excesses. Catalytic enantioselective addition of ethyl diazoacetate to ketones was not yet described, thus we took the preliminary result obtained in the reaction of acetophenone in the presence of *N*-pyrrolidinylnorephedrine **1** as the chiral ligand (67% *ee*, entry 5), and we performed several experiments in order to improve yields and enantiomeric excesses, some of these are illustrated in Table 1.

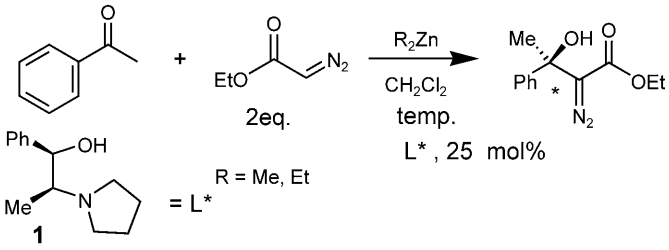
The background reaction is quite fast for the addition of ethyl diazoacetate to ketones, and proceeds without the need of a chiral ligand. The fast background reaction imposed the use of a high percentage of the chiral ligand (25 mol%). However, substituted norephedrine derivatives are inexpensive, and they have found industrial application as chiral ligands in the large scale synthesis of Efavirenz described by Merck.[18] We have found two complementary procedures for this enantioselective reaction. In the first procedure, Et_2Zn was used without additives, while in the other procedure, the less reactive Me_2Zn was employed in the presence of $Ph_3P{=}S$ as additive.[18] The two procedures were applied to a series of ketones, and the results obtained are illustrated in Table 2.

All the reactions were run at −25 °C in order to minimize the effect of the background reaction. The two methods showed different selectivity in function of the ketones employed, and they are complementary. In general, with acetyl aromatic ketones the employment of the more reactive Et_2Zn is recommended.

However, in order to obtain good *ee*s it is necessary to stop the reaction after 48 h. Prolonged reaction times are detrimental to enantioselectivity (Table 2). For α-halo-substituted aromatic ketones, the use of Me_2Zn in combination with triphenylphosphine sulfide afforded good enantiomeric excesses and yields. The reaction was quite sluggish at lower temperatures without the admission of additives. It is worth adding that a catalytic enantioselective addition of an enolate to α-halo-substituted ketones is realized for the first time, giving access to highly functionalized building blocks. Transformation of the diazo adduct **2** to **3** was used to establish the absolute configuration of products (Scheme 2). The reduction occurs in quantitative yield using PtO_2 as catalyst in 5 mol% with no racemization (see Supporting Information for details). Tentatively we suggest for the reaction a mechanism in which the diazoacetate is deprotonated by R_2Zn. In fact, the treatment of ethyl diazoacetate with Me_2Zn for two hours at room temperature, followed by quenching with CD_3OD, gave α-deuterated ethyl diazoacetate, which was detected by ^{13}C NMR.[19]

We investigated some transformations of the obtained diazo esters to demonstrate their synthetic utility. Unfortunately, the adducts are quite sensitive to basic conditions. It is well known that α-diazo-β-hydroxy esters are unstable under basic and acidic conditions.[15] All attempts to protect the tertiary alcohol in the presence of strong bases or amines gave starting materials through a retro-aldol pathway. The reduction with DIBAL, $LiAlH_4$ or different hindered hydrides provided a complete reduction of ester and diazo groups, in low yield. The adducts derived from ketones are much more sensitive to a retro-aldol pathway than the corresponding derivatives obtained from aldehydes. In order to stabilize the adducts we investigated the possibility of protecting the hindered tertiary alcohols in several reactions. Remarkably, working in excess of TMSOTf (trimethylsilyl triflate) in the presence of imidazole as base (alternative bases led to retro-aldolization of the products) the

Table 1. Addition of diazoacetatate to acetophenone.



