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One-step deprotonation route to zinc amide and ester enolates for use in aldol reactions and Negishi couplings

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Abstract—Simple amides and esters are conveniently deprotonated by $Zn(tmp)_2$ (tmp = 2,2,6,6-tetramethylpiperidinyl anion) to generate Zn enolates. Enolates formed by this method are suitable for use in aldol reactions that tolerate base-sensitive functional groups. Additionally, the Zn enolates are readily coupled with aryl bromides using typical Pd-catalyzed coupling methods.

Zinc amide and ester enolates (i.e. Reformatsky reagents) are frequently used as mild carbon nucleophiles in synthetic organic chemistry.[1] Their uses include addition reactions with ketones, aldehydes, and activated alkenes.[2] They are also key reactants in some Pd-mediated coupling reactions.[3] The preparation of zinc amide and ester enolates is generally achieved by one of two methods.[4] The first involves the insertion of activated zinc metal into an α-halogenated amide or ester. Alternatively, deprotonation of a carboxy amide or ester with a strong base (e.g. BuLi, LDA) followed by transmetallation with ZnX_2 (X = halide) is also frequently used. In the interest of developing a more convenient route to Zn enolates we have been exploring the use of simple Zn species as bases for the deprotonation of amides and esters. In this context, we recently reported the direct formation of zinc amide enolates by reaction of carboxy amides with a mixture of $ZnPh_2$ and simple amines.[5] The role of the amine in these reactions is to form an intermediate zinc amido species (e.g. $PhZnNR_2$) that is competent for the deprotonation of the carboxy amide.[6] To expand the usefulness and scope of this approach we have investigated the use of zinc bis(amido) species for the synthesis of amide and ester enolates. In this communication, we report that Zn amide and ester enolates can be conveniently prepared by the deprotonation of carboxy amides and esters with $Zn(tmp)_2$[7] (tmp = 2,2,6,6-tetramethylpiperidinyl anion). This route is highly tolerant of base-sensitive functionality, and the resulting enolates can be effectively used in aldol and Pd-catalyzed coupling reactions.

The deprotonation of simple amides and esters by Zn amidos is essentially unexplored.[8] We recently reported that the equilibrium reaction of *N*,*N*-diethylacetamide (DEA) with $Zn[N(SiMe_3)_2]_2$ at 50 °C only led to the partial formation of the Zn enolate and hexamethyldisilazane.[5] The use of the more basic $Zn(tmp)_2$ in place of $Zn[N(SiMe_3)_2]_2$ was anticipated to shift this equilibrium to strongly favor the enolate product. This was found to be the case when a C_6D_6 solution of $Zn(tmp)_2$ was reacted with 2.0 equiv of DEA at ambient temperature. ^1H NMR spectroscopic data acquired after 30 min indicated the complete consumption of $Zn(tmp)_2$ and the formation of tmp-H. The presence of $Zn[CH_2C(O)NEt_2]_2$ is implied by mass balance, but this was not confirmed spectroscopically due to the broadness and complexity of its NMR spectrum.

The reaction of $Zn(tmp)_2$ with 2.05 equiv of DEA was repeated in toluene solution over 2 h.[9] To the in situ prepared $Zn[CH_2C(O)NEt_2]_2$ was added 1.5 equiv of PhCHO (Table 1, Eq. 1). The reaction was stirred at ambient temperature for 4 h and then quenched. The expected aldol product was formed in 92% yield (entry 1). The use of the more hindered amide *N*,*N*-diethylpropionamide gave similar results, but it was necessary to heat the $Zn(tmp)_2$/amide mixture to 50 °C for 24 h to completely form the zinc amide enolate $Zn[CH(Me)C(O)NEt_2]_2$. This enolate was then reacted

