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The metalation of 4,4-dimethyloxazoline using $\text{TMPZnCl}\cdot\text{LiCl}$ provides a stable 2-zincated oxazolinyl reagent which readily undergoes palladium-catalyzed Negishi cross-couplings allowing a new access to 2-aryloxazolines. Cu-mediated acylation and allylation reactions also proceed in good yields.

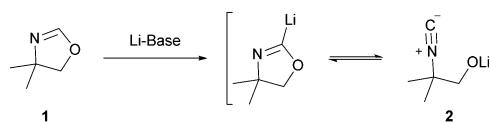
Oxazolines are an important class of heterocycles that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal properties,¹ but also possess high utility in organic synthesis² since this heterocycle was found to be an excellent *ortho*-directing group.³ However, the direct lithiation of oxazolines in position 2⁴ is difficult due to a facile fragmentation of these heterocycles leading to isonitriles of type 2 (Scheme 1).⁵

2-Aryloxazolines can be prepared using several methods, such as condensations⁶ or similar multi-component reactions,⁷ as well as C–H activations using diverse transition-metal catalysts.⁸ However, to date the direct zination and transition-metal catalyzed cross-coupling of the oxazoline scaffold has not yet been reported. This reaction is especially interesting, as 2-aryloxazolines often exhibit potential biological activity.⁹ Recently, we have described the synthesis of the highly active sterically hindered zinc base $\text{TMPZnCl}\cdot\text{LiCl}$ ¹⁰ (3; TMP = 2,2,6,6-tetramethylpiperidyl) which has proven to be especially efficient for the metalation of sensitive heterocycles while displaying an excellent functional group tolerance.¹¹

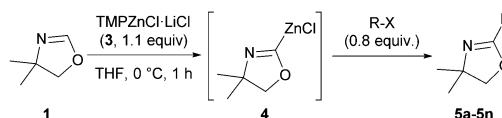
Herein, we report the direct zination of 4,4-dimethyloxazoline (1) using $\text{TMPZnCl}\cdot\text{LiCl}$ (3) and a subsequent quenching of the resulting zinc species with various electrophiles. Thus, treatment of 4,4-dimethyloxazoline (1) with $\text{TMPZnCl}\cdot\text{LiCl}$ (3, 1.1 equiv.) leads smoothly to the formation of the corresponding 4,4-dimethyl-oxazolinylzinc (4) species within 1 h at 0 °C in 94% yield as determined by GC-analysis after allylation.¹² In contrast to the corresponding lithium derivative (Scheme 1), this zinc reagent is

Zincation of 4,4-dimethyloxazoline using $\text{TMPZnCl}\cdot\text{LiCl}$. A new preparation of 2-aryloxazolines†

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Scheme 1 Ring opening of 4,4-dimethyloxazoline (1) upon lithiation.



Scheme 2 Zincation of 4,4-dimethyloxazoline (1) using $\text{TMPZnCl}\cdot\text{LiCl}$ (3).

perfectly stable at 25 °C and shows no tendency to undergo a ring fragmentation. Thus, the zinc reagent (4) undergoes smooth carbon–carbon bond formation with electrophiles leading to 2-substituted oxazolines of type 5 in 64–92% yield (Scheme 2).

Negishi cross-coupling reactions¹³ of the oxazolinylzinc reagent (4) with electron-rich and -poor *para*-functionalized aryl bromides and iodides (FG = CF₃, CO₂Et, CN, OMe, Cl) using Pd(dba)₂ (3 mol%) or Pd(OAc)₂ (3 mol%) and SPhos (6 mol%)¹⁴ furnished the corresponding 2-aryloxazolines 5a–e in 71–92% yield (Table 1, entries 1–5).

Also, the oxazolinylzinc species (4) reacts with the disubstituted diethyl 5-bromoisonphthalate to provide the desired product (5f) in 68% yield (entry 6). Additionally, a cross-coupling reaction with 3-iodocyclohexenone affords the oxazoline (5g) in 68% yield (entry 7). Moreover, after transmetalation with CuCN·2LiCl¹⁵ acylation reactions employing various acid chlorides afford 2-acyl-2-oxazolines.¹⁶ Thus, the reaction with benzoyl chloride leads to the acylated oxazoline (5h) in 69% yield (entry 8). The 4,4-dimethyl-oxazolinylzinc reagent (4) also reacts well with various electron-poor benzoyl chlorides bearing halogen-substituents, as well as 2-thiophenecarbonyl chloride to provide the ketones (5i–l) in 64–76% yield (entries 9–12). In addition, the zinated species undergoes a Cu-mediated allylation reaction with 3-bromocyclohexene affording the allylated product (5m) in 79% yield (entry 13). Finally, an *in situ* performed Sonogashira reaction¹⁷ with phenylacetylene in