Entry[a]	R_2Z	T [°C]	t [h]	Additive	Yield [%][b]	*ee* [%][c]
1	Et	0	6	–	–	44
2	Et	−25	48	–	25	**78**
3	Et	−35	24	–	25	**78**
4	Me	r.t.	24	–	70	26
5	Me	0	3	–	40	67
6	Me	−25	48	–	37	60
7	Me	0	24	$Ph_3P{=}O$	65	6[d]
8	Me	−25	72	$Ph_3P{=}O$	52	54[d]
9	Me	−25	72	$Ph_3P{=}S$	43	65[d]

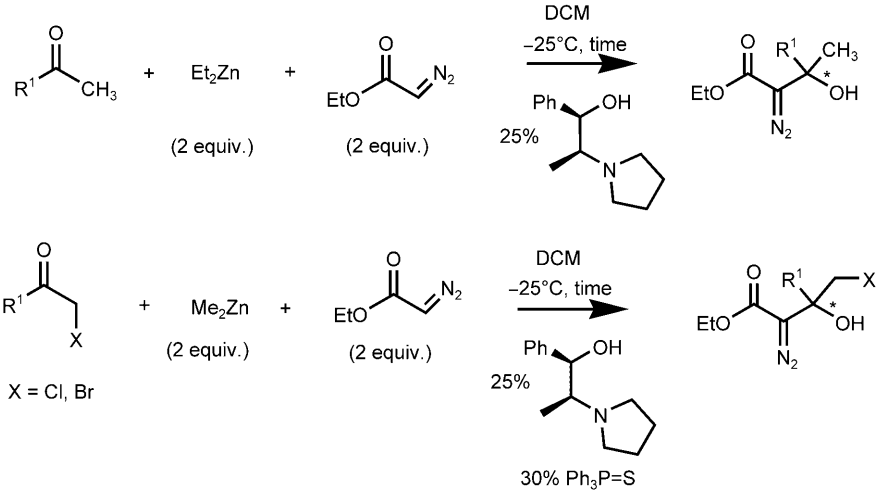
[a] All the reactions were performed in DCM at the indicated temperature. To a solution of R_2Zn (2 equiv., R = Me, Et) in CH_2Cl_2 (0.04 M) the ligand was added (0.25 equiv.), then the solution was stirred for 5 min at room temperature. Acetophenone (1 equiv.) and ethyl diazoacetate (2 equiv.) were added by syringe at the indicated temperature. The reaction was quenched with water after the indicated hours, and the product isolated after usual work-up.

[b] Isolated yield after chromatographic purification.

[c] Enantiomeric excess was evaluated using a chiral HPLC analysis (see supporting information for details). Absolute (*R*) configuration was established by correlation after reduction.

[d] 30 mol% of additive were used. The additive was added at room temperature to the reaction before the addition of the diazoacetate and the ketone.

Table 2. Addition of ethyl diazoacetate to aromatic and aliphatic ketones.