Keywords: Zinc; Amide enolate; Ester enolate; Reformatsky; Amido; Aldol; Negishi coupling.
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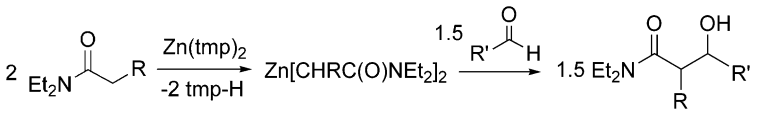
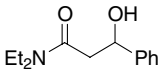
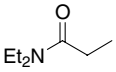
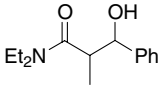
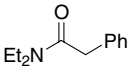
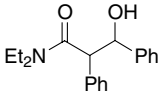
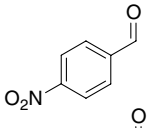
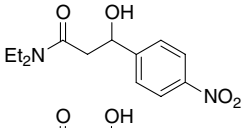
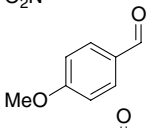
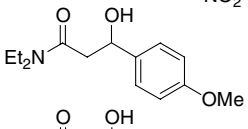
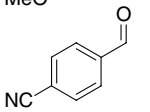
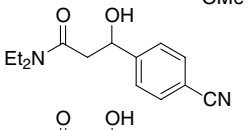
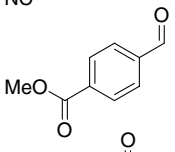
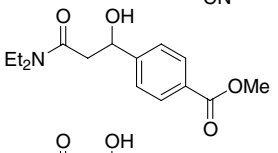
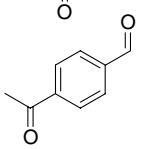
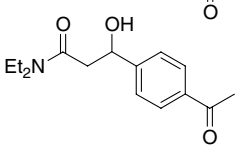
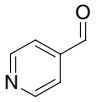
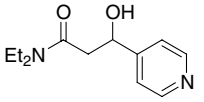
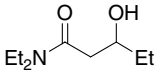
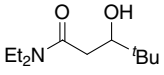
Table 1. Reactions of in situ formed Zn amide enolates with aldehydes[a]



(1)

Entry	Amide	Aldehyde	Product	Yield (%)[b]
1	DEA	PhCHO		92[c]
2		PhCHO		85[c,d]
3		PhCHO		99[c,e]
4	DEA			89
5	DEA			91
6	DEA			80[f]
7	DEA			85
8	DEA			93
9	DEA			86
10	DEA	EtCHO		85
11	DEA	^{t}BuCHO		86[f]

[a] General conditions: (i) 1 equiv (75.0 μmol) $Zn(tmp)_2$, 2.05 equiv amide, PhMe (1.0 mL), 2 h, ambient temperature. (ii) 1.50 equiv of aldehyde, 4 h, ambient temperature.

[b] Yields are for pure isolated material and are an average of two runs.

[c] Yield was determined by ^{1}H NMR spectroscopy by comparison to an internal standard (1,3,5-trimethoxybenzene).

[d] Zinc metallation step performed at 50 °C for 24 h and the reaction with PhCHO was performed at ambient temperature for 12 h. *syn:anti* = 2:1.

[e] *syn:anti* = 1:1.4.

[f] 3.00 equiv of DEA were used.

with PhCHO at ambient temperature to form the addition product in 85% overall yield (entry 2) and low diastereoselectivity (*syn*:*anti* = 2:1). The α-phenyl substituted amide *N*,*N*-diethyl-2-phenylacetamide was also found to be an acceptable substrate. It formed the expected aldol product in 99% yield (entry 3) and low diastereoselectivity (*anti*:*syn*, 1.4:1).

