Metalation of Alkenes

Selective Magnesiation or Zincation of Highly Functionalized Alkenes and Cycloalkenes Using 2,2,6,6-Tetramethylpiperidyl Bases**

Tomke Bresser and Paul Knochel*

Dedicated to Professor Carmen Najera on the occasion of her 60th birthday

The preparation of substituted aromatic molecules and heterocycles is of great importance because of the potential biological activity of such structures, which are present in many pharmaceuticals or agrochemicals.^[1] The functionalization of these compounds has often been achieved by directed metalation using various bases.^[2] Mg and Zn TMP bases complexed with lithium chloride, such as TMPMgCl·LiCl (1, TMP = 2,2,6,6-tetramethylpiperidyl),^[3] $TMP_2Mg \cdot 2$ LiCl (2),^[4] TMPZnCl·LiCl (3),^[5] and TMP₂Zn·2MgCl₂·2 LiCl (4)^[6] have proven to be especially versatile metalating agents. In contrast to aromatic and heteroaromatic systems, the directed deprotonation of functionalized non-aromatic and olefinic systems is more difficult and sensitive, as substituents such as a nitro or a trifluoromethylcarbonyl group are usually not tolerated. Furthermore, when the alkenes contain an ester or a nitrile substituent, lithiation temperatures between -113and -95°C are required.^[7] Herein, we report that the kinetically very active TMP bases 1-4 allow the smooth metalation of various substituted olefins of type 5 under practical reaction conditions to give highly functionalized unsaturated organometallic compounds of type 6 (Scheme 1).

Quenching of these compounds with various electrophiles E^+ provides polyfunctional alkenes of type **7–9** with high chemoselectivity. Remarkably, this method allows the first reported preparation of α -zincated nitroolefins (**6**: FG¹=NO₂; MetX = ZnCl) and β -zincated trifluoromethyl

$\begin{array}{ccc} FG^2 & H \\ \searrow = \swarrow \\ H & FG^1 \end{array}$	TMPMgCl·LiCl (1) or TMP ₂ Mg·2LiCl (2) or TMPZnCl·LiCl (3) or TMP ₂ Zn·2LiCl (4)	$H = FG^2 = MX$ $H = FG^1$	$\xrightarrow{E^{+}} \overset{FG^{2}}{\overset{E}{\underset{H}{\overset{FG^{1}}{\overset{E}{\overset{FG^{1}}{\overset{E}{\overset{FG^{1}}{\overset{E}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{E}{\overset{FG^{1}}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}}{\overset{FG^{1}}{\overset{FG^{1}}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}{\overset{FG^{1}}}{\overset{FG^{1}}}{\overset{FG^{1}}}{\overset{FG^{1}}}{\overset{FG^{1}}}{\overset{FG^{1}}}{\overset{G^{1}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}$
5	01 1111 2211 22101 (1)	6	7 : FG ¹ = NR ₂ , OR,
$EG^1 = NO_2$	CN, NR ₂ , OR, SO ₂ Ph	SO ₂ Ph 8: FG ¹ = CN	
	t, COCF ₃ , alkyl or aryl; M	9 : $FG^1 = NO_2$	

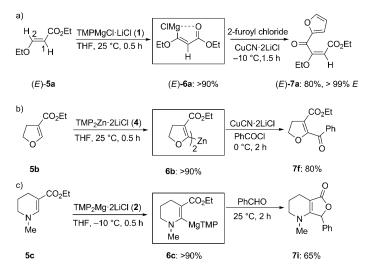
Scheme 1. Chemoselective metalation of functionalized alkenes. FG = functional group.

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ketones (6: $FG^2 = COCF_3$; $FG^1 = NMe_2$; MetX = ZnCl; see Tables 1–3). Also, the zincation or magnesiation of various unsaturated esters can now be carried out under practical conditions (between $-30^{\circ}C$ and $25^{\circ}C$).

