$Zn(tmp)_2$: A Versatile Base for the Selective Functionalization of C−H Bonds

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Summary: $Zn(tmp)_2$ (tmp = 2,2,6,6-tetramethylpiperidinyl anion) is an effective base for the mild deprotonation of a broad range of substrates. Functionalized organozincs thus prepared are conveniently coupled with aryl bromides using typical Pd-catalyzed coupling methods.

The selective functionalization of C−H bonds is an area of paramount importance for the efficient synthesis of complex molecules.[1] In this context, it is necessary to develop diverse methods to effectively meet this challenge. One important approach is the directed metalation of relatively nonacidic C−H bonds using metal bases. These metalations are commonly performed using strong bases that include organolithiums and lithium amides.[2] The drawbacks associated with these reagents vary but may include undesirable nucleophilicity, redox chemistry, and instability in common solvents (e.g., THF). Also, in many cases these deprotonation reactions require careful temperature control and the absence of reactive functional groups.

One potential solution to these problems is to use organozinc bases, which are known to be highly tolerant of base-sensitive functionalities.[3] To date, this approach has been most fruitful for anionic zincate bases of the formulation $M[ZnR_2(tmp)]$ (M = Li, Na; tmp = 2,2,6,6-tetramethylpiperidinyl anion).[4] In comparison, the use of neutral organozincs in this context has been largely unexplored. The reason behind this is that deprotonations of carbon acids by commercially available organozinc reagents (e.g., $ZnEt_2$, $ZnPh_2$) are plagued by slow kinetics. Thus, neutral organozincs are only competent to deprotonate fairly acidic carbon acids that have pK_a[5] values (in DMSO) below 29.[6] To get around the poor kinetics associated with organozincs, it should be possible to use amidozinc reagents instead.[7] However, this approach is largely unexplored, with reports being limited to reactions involving ketones, β-amino esters, and Ph_3PCH_2.[8] In this submission, we examine the use of four readily prepared zinc amides as bases for stoichiometric deprotonations of a broad range of carbon acids. These studies indicate that $Zn(tmp)_2$[9] is a particularly effective and versatile base for the selective deprotonation of substrates that include esters, amides, ketones, phosphonates, 2-picoline, pyridine *N*-oxide, DMSO, and Me_2SO_2.[10] $Zn(tmp)_2$ is highly soluble and can be stored conveniently as a solution in toluene. Additionally, the zincated products are useful nucleophiles and can be conveniently coupled with aryl bromides using typical Pd-catalyzed coupling methods.

Bulky zinc amido bases were selected for investigation to minimize the formation of less reactive bridged species. We began our experiments with ethylzinc diisopropylamide ($EtZnN^iPr_2$) and ethylzinc diphenylamide ($EtZnNPh_2$). Previously a report had indicated that each of these two bases only partially deprotonated 2,2-dimethyl-3-pentanone (in C_6D_6) to form the corresponding Zn ketone enolate in reactions that were essentially thermoneutral.[8a] We expanded on these studies with a broader range of substrates and have observed somewhat surprising reactivity, in light of the earlier report. The ability of the ethylzinc amides to deprotonate a series of carbon acids in C_6D_6 solution was explored as described in eq 1 (Table 1). Yields were determined by ^1H NMR spectroscopy relative to an internal standard (PhMe). These were also confirmed by deuterium incorporation after quenching with 99.9% D_2O. $EtZnN^iPr_2$ was found to be an effective base for the quantitative deprotonation of both 2-methyl-3-pentanone and dimethyl methylphosphonate (DMMP) at ambient temperature (entries 1 and 2). In contrast, reaction of $EtZnN^iPr_2$ with *tert*-butyl acetate (^tBuOAc) failed to yield any of the enolate product (entry 3). Instead, significant quantities of *N*,*N*-diisopropylacetamide were formed. $EtZnN^iPr_2$ only partially deprotonated *N*,*N*-diethylacetamide (DEA) after 30 min at ambient temperature (entry 4). Heating the mixture to 50 °C, however, led to decomposition of the enolate. Thus, the above studies indicate

