The direct α-zincation of amides, phosphonates and phosphine oxides by H–Zn exchange†

Mark L. Hlavinka, Jeffrey F. Greco and John R. Hagadorn*

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Stoichiometric or catalytic quantities of simple 2° amines greatly increase the rate of H–Zn exchange between $ZnPh_2$ and a range of relatively non-acidic substrates, allowing for the convenient and direct preparation of α-functionalized organozincs.

Functionalized organozincs are frequently used as C-nucleophiles in the synthesis of complex organic molecules.[1] Due to their low basicities they tolerate a wide range of sensitive functional groups, yet they react with many electrophiles and readily undergo transmetalation reactions with transition-metal salts. Thus, they are indispensable intermediates in many C–C bond-forming reactions,[2] particularly those mediated by Cu and Pd complexes.[3] The preparation of functionalized organozincs is commonly performed either by the direct insertion of activated Zn into carbon–halogen bonds or by the transmetalation of organolithium reagents with zinc halides.[4] More recently, alkenylzinc and related derivatives have been accessed by transmetalation of Zr- and Pd-containing intermediates with Zn sources.[5] Conspicuously, the straightforward production of functionalized organozincs by H–Zn exchange (*i.e.* deprotonation) is rarely used due to the kinetic inertness of common organozincs (*e.g.* $ZnEt_2$, $ZnPh_2$). In this communication, however, we report that stoichiometric or catalytic quantities of 2° amines increase the rate of H–Zn exchange between $ZnPh_2$ and a range of relatively inert carbon acids. By this method α-functionalized organozincs have been conveniently prepared starting from simple amides, phosphonates, and phosphine oxides. The amine-promoted H–Zn exchange process involves the intermediacy of Zn amido species which are competent for the deprotonation of the functionalized substrates.

The deprotonation of carbon acids is often limited by slow kinetics.[6] As a result dialkylzincs and $ZnPh_2$ are only able to deprotonate carbon acids that have pK_a[7] values below 29. Reported examples have involved ketones,[8] $MeNO_2$,[9] dimethyl malonate,[10] fluorene,[11] and terminal alkynes.[12,13] The reported reactivity of Zn amidos has likewise been limited to acidic substrates.[14] Consistent with the aforementioned studies, we observed no reaction between ZnR_2 (R = Et, Ph) and *N,N*-diethylacetamide (DEA, $pK_a = 35$[7]) or *N,N*-diisopropylacetamide (DIPA) in C_6D_6 solution at 75 °C over several days. To our surprise, the addition of Et_2NH to the above solutions led to the formation of measurable quantities of α-zincated amides (eqn (1)).

Following this observation we initiated a systematic study of the deprotonation of DEA by $ZnPh_2$ promoted by a range of different amines. Initial studies revealed that both 1° and 2° amines were able to accelerate the H–Zn exchange reaction. For example, heating a mixture of DEA, 1 equiv. *t*-$BuNH_2$, and 2 equiv. $ZnPh_2$ to 50 °C for 24 h formed the α-zincated amide in 26% yield (Table 1, entry 1). The use of Et_2NH under the same conditions gave a yield of 47% (entry 2). In contrast, all 3° amines and pyridines were ineffective (entries 3–5).

$$ZnR_2 + CH_3C(O)NR'_2 \xrightarrow{\text{amine}} RZn[CH_2C(O)NR'_2] + RH \quad (1)$$

The steric profile of an amine is important in determining its activity. Thus while Et_2NH was moderately effective, the bulkier *i*-Pr_2NH afforded only 7% of the zincated product (entry 6). Small cyclic amines gave the best results. For example, the use of 1 equiv. of morpholine with 2 equiv. $ZnPh_2$ gave 91% yield (entry 10). Repeating the reaction with 3 equiv. $ZnPh_2$ did not significantly increase the yield (entry 11), but the use of 1 equiv. $ZnPh_2$ gave a reduced yield of 62% (entry 12). The use of substoichiometric quantities of the amines gave low to modest yields, but with multiple turnovers based on amine. For example, the reaction of DEA, 0.1 equiv. pyrrolidine, and 1.1 equiv. $ZnPh_2$ afforded the zincated product in 40% yield (entry 15). Lastly, the use of $ZnEt_2$ instead of $ZnPh_2$ gave relatively poor results (entry 16).