The reaction of ethyl (2E)-3-ethoxyacrylate ((E)-5a) with TMPMgCl·LiCl (1; 1.2 equiv, THF, 25°C, 0.5 h) led to a highly regioselective magnesiation at the 2-position to afford the magnesium reagent (E)-6a (>90%, Scheme 2a). The stereoselective copper-mediated acylation^[8] of (E)-6a with 2-furoyl chloride (2 equiv) provided the *E*-ketoester ((*E*)-7a) in 80% yield. Similarly, the functionalized magnesium reagent (E)-6a was acylated with pivaloyl chloride and morpholine-4-carbonyl chloride to give the E-1,4-dicarbonyl compounds (E)-7b and c in 58 and 84% yield, respectively (Table 1, entries 1 and 2). The copper-catalyzed allylation^[8] of (E)-6a with 3-bromocyclohexene or its addition to CyCHO stereoselectively provided the ester (E)-7d (83%; Table 1, entry 3) and the lactone 7e (85%; entry 4). The sensitive dihydrofuran $5b^{[9]}$ was cleanly metalated with TMP₂Zn·2 LiCl (4; 0.6 equiv, 25°C, 0.5 h) to afford the diorganozinc compound 6b (>90%). A copper-mediated acylation^[8] with PhCOCl provides the ketoester 7f in 80% yield (Scheme 2b). The zinc reagent 6b was also allylated with ethyl 2-(bromomethyl)acrylate^[10] or underwent a Negishi cross-coupling reaction^[11] with 1-chloro-4-iodobenzene (3% [Pd(dba)₂], 6% P(2furyl)₃, 25 °C, 3 h)^[12] to give the expected dihydrofurans 7g and h in 83 and 55% yield, respectively (Table 1, entries 5 and 6). The related tetrahydropyridine $5c^{[9]}$ requires a stronger



Scheme 2. β -Metalation of unsaturated esters using TMP bases 1, 2, and 4, and subsequent functionalization with electrophiles.



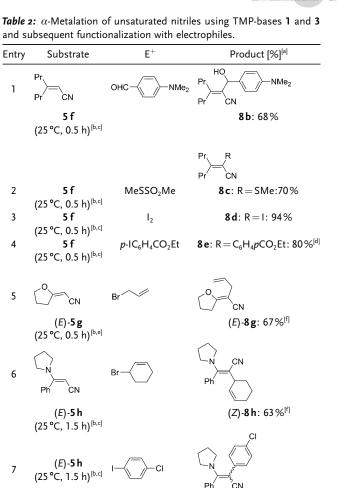
Table 1: β -Magnesiation or zincation of unsaturated carbonyl compounds using TMP bases 1–4 and subsequent quenching with electrophiles.

Entry	Substrate	E+	Product [%] ^[a]
1	CO ₂ Et	CI tBu	O= CO₂Et EtO
	(<i>E</i>)- 5 a (25 °C, 0.5 h) ^[b,c]		(<i>E</i>)- 7 b : 84 % ^[d]
2	(E) -5 a (25 °C, 0.5 h) ^[b,c]		$O = CO_2Et$ EtO
3	(E)- 5 a (25 °C, 0.5 h) ^[b,c]	Br	(E)-7 c: $58 \%^{[d]}$ EtO (E)-7 d: $83 \%^{[e]}$
4	(<i>E</i>) -5 a (25 °C, 0.5 h) ^[b,c]	С—сно	
5	CO ₂ Et	$= \left\langle \begin{array}{c} -Br \\ CO_2Et \end{array} \right\rangle$	7 e: 85 %
	5 b (25 °C, 0.5 h) ^[b,f]		7 g : 83 % ^[e] ,⊂O ₂ Et
6	5 b (25 °C, 0.5 h) ^[b,f]	CI	o C ci
			7h: 55% ^[g] CO ₂ Et N R Me
7	5 c (−10 °C, 0.5 h) ^[b,h]	<i>p</i> -IC ₆ H ₄ OMe	7j: R=C ₆ H₄pOMe: 80% ^[g]
8	(−10°C, 0.5 h) ^[b,h]	<i>p</i> -ClC ₆ H _{4C} OCl	7 k: R = COC ₆ H ₄ pCl: 50% ^[d]
9	7 e (–30 °C, 20 min) ^[b,h]	I ₂	71: R=1: 88%
10	7e	$Cl_3F_3C_2$	7 m: R=Cl: 67%
11	(–30 °C, 20 min) ^[b,h] 7 e	allyl bromide	7 n : R=allyl: 64% ^[e]
12	(-30°C, 20 min) ^[b,h] 7 e (-30°C, 20 min) ^[b,h]	p-IC ₆ H₄OMe	7 o : R=C ₆ H ₄ pOMe: 68% ^[g]
13	CO ₂ Et PhO ₂ S (E)- 5 d (25 °C, 15 min) ^[b,]	=√Br CO₂Et	PhO ₂ S (E)- 7 p : 67% ^[e]
14	(25 °C, 15 mm) COCF ₃ Me ₂ N (E)- 5 e (25 °C, 0.5 h) ^[5,i]	$=$ CO_2Et	EtO_2C Me $COCF_3$ Me_2N $(E)-7 r: 85\%^{[e]}$