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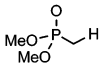
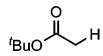
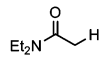
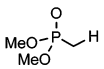
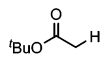
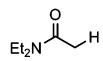
Table 1. Substrate Deprotonations by Ethylzinc Amido Bases[a]

$$EtZnNR'_2 + FG\text{-}R\text{-}H \longrightarrow EtZn[R\text{-}FG] + HNR'_2 \quad \text{(eq 1)}$$

Entry	Base ($EtZnR'_2$)	Substrate (FG-R-H)	Zn product ($EtZn[R\text{-}FG]$)	% Yield (conditions)[b]
1	$EtZnN^iPr_2$		$EtZn[CHMeC(O)^iPr]$[c]	100 (12 h)
2	$EtZnN^iPr_2$		$EtZn[CH_2P(O)(OMe)_2]$	100 (0.5 h)
3	$EtZnN^iPr_2$		$EtZn[CH_2C(O)O^tBu]$	dec. (0.5 h)
4	$EtZnN^iPr_2$		$EtZn[CH_2C(O)NEt_2]$	62 (0.5 h) dec. (12 h, 50 °C)
5	$EtZnNPh_2$		$EtZn[CHMeC(O)^iPr]$[c]	100 (20 h)
6	$EtZnNPh_2$		$EtZn[CH_2P(O)(OMe)_2]$	15 (0.5 h) 23 (18 h, 50 °C)
7	$EtZnNPh_2$		$EtZn[CH_2C(O)O^tBu]$	11 (6 h) dec. (18 h, 50 °C)
8	$EtZnNPh_2$		$EtZn[CH_2C(O)NEt_2]$	8 (6 h) 11 (18 h, 50 °C)

[a] Reaction conditions: $EtZnNR'_2$ (1.0 equiv), substrate (1.1 equiv), PhMe (1.0 equiv), and C_6D_6 (0.6 mL) were combined, reaction temperature 23 ± 2 °C, unless indicated otherwise. [b] Yields were determined (^{1}H NMR) relative to an internal standard (PhMe) and were confirmed by deuterium incorporation following quenching with 99.9% D_2O. [c] Stereochemistry of the Zn enolate product was not determined.

that the use of $EtZnN^iPr_2$ as a base is limited by unwanted side reactivity. The use of $EtZnNPh_2$ in a similar series of reactions (entries 5−8) gave poor results. Only the most acidic substrate, 2-methyl-3-pentanone, was cleanly deprotonated at 23 °C to form the enolate product (entry 5). It is an ineffective base for DMMP, DEA, and ^{t}BuOAc (entries 6−8). In each case only partial conversion was observed, even at 50 °C.[11] We attribute the poor performance of $EtZnNPh_2$ (compared to $EtZnN^iPr_2$) to the relatively low basicity of the diphenylamido anion, which is attributed to both electronic factors and its greater tendency to act as a bridging ligand.

Since both $EtZnN^iPr_2$ and $EtZnNPh_2$ demonstrated limited reactivity toward carbon acids, we explored the use of alternative Zn amido bases. These included the homoleptic zinc amides $Zn[N(SiMe_3)_2]_2$ and $Zn(tmp)_2$. The abilities of these bases to deprotonate functionalized carbon acid substrates were examined using the same method described previously for the ethylzinc amides. The results are shown in Table 2. $Zn[N(SiMe_3)_2]_2$ was found to react with 2.1 equiv of 2-methyl-3-pentanone over 24 h at 50 °C to form $Zn[CHMeC(O)^iPr]_2$ and $HN(SiMe_3)_2$ in 91% yield (entry 1). Repeating the reaction at 80 °C gave identical results, suggesting that a thermodynamic equilibrium may have been reached. Related reactions of $Zn[N(SiMe_3)_2]_2$ with less acidic substrates formed only low yields of the zincated products.[12] For example, the reaction of $Zn[N(SiMe_3)_2]_2$ with DMMP proceeded only 12% to completion after 24 h at 50 °C (entry 2). Heating to 80 °C led to reactant decomposition. Similar results were obtained for related reactions with ^{t}BuOAc and DEA (entries 3 and 4). Interestingly, heating a mixture of $Zn[CH_2P(O)(OMe)_2]_2$ and $HN(SiMe_3)_2$ in C_6D_6 (or CD_2Cl_2 or d_8-THF) to 50 °C failed to give any observable reaction, suggesting that poor kinetics may be contributing to the low reactivity of $Zn[N(SiMe_3)_2]_2$ with the non-ketone substrates.