Reformatsky amides are frequently used in addition reactions with unsaturated substrates and in transmetalations with transition-metal salts.[15] The solutions of α-zincated amides described in Table 1 are conveniently used in this context. $PhZn[CH_2C(O)NEt_2]$[16] was reacted with 1 equiv. PhCHO in toluene solution for 12 h and quenched with $NH_4Cl(aq)$. The expected addition product $Et_2NC(O)CH_2CH(Ph)OH$[17] was formed in 57% yield.[18] The use of 10 equiv. PhCHO increased the yield to 78%. Reaction of the same preparation of $PhZn[CH_2C(O)NEt_2]$ with 10 equiv. I_2 afforded *N,N*-diethyl-1-iodoacetamide[19] in 88% yield.

Amine-promoted H–Zn exchange is potentially useful for many substrates in addition to carboxy amides. Preliminary screening has revealed promising results for a diverse set of functionalized organics. Experiments with Me_3PO and $Me(MeO)_2PO$ (DMMP) are shown in Table 2. Relative to DEA, these substrates display greater reactivity with $ZnPh_2$–amine mixtures. For example, Me_3PO was zincated quantitatively in the presence of 1 equiv. morpholine and 2 equiv. $ZnPh_2$ at 50 °C over 24 h (entry 2). Catalytic quantities of amines were also found to be very effective. The use of only 0.1 equiv. pyrrolidine and 1.1 equiv. $ZnPh_2$ formed the zincated product in 99% yield (entry 4). H–Zn exchange

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Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado, USA. E-mail: hagadorn@colorado.edu; Fax: +1 303 492 5894; Tel: +1 303 492 5717

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Table 1 α-Zincation experiments of carboxyl amides[a]

Entry	Amide	Amine (equiv.)	Zn source (equiv.)	Yield[b]
1	DEA	t-BuNH_2 (1.0)	$ZnPh_2$ (2.0)	26%
2	DEA	Et_2NH (1.0)	$ZnPh_2$ (2.0)	47%
3	DEA	Et_3N (1.0)	$ZnPh_2$ (2.0)	0%
4	DEA	Pyridine (1.0)	$ZnPh_2$ (2.0)	4%
5	DEA	4-(Dimethylamino) pyridine (1.0)	$ZnPh_2$ (2.0)	0%
6	DEA	i-Pr_2NH (1.0)	$ZnPh_2$ (2.0)	7%
7	DEA	$(Me_3Si)_2NH$ (1.0)	$ZnPh_2$ (2.0)	0%
8	DEA	Piperidine (1.0)	$ZnPh_2$ (2.0)	90%
9	DEA	Pyrrolidine (1.0)	$ZnPh_2$ (2.0)	88%
10	DEA	Morpholine (1.0)	$ZnPh_2$ (2.0)	91%
11	DEA	Morpholine (1.0)	$ZnPh_2$ (3.0)	93%
12	DEA	Morpholine (1.0)	$ZnPh_2$ (1.0)	62%
13	DEA	Morpholine (0.10)	$ZnPh_2$ (1.1)	30%
14	DEA	Piperidine (0.10)	$ZnPh_2$ (1.1)	18%
15	DEA	Pyrrolidine (0.10)	$ZnPh_2$ (1.1)	40%
16	DEA	Morpholine (1.0)	$ZnEt_2$ (2.0)	22%
17	DEA	None	$Zn[N(SiMe_3)_2]_2$ (1.0)	49%[c]
18	DIPA	Morpholine (1.0)	$ZnPh_2$ (2.0)	86%

[a] Reaction conditions: amide (1.0 equiv.), amine, Zn source, toluene (2 mL), 50 °C, 24 h. [b] Yields were determined from the ratio of deuterated to non-deuterated substrate following quenching of the reaction mixture with 99.9% D_2O. [c] Initial concentrations of $Zn[N(SiMe_3)_2]_2$ and DEA were both 0.046 M.