[a] Yield of analytically pure isolated product.[b] Metalation conditions. [c] TMPMgCl·LiCl. [d] 1.1 equiv CuCN·2 LiCl was added. [e] 5% CuCN·2 LiCl was added. [f] TMP₂ZnCl·2 LiCl. [g] 3% [Pd(dba)₂] (dba=*trans*,*trans*dibenzylidineacetone) and 6% P(2-furyl)₃ were added. [h] TMP₂MgCl·2 LiCl. [j] TMPZnCl·LiCl.

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[a] Yield of analytically pure isolated product. [b] Metalation conditions. [c] TMPMgCl·LiCl. [d] 3% [Pd(dba)₂] and 6% P(2-furyl)₃ were added. [e] TMPZnCl·LiCl. [f] 5% CuCN·2 LiCl was added.

8i: 88% (E/Z=50:50)^[d]

TMP base: TMP₂Mg·2 LiCl (**2**). This base can magnesiate the N-heterocycle **5c** at -10 °C within 0.5 h to give the magnesium species **6c** (>90%), reaction of which with PhCHO (2 equiv) gave the bicyclic lactone **7i** in 65% yield (Scheme 2 c). Similarly, an acylation of the copper derivative of **6c**^[8] with 4-chlorobenzoyl chloride or a palladium(0)-catalyzed cross-coupling reaction^[11] using 4-iodoanisole led to the new tetrahydropyrimidines **7j–k** in 50–80% yield (Table 1, entries 7 and 8).

Deprotonation of the lactone **7e** using TMP₂Mg·2 LiCl (**2**; -30 °C, 20 min) gave the corresponding Mg intermediate, which was quenched with iodine to give the iodolactone **7l** in 88 % yield (Table 1, entry 9). Chlorination of this Mg reagent with Cl₃F₃C₂ or a copper-catalyzed allylation with allyl bromide^[8] or a palladium-catalyzed Negishi cross-coupling reaction^[11] led to the functionalized lactones **7m–o** in 64–68 % yield (Table 1, entries 10–12). Ethyl (2*E*)-3-(phenylsulfony-l)acrylate ((*E*)-**5d**)^[9] was also smoothly zincated at 25 °C using TMPZnCl·LiCl (**3**; 1.2 equiv, 15 min). The metalation also occurs at the β -position to afford the corresponding organo-zinc that undergoes a copper-mediated allylation^[8] with ethyl 2-(bromomethyl)acrylate^[10] to furnish the ester (*E*)-**7p** in 67 % yield (Table 1, entry 13).

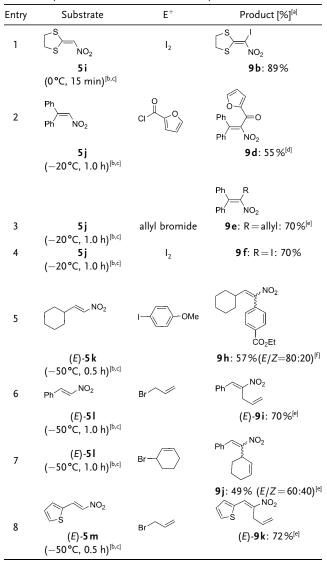


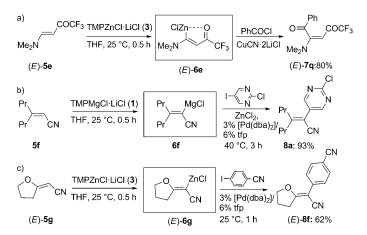
Table 3: α -Metalation of unsaturated nitroolefins using TMPZnCl·LiCl **3** and subsequent functionalization with electrophiles.