Fortunately, $Zn(tmp)_2$[9] was found to be a much more effective base for the rapid and quantitative deprotonation of numerous substrates. For example, the reaction of $Zn(tmp)_2$ with 2.1 equiv of DMMP in C_6D_6 formed significant amounts of $Zn[CH_2P(O)(OMe)_2]_2$ and tmpH after only 2 min at ambient temperature (Figure 1B). After 10 min all the $Zn(tmp)_2$ had been consumed (Figure 1C) and quantitative conversion (relative to internal standard) had occurred (Table 2, entry 6). Equally good results were obtained for the zincations of 2-methyl-3-pentanone (entry 5), ^{t}BuOAc (entry 7), and DEA (entry 8). The reaction with the ketone required 4 h to go to completion, but each of the others was finished in less than 30 min. Preliminary studies also indicate that $Zn(tmp)_2$ displays similar reactivity in other solvents, including polar and coordinating ones. For example, the reaction of DEA with $Zn(tmp)_2$ in either CD_2Cl_2 or d_8-THF quantitatively afforded $Zn[CH_2C(O)NEt_2]_2$ and 2 equiv of tmpH after 10 min at ambient temperature.

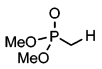
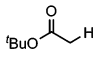
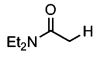
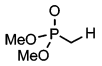
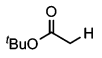
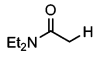
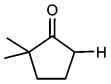
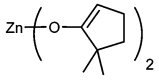
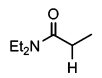
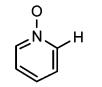
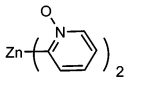
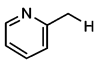
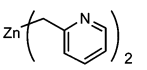
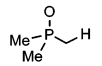
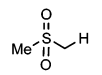
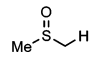
Following these promising results, the ability of $Zn(tmp)_2$ to deprotonate other substrates was explored. Substrates tested include the cyclic ketone 2,2-dimethylcyclopentanone and the secondary amide *N*,*N*-diethylpropionamide. Zincation of the ketone proceeds to completion at ambient temperature in 10 min (Table 2, entry 9), while the secondary amide required heating to 50 °C for 30 h (entry 10). Further screening of carbon acids has revealed that $Zn(tmp)_2$ is an effective base for a surprisingly broad range of substrates. For example, C_6D_6 solutions of $Zn(tmp)_2$ react with 2 equiv of pyridine *N*-oxide in 10 min at ambient temperature to quantitatively yield the ortho-zincated product (entry 11). Likewise, the zincation of 2-picoline proceeds cleanly at 50 °C over 17 h to yield $Zn[CH_2Py]_2$ (entry 12). Similarly pleasing results were obtained for related deprotonations of dimethyl sulfoxide (DMSO), dimethyl sulfone, and

(11) Heating the solutions to 80 °C led to the slow formation of ethane.

(12) Structural studies of Zn enolates related to those described here: (a) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403−1407. (b) Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E. *J. Am. Chem. Soc.* **2005**, *127*, 13106−13107. (c) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2005**, *24*, 4116−4118. (d) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2006**, *25*, 3501−3507. (e) Garner, L. E.; Zhu, H.; Hlavinka, M. L.; Hagadorn, J. R.; Chen, E. Y.-X. *J. Am. Chem. Soc.* **2006**, *128*, 14822−14823.