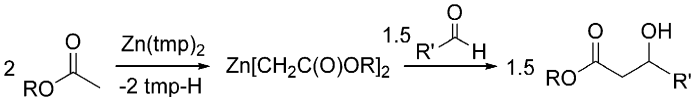
The $Zn(tmp)_2$-mediated aldol reaction can be performed with aldehydes bearing a variety of common functional groups. For example, in situ generated DEA enolate reacted with *para*-substituted aryl aldehydes featuring nitro, methoxy, cyano, and ester functionalities (entries 4–7) to form the expected aldol products in good yields. Selective aldehyde addition can also be performed in the

presence of ketones (entry 8). Lastly, both pyridyl-substituted and aliphatic aldehydes were also found to be suitable substrates (entries 9–11).

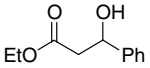
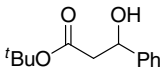
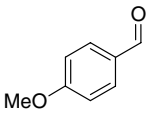
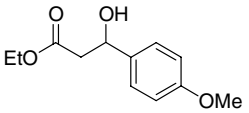
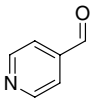
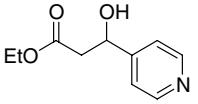
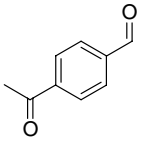
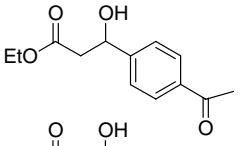
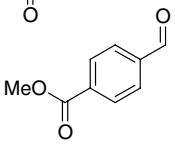
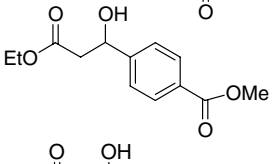
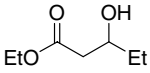
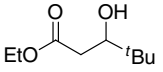
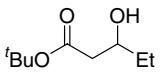
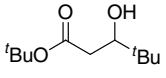
The use of $Zn(tmp)_2$ was expanded to include ester aldol production (Table 2, Eq. 2). For example, $Zn(tmp)_2$ was reacted with 2.05 equiv of ethyl acetate (EtOAc) at 5 °C for 1 h to generate the Zn ester enolate $Zn[CH_2C(O)OEt]_2$. The addition of 1.5 equiv of PhCHO to this solution formed the aldol product in 81% yield (entry 2). Repeating the reaction at ambient temperature resulted in a lower yield (61%). In contrast, reactions involving the more hindered *tert*-butyl acetate (^{t}BuOAc) gave high yields when the reactions were performed at ambient temperature. As was observed for the amide aldol reactions above, the ester aldol reactions can be performed in the presence of many common funcitonalities (entries 4–7) and by using aliphatic aldehyde substrates (entries 8–11).

The use of Zn amide and ester enolates in Pd-catalyzed coupling reactions is currently of significant interest.[3] Our preliminary studies indicate that amide and ester enolates generated via $Zn(tmp)_2$ are highly effective in this context (Table 3, Eq. 3). For example, $Zn(tmp)_2$ reacted with 2.05 equiv of ^{t}BuOAc over a couple of hours

Table 2. Reactions of in situ formed Zn ester enolates with aldehydes[a]

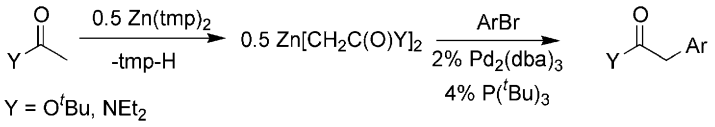


(2)