Communications

 [a] Yield of analytically pure isolated product. [b] Metalation conditions.
 [c] TMPZnCl·LiCl. [d] 1.1 equiv CuCN·2 LiCl was added. [e] 5% CuCN·2 LiCl was added. [f] 3% [Pd(dba)₂] and 6% P(2-furyl)₃ were added.

Remarkably, TMPZnCl-LiCl (3) also allows the β -zincation (25 °C, 0.5 h) of (3*E*)-4-(dimethylamino)-1,1,1-trifluorobut-3-en-2-one ((*E*)-5e),^[9] which bears a sensitive CF₃CO group. Acylation^[8] of the resulting organozinc (*E*)-6e with PhCOCl led to the expected new functionalized amine (*E*)-7q in 80% yield (Scheme 3 a). Allylation of intermediate (*E*)-6e led to the dienic trifluoromethyl ketone (*E*)-7r (85%, entry 14) after double-bond isomerization during chromatographic purification. Alkenylmagnesium compounds of type 6, which bear an electron-withdrawing group such as a nitrile,^[13] were previously prepared by a Br/Mg exchange reaction using *i*PrMgCl·LiCl starting from an α -bromonitrile.^[14]

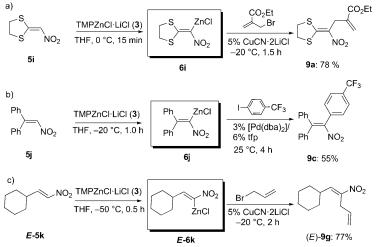
Remarkably, when using TMPMgCl·LiCl (1; 1.2 equiv), the unsaturated nitrile $5 f^{[9]}$ was directly magnesiated (25 °C, 0.5 h) to give the magnesium reagent 6 f (>90%) that undergoes a palladium(0)-catalyzed cross-coupling with



Scheme 3. Metalation of an unsaturated trifluoromethyl ketone and nitriles using TMP bases 1 and 3, and subsequent functionalization. Pr = propyl, $tfp = P(2-furyl)_3$.

2-chloro-5-iodopyrimidine^[11] to give the unsaturated nitrile 8a in 93% yield (Scheme 3b). The magnesium reagent 6 f was also trapped with 4-(dimethylamino)benzaldehyde, MeS-SO₂Me, iodine, or submitted to a Negishi cross-coupling reaction^[11] to prove the new functionalized unsaturated nitriles 8b-e in 68-94 % yield (Table 2, entries 1-4). Reaction of the dihydrofuran acetonitrile (*E*)- $5g^{[9]}$ with TMPZnCl·LiCl (3; 1.2 equiv) led to a stereoselective zincation (25°C, 0.5 h) to afford the alkenylzinc compound (E)-6g that underwent a palladium-catalyzed cross-coupling with 4-iodo-benzonitrile^[11] to produce the dinitrile (E)-8 f in 62% yield (Scheme 3 c). The zinc reagent (E)-6 g is remarkably stable with respect to β -elimination, and reacted with allyl bromide to give (E)-8g in 67% yield (Table 2, entry 5). Also, the pyrrolidyl acrylonitrile $((E)-5h)^{[9]}$ was easily magnesiated with TMPMgCl·LiCl (1; 1.2 equiv, 25 °C, 1.5 h) to provide the Mg species, which was allylated with 3-bromocyclohexene in the presence of 5% CuCN·2 LiCl^[8] to give the aminonitrile (Z)-8h in 63% yield (Table 2, entry 6). Palladium-catalyzed cross-coupling of the Mg compound with 4-iodo-chlorobenzene^[11] generated the nitrile **8i** as an E/Z mixture (88%, entry 7).