Table 2. Substrate Deprotonations by Homoleptic Zinc Amido Bases[a]

$$Zn(amido)_2 + 2\ FG\text{-}R\text{-}H \longrightarrow Zn[R\text{-}FG]_2 + 2\ amine \quad (eq\ 2)$$

Entry	Base (Zn(amido)$_2$)	Substrate (FG-R-H)	Zn product (Zn[R-FG]$_2$)	% Yield (conditions)[b]
1	Zn[N(SiMe$_3$)$_2$]$_2$		Zn[CHMeC(O)^{i}Pr]$_2$[d]	91 (24 h, 50 °C) 91 (24 h, 80 °C)
2	Zn[N(SiMe$_3$)$_2$]$_2$		Zn[CH$_2$P(O)(OMe)$_2$]$_2$	12 (24 h, 50 °C) decomp. (24 h, 80 °C)
3	Zn[N(SiMe$_3$)$_2$]$_2$		Zn[CH$_2$C(O)O^{t}Bu]$_2$	7 (24 h, 50 °C) decomp. (24 h, 80 °C)
4	Zn[N(SiMe$_3$)$_2$]$_2$		Zn[CH$_2$C(O)NEt$_2$]$_2$	25 (48 h, 50 °C) decomp. (24 h, 80 °C)
5	Zn(tmp)$_2$		Zn[CHMeC(O)^{i}Pr]$_2$[d]	100 (4h)
6	Zn(tmp)$_2$		Zn[CH$_2$P(O)(OMe)$_2$]$_2$	100 (10 min)
7	Zn(tmp)$_2$		Zn[CH$_2$C(O)O^{t}Bu]$_2$	100 (30 min)
8	Zn(tmp)$_2$		Zn[CH$_2$C(O)NEt$_2$]$_2$	100[c] (5 min)
9	Zn(tmp)$_2$			100 (10 min)
10	Zn(tmp)$_2$		Zn[CHMeC(O)NEt$_2$]$_2$[d]	100 (30 h, 50 °C)
11	Zn(tmp)$_2$			100 (10 min)
12	Zn(tmp)$_2$			100 (17 h, 50 °C)
13	Zn(tmp)$_2$		Zn[CH$_2$P(O)Me$_2$]$_2$	100 (10 min)
14	Zn(tmp)$_2$		Zn[CH$_2$S(O)$_2$Me]$_2$	100 (10 min)
15	Zn(tmp)$_2$		Zn[CH$_2$S(O)Me]$_2$	100 (10 min)

[a] Reaction conditions: (i) ZnNR$_2$ (1.0 equiv), carbon acid (R−H) (2.1 equiv), PhMe (2.0 equiv) (internal standard), and C_6D_6 (0.6 mL) were combined, reaction temperature was 23 ± 2 °C unless indicated otherwise; (ii) D_2O (99.9%) (excess). [b] Yields were determined (^{1}H NMR) relative to an internal standard (PhMe) and were confirmed by deuterium incorporation following quenching with 99.9% D_2O. [c] Identical yields were obtained in CD_2Cl_2 and d_8-THF solutions. [d] Stereochemistry of the Zn enolate product was not determined.

trimethylphosphine oxide, which each occurred at ambient temperature within 10 min (entries 13−15).

The use of zinc enolates in Pd-catalyzed coupling reactions is an area of current interest.[13] Thus, it was of interest to us to determine whether the broad range of zinc enolates formed directly via Zn(tmp)$_2$ deprotonations[14] would be suitable for this purpose. Zn(tmp)$_2$ was reacted with DEA in C_6D_6 to generate the expected zinc enolate within 5 min. Combining this solution with 2 mol % of $Pd_2(dba)_3$ (dba = *trans*,*trans*-dibenzylideneacetone), 4 mol % of P^{t}Bu$_3$, 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 amide was formed in 94% yield (Table 3, entry

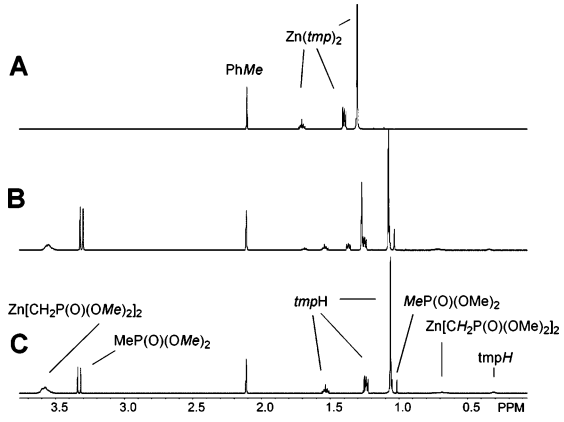
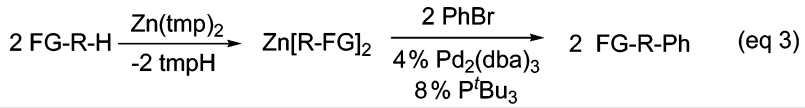