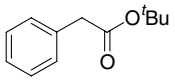
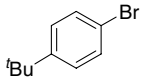
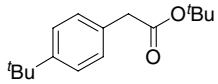
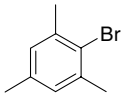
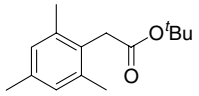
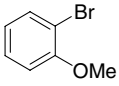
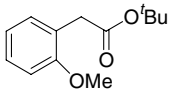
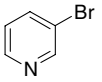
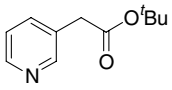
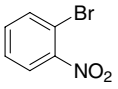
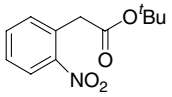
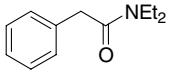
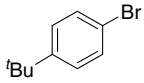
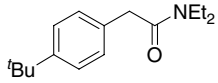
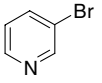
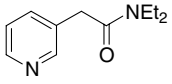
Entry	Ester	Aldehyde	Product	Temperature (°C)	Yield (%)
1	EtOAc	PhCHO		Ambient	61[b]
2				5	81[b]
3	^{t}BuOAc	PhCHO		Ambient	93[b]
4	EtOAc			5	82[b]
5	EtOAc			5	84[c]
6	EtOAc			5	85[b]
7	EtOAc			5	89[c]
8	EtOAc	EtCHO		5	42[b,d]
9	EtOAc	^{t}BuCHO		5	64[b,d]
10	^{t}BuOAc	EtCHO		Ambient	92[b]
11	^{t}BuOAc	^{t}BuCHO		Ambient	95[b]

[a] General conditions: (i) 1 equiv (75 μmol) of $Zn(tmp)_2$, 2.05 equiv ester, PhMe (1.0 mL), 1 h. (ii) 1.50 equiv of RCHO, 3 h, 5 °C.
[b] Yield was determined by ^{1}H NMR spectroscopy by comparison to an internal standard (1,3,5-trimethoxybenzene).
[c] Yields are for pure isolated material and are an average of two runs.
[d] 3.00 equiv of the ester were used.

Table 3. Pd-catalyzed coupling reactions of in situ formed Zn enolates[a]



(3)

Entry	Amide/ester	Aryl halide	Product	Yield (%)[b]
1	^{t}BuOAc	PhBr		96
2	^{t}BuOAc			75
3	^{t}BuOAc			74
4	^{t}BuOAc			84
5	^{t}BuOAc			72
6	^{t}BuOAc			46
7	DEA	PhBr		94
8	DEA			81
9	DEA			45

[a] General conditions: (i) 1 equiv (75 μmol) of $Zn(tmp)_2$, 2.05 equiv ester/amide, PhMe (1.0 mL), 2 h. (ii) 2.00 equiv of aryl halide, 2% $Pd_2(dba)_3$, 4% $P(^tBu)_3$, 24 h, ambient temperature.

[b] Yield was determined by ^{1}H NMR spectroscopy by comparison to an internal standard (1,3,5-trimethoxybenzene). Reaction times and conditions were not optimized.

to generate the expected ester enolate. Combining this solution with 2 mol % $Pd_2(dba)_3$ (dba = *trans,trans*-dibenzylideneacetone), 4 mol % $P(^tBu)_3$, and 2 equiv of PhBr formed a purple solution that was stirred for 24 h. The reaction was then quenched with $NH_4Cl_{(aq)}$. Analysis of the crude product by ^{1}H NMR against an internal standard indicated that the expected α-phenylated product $PhCH_2C(O)O^tBu$ was formed in 96% yield (entry 1). Repeating the reaction using DEA in place of the ester formed $PhCH_2C(O)NEt_2$ in 94% yield (entry 7). The use of several substituted (e.g. –OMe, $–NO_2$, pyridyl) aryl bromides in couplings with ^{t}BuOAc and DEA was also briefly examined. These afforded the expected products in moderate to good yields.

In summary, we have reported that amides and esters are conveniently deprotonated using $Zn(tmp)_2$ to generate Zn enolates. Enolates formed by this method are suitable for use in aldol reactions that tolerate base-sensitive functional groups. Additionally, the Zn enolates are readily coupled with aryl bromides using typical Pd-catalyzed coupling methods. The use of $Zn(tmp)_2$ and other zinc amidos for the convenient deprotonation of functionalized organics should allow for the expanded use of Zn-based nucleophiles in organic synthesis.

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Supplementary data

Experimental details and characterization data are presented as supplementary data. These can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.093.

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