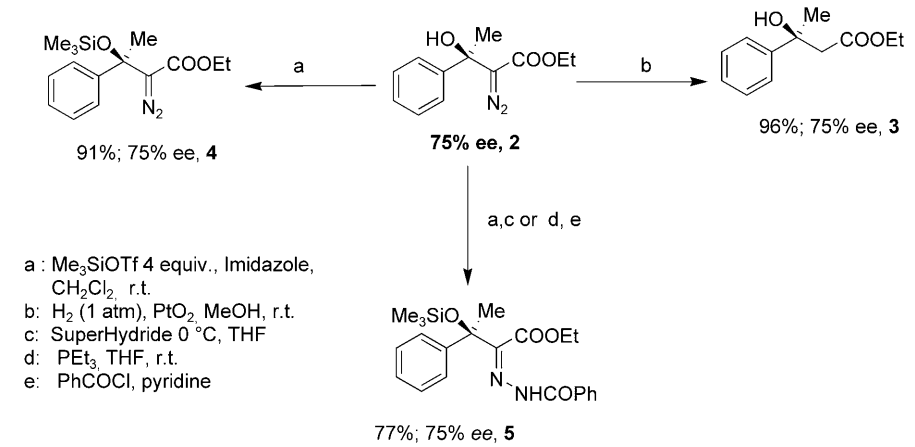


Entry[a]	Ketone	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	$C_6H_5COCH_3$	24	25	78
2[d]	$C_6H_5COCH_3$	48	40	74
3	$C_6H_5COCH_3$	72	43	56
4	*p*-$ClC_6H_5COCH_2Br$	24	25	74
5	*p*-$ClC_6H_5COCH_2Br$	72	62	70
6	$C_6H_5COCH_2Br$	24	20	76
7	$C_6H_5COCH_2Br$	72	69	69
8	$C_6H_5COCH_2Cl$	48	63	**80**
9	*p*-$ClC_6H_5COCH_2Cl$	48	66	68
10[d]	2-Naphthyl$COCH_3$	48	60	66
11[d]	*m*-$CH_3C_6H_5COCH_2Cl$	48	40	64
12[d]	2-Benzofuryl$COCH_3$	48	25	**80**
13	*p*-$FC_6H_5COCH_2Br$	72	71	72
14	*p*-$FC_6H_5COCH_2Cl$	72	77	68
15[d]	*p*-$BrC_6H_5COCH_3$	72	70	42
16[d]	*p*-$BrC_6H_5COCH_3$	24	37	74
17[d]	*p*-$FC_6H_5COCH_3$	72	59	36
18[d]	*p*-$FC_6H_5COCH_3$	24	20	**80**
19[d]	*o*-$ClC_6H_5COCH_3$	24	30	**80**
20	*p*-$CH_3C_6H_5COCH_2Cl$	48	72	**80**
21[d]	*i*-Pr$COCCH_3$	24	20	**87**
22[d]	*i*-Pr$COCCH_3$	48	25	74
23[d]	Cyclohexyl$COCH_3$	48	54	74

[a] All the reactions were performed in DCM at −25 °C using the general procedure.
[b] Isolated yield after chromatographic purification.
[c] Enantiomeric excess was evaluated using a chiral HPLC analysis (see Supporting Information for details).
[d] Performed with Et_2Zn (2 equiv.) instead of Me_2Zn at −25 °C without additives.

corresponding TMS ether **4** was isolated in high yield (Scheme 2, a). Reduction of the diazo group of **4** was carried out with $LiEt_3BH$[20] or with phosphines,[21] and the derivative was isolated as a single diastereoisomer after reaction with benzoyl chloride. We found that the reductive cleavage of the diazo group can be carried out also by PEt_3.[21] It is worth mentioning that the unprotected **5** was quite unstable and showed traces of decomposition at −25 °C after a few hours. The product is unstable towards mild acids and it was stabilized by the preparation of the corresponding benzoylamide **5.** Unfortunately, all attempts to perform the reduction of **5** with SmI_2 as described for the diazo derivatives of aldehydes[20] gave complex mixtures of products, in which the cleavage of the N–N group was not observed. Treatment with Raney nickel gave extensive decomposition. Other tailored reagents and reaction conditions in order to improve yield and selectivity of this difficult transformation are currently under investigation in our laboratory.

In summary, we report the first enantioselective addition of ethyl diazoacetate to ketones, that gives



Scheme 2. Transformation of the diazo adducts occurred with no racemization.

access to highly functionalized building blocks. For the first time, the addition of enolate to α-halo ketones is realized in a highly enantioselective manner.

Many opportunities are now opened up to explore the facile generation of zinc enolates in the presence of norephedrine derivatives for the controlled formation of quaternary stereogenic centres. These and other options are under active investigation in our laboratory.

Experimental Section

General Procedure for the Addition to α-Halo Ketones

To a solution of Me_2Zn (2 equiv.) in dichloromethane (DCM) at room temperature *N*-pyrrolidinylnorephedrine (25 mol%) was added under nitrogen and the resulting solution was stirred for 5 min. The flask was cooled to −25 °C and $Ph_3P{=}S$ (30 mol%) was added as solid, followed after 5 min by the ketones (1 equiv.) and diazoacetate (2 equiv.), added by syringe. The flask was kept at −25 °C for the indicated time without stirring then quenched with water. After usual work-up the resulting oil was purified by chromatography (*n*-hexane:acetone, 9:1).

General Procedure for the Addition to Methyl Ketones

To a solution of Et_2Zn (2 equiv.) in DCM at room temperatue *N*-pyrrolidinylnorephedrine (25 mol%) was added under nitrogen and the resulting solution was stirred for 5 min. The flask was cooled to −25 °C and the ketone (1 equiv.) and the diazoacetate (2 equiv.) were added by syringe. The flask was kept at −25 °C for the indicated time without stirring then quenched with water. After usual work-up the resulting oil was purified by chromatography (*n*-hexane:acetone, 9:1).

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