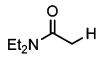
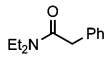
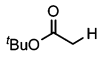
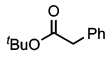
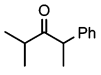
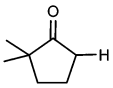
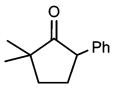
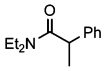
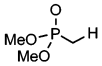
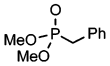
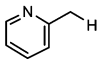
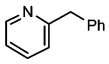
Figure 1. 500 MHz ^{1}H NMR spectra of the reaction of Zn(tmp)$_2$ with 2.1 equiv DMMP in C_6D_6: (A) Zn(tmp)$_2$ and internal standard (PhMe) before addition of DMMP; (B) 2 min after the addition of DMMP; (C) 10 min after the addition of DMMP.

(13) (a) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976−4985. (b) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182−5191. (c) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176−11177. (d) Bentz, E.; Moloney, M. G. *Tetrahedron Lett.* **2004**, *45*, 7395−7397.

(14) Formed in situ using the conditions described in Table 2.

Table 3. Pd-Catalyzed Phenylations of in Situ Formed Zinc Enolates[a]



Entry	Substrate (FG-R-H)	Product (FG-R-Ph)	Yield (%)[b]
1			94
2			96
3			73
4			83
5			86
6			70
7			89
8			87

[a] Reaction conditions: (i) $Zn(tmp)_2$ (1.0 equiv), substrate (2.1 equiv), and PhMe (1 mL) were combined, for each substrate, the temperature and time used for this deprotonation step is indicated in Table 2; (ii) PhBr (2.0 equiv), $Pd_2(dba)_3$ (0.04 equiv), and $P(^tBu)_3$ (0.08 equiv) were combined, 24 h, 23 ± 2 °C. [b] Yields determined by ^1H NMR spectroscopy relative to an internal standard (1,3,5-trimethoxybenzene). Reaction times and conditions were not optimized.

1). In a similar manner, the zinc enolates of *N*,*N*-diethylpropionamide (entry 5) and ^{t}BuOAc (entry 2) were phenylated in 86% and 96% yields, respectively. α-Phenylations of zinc ketone enolates were also successful, but in slightly lower yields (entries 3 and 4). The zinc enolate of DMMP, $Zn[CH_2P(O)(OMe)_2]_2$, was phenylated in 70% yield (entry 6).

Arylations were also accomplished using pyridine-contaning substrates. This is of particular interest, as N-heterocycles are indispensable moieties in the construction of many complex organics.[15] The selective zincation of these compounds using $Zn(tmp)_2$ provides a novel approach to their functionalization. For example, the ortho phenylation of pyridine *N*-oxide was achieved in 89% yield (Table 3, entry 7) by zincation using $Zn(tmp)_2$ followed by a standard Negishi coupling. The phenylation of the 2-methyl group of 2-picoline was achieved in a simlarly high yield (entry 8).

In conclusion, we have examined the use of zinc amido compounds as bases for the deprotonation of C−H bonds. Both steric bulk and alkyl substitution were found to be beneficial. Accordingly, our studies revealed that $Zn(tmp)_2$ is a remarkably effective base, deprotonating a wide range of functionalized organics under mild conditions. These include ketones, carboxylic esters and amides, phosphonates, pyridine *N*-oxides, 2-methylpyridines, sulfoxides, sulfones, and phosphine oxides. Zinc enolates of these carbon acids are readily coupled with aryl bromides using standard Pd-catalyzed coupling methods. $Zn(tmp)_2$ is a soluble and versatile base for the convenient deprotonation of fuctionalized organics. Its use should allow for the expanded application of Zn-based nucleophiles in organic synthesis.

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Supporting Information Available: Text giving full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OM700475T

(15) Pozharski, A.; Soldartenko, A.; Katritsky, A. *Heterocycles in Life and Society;* Wiley: New York, 1997.