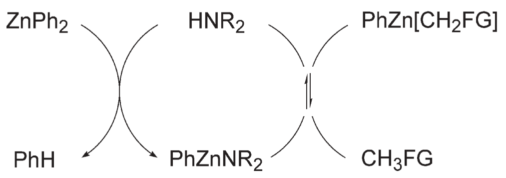
Table 2 α-Zincation experiments of other substrates[a]

Entry	Substrate[b]	Amine (equiv.)	Zn source (equiv.)	Yield[c]
1	Me_3PO	None	$ZnPh_2$ (2.0)	0%
2	Me_3PO	Morpholine (1.0)	$ZnPh_2$ (2.0)	100%
3	Me_3PO	Morpholine (0.1)	$ZnPh_2$ (1.1)	72%
4	Me_3PO	Pyrollidine (0.1)	$ZnPh_2$ (1.1)	99%
5	Me_3PO	None	$Zn[N(SiMe_3)_2]_2$ (1.0)	91%[d]
6	DMMP	None	$ZnPh_2$ (2.0)	0%
7	DMMP	Morpholine (1.0)	$ZnPh_2$ (2.0)	97%
8	DMMP	Morpholine (0.1)	$ZnPh_2$ (1.1)	51%
9	DMMP	Piperidine (0.1)	$ZnPh_2$ (1.1)	77%
10	DMMP	None	$Zn[N(SiMe_3)_2]_2$ (1.0)	56%[d]

[a] Reaction conditions: substrate (1.0 equiv.), amine, Zn source, toluene (2 mL), 50 °C, 24 h. [b] DMMP is $Me(MeO)_2PO$. [c] Yields were determined from the ratio of deuterated to non-deuterated substrate following quenching of the reaction mixture with 99.9% D_2O. [d] Initial concentrations of $Zn[N(SiMe_3)_2]_2$ and substrate were both 0.046 M.

reactions using $Me(MeO)_2PO$ gave similar results, although slightly lower yields were obtained (entries 7–9).

A simplified[20] mechanism for the H–Zn exchange is shown in Scheme 1. First the 2° amine reacts with $ZnPh_2$ to generate $PhZnNR_2$.[21] Then this intermediate reacts with the substrate (CH_3FG) (where FG is a functional group) to form α-zincated $PhZn[CH_2FG]$ and HNR_2. The deprotonation of the substrate is expected to be reversible, with a K_{eq}[22] dependent on the heterolytic dissociation constants of the four reactants.[14a,23]



Scheme 1 Proposed mechanism for the formation of α-functionalized organozincs by amine-promoted H–Zn exchange.

The first step of the mechanism was explored by observing the reaction rate of $ZnPh_2$ with various amines. Heating a mixture of $ZnPh_2$, 1 equiv. morpholine, and CD_2Cl_2 to 50 °C gave complete conversion to $PhZn(NC_4H_8O)$ and PhH within 15 min. The other cyclic amines from Table 1 were also quickly deprotonated by $ZnPh_2$. Repeating the reaction with i-Pr_2NH, however, gave <5% conversion after 20 h. Thus the hindered amines (*i.e.* i-Pr_2NH, $(Me_3Si)_2NH$) are ineffective promoters of H–Zn exchange because they do not form Zn amidos at a reasonable rate. The use of $ZnEt_2$ instead of $ZnPh_2$ similarly results in the slow formation of a Zn amido. Heating $ZnEt_2$ and 1 equiv. morpholine in CD_2Cl_2 to 50 °C gave <30% conversion after 20 h.

The second step of the mechanism involves the reversible deprotonation of a carbon acid by a Zn amido. Related chemistry has been reported for EtZnN(i-Pr)$_2$ and $EtZnNPh_2$, which partially deprotonate t-BuC(O)Et ($pK_a \cong 28$) to form Zn enolate and amine.[14a] Our studies indicate that Zn amidos are capable of deprotonating less acidic substrates with pK_a values up to 35. Thus heating a toluene solution of mononuclear $Zn[N(SiMe_3)_2]_2$ (0.046 M) and 1 equiv. DEA (0.046 M) to 50 °C for 22 h led to 49% zincation (entry 17, Table 1). Repeating the reaction with Me_3PO and $Me(MeO)_2PO$ gave 91 and 56% zincation, respectively (Table 2, entries 5, 10).[24] In all cases, increasing the reaction times did not lead to significant changes in yield, thus indicating that thermodynamic equilibrium had been reached.

In conclusion, stoichiometric or catalytic quantities of simple 2° amines increase the rate of H–Zn exchange between $ZnPh_2$ and a range of functionalized substrates. Key to this process is the intermediacy of Zn amido species which are competent for the deprotonation of functionalized carbon acids. Using this method α-zincated derivatives of amides, phosphonates, and phosphine oxides have been conveniently prepared for the first time without the use of strongly basic or halogenated reactants.

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