a-Metalated nitroolefins are elusive intermediates and their preparation has not been reported to date.^[15] This metalation can be achieved using TMPZnCl·LiCl (3). Thus, the dithiolane nitroolefin (5i)^[9] was smoothly zincated using TMPZnCl·LiCl (3; 1.2 equiv) at 0°C within 15 min to provide the α -zincated nitroolefin **6i** (>95%), which was allylated with ethyl 2-(bromomethyl)acrylate^[8,10] to afford the nitroolefin 9a in 78% yield (Scheme 4a). The zinc species 6i was also iodinated; the resulting iodide 9b was isolated in 89% yield (Table 3, entry 1). Remarkably, the diphenylnitroolefin $(5j)^{[9]}$ could be converted into the alkenylzinc 6j using TMPZnCl·LiCl (3; 1.2 equiv, -20°C, 1.0 h). This zinc reagent underwent a palladium-catalyzed cross-coupling with 1-iodo-4-(trifluoromethyl)benzene^[11] to give the triarylated nitroolefin 9c in 55% yield (Scheme 4b). Additionally, the zincated nitroolefin was quenched with 2-furoyl chloride, allyl bromide, or iodine to provide the corresponding nitroolefins 9d-f in 55-70% vield (Table 3, entries 2-4). Similarly,



Scheme 4. α -Metalation of unsaturated nitroolefins using TMPZnCl·LiCl (3) and subsequent functionalization with electrophiles.

2-cyclohexyl-nitroethylene $((E)-5\mathbf{k})^{[9]}$ was zincated with TMPZnCl·LiCl (**3**; 1.2 equiv, -50 °C, 0.5 h) to give the zinc species (*E*)-**6k**, which was trapped with allyl bromide^[8] to give the α -functionalized nitroolefin (*E*)-**9g** in 77 % yield (Scheme 4c). Furthermore, the zincated nitroolefin (*E*)-**6k** underwent a palladium(0)-catalyzed cross-coupling^[11] with ethyl 4-iodobenzoate to give the nitro derivative **9h** (57 % yield, E/Z = 80:20; Table 3, entry 5). Likewise, β -trans-nitrostyrene ((*E*)-**51**) reacted with the zinc base **3** (1.2 equiv, -50 °C, 1.0 h), and the resulting alkenylzinc reagent underwent a coppermediated allylation^[8] with allyl bromide to give (*E*)-**9i** as one isomer in 70 % yield (Table 3, entry 6). However, trapping the zincated nitrostyrene (*E*)-**51** with 3-bromocyclohexene led to the allylated product **9j** as a 60:40 mixture of isomers (49 %, entry 7).

Finally, 2-[(*E*)-2-nitrovinyl]thiophene $((E)-5\mathbf{m})^{[9]}$ was metalated at the α -position of the nitro group with TMPZnCl·LiCl (**3**; 1.2 equiv, 0.5 h, -50 °C) and the resulting zinc species was trapped with allyl bromide to give the new substituted olefin (*E*)-**9k** in 72 % yield (Table 3, entry 8).

In summary, we have shown that the kinetically highly active bases **1–4** allow a smooth magnesiation or zincation of several new classes of highly functionalized olefins. In particular, new β -zincated unsaturated trifluoromethyl ketones and α -zincated nitroolefins have been prepared and successfully reacted with electrophiles. Further extensions of this work are currently underway.

Experimental Section

Typical procedure for the metalation of substituted vinylic substrates ((*E*)-9**i**):

TMPZnCl·LiCl (3; 1.3 M in THF, 2.77 mL, 3.6 mmol) was added to a solution of β -trans-nitrostyrene ((*E*)-**5**1; 450 mg, 3.0 mmol) in THF (3 mL) at -50 °C and the mixture was stirred for 1 h. After this time, CuCN·2 LiCl (1M solution in THF, 0.15 mL, 5 mol%) was added. After 5 min of stirring, allyl bromide (720 mg, 6.0 mmol) was added and the mixture was slowly warmed to -20 °C over 2 h. After the workup and purification by flash chromatography (ether/2-methyl pentane 1:9), the nitroolefin (E)-9i (397 mg, 70%) was isolated as a yellow oil.

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