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Table 1 2-Substituted 4,4-dimethyloxazolines of type **5** Obtained by zincation using $\text{TMPZnCl}\cdot\text{LiCl}$ (**3**) and Reaction with electrophiles

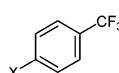
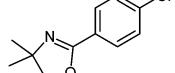
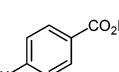
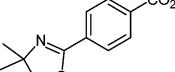
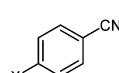
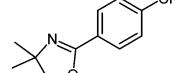
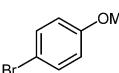
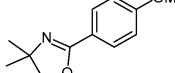
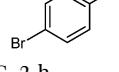
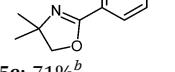
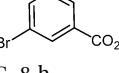
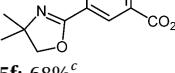
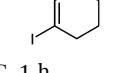
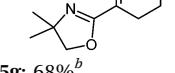
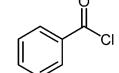
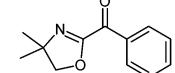
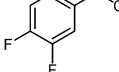
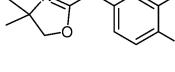
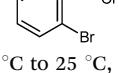
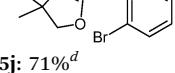
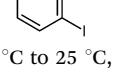
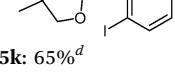
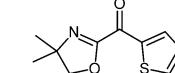
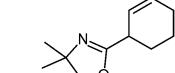
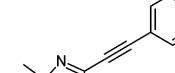
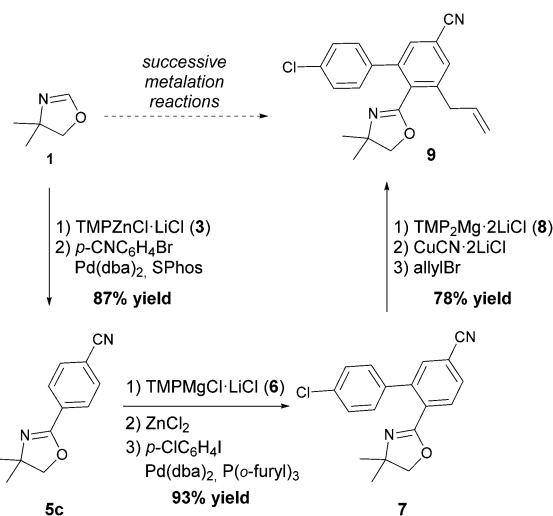
Entry	Electrophile/conditions	Product/yield ^a (%)
1	 50 °C, 4 h (X = I) 50 °C, 3 h (X = Br)	 5a: 79% ^b (X = I) 77% ^c (X = Br)
2	 50 °C, 4 h (X = I) 50 °C, 3 h (X = Br)	 5b: 78% ^b (X = I) 92% ^c (X = Br)
3	 50 °C, 4 h (X = I) 50 °C, 2 h (X = Br)	 5c: 80% ^b (X = I) 87% ^c (X = Br)
4	 50 °C, 4 h	 5d: 82% ^b
5	 50 °C, 2 h	 5e: 71% ^b
6	 50 °C, 8 h	 5f: 68% ^c
7	 25 °C, 1 h	 5g: 68% ^b
8	 −40 °C to 25 °C, 2 h	 5h: 69% ^d
9	 −40 °C to 25 °C, 2 h	 5i: 76% ^d
10	 −40 °C to 25 °C, 4 h	 5j: 71% ^d
11	 −40 °C to 25 °C, 4 h	 5k: 65% ^d

Table 1 (continued)

Entry	Electrophile/conditions	Product/yield ^a (%)
12	 −40 °C to 25 °C, 2 h	 5l: 64% ^d
13	 −40 °C to 25 °C, 6 h	 5m: 79% ^d
14	 25 °C, 4 h	 5n: 71% ^e

^a Isolated yield of analytically pure product. ^b Pd-catalyzed cross-coupling using 3 mol% $\text{Pd}(\text{OAc})_2$ and 6 mol% SPhos. ^c Pd-catalyzed cross-coupling using 3 mol% $\text{Pd}(\text{dba})_2$ and 6 mol% SPhos. ^d A transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$ (1.2 equiv.) was performed. ^e Pd-catalyzed cross-coupling using 3 mol% $\text{Pd}(\text{dba})_2$ and 6 mol% $\text{P}(\text{o-furyl})_3$, 4 mol% CuI and NEt_3 (1.2 equiv.).

**Scheme 3** Extended metalation of 4,4-dimethyloxazoline (**1**) and its use as a directing group.

the presence of $\text{Pd}(\text{dba})_2$ (3 mol%), Farina's ligand¹⁸ ($\text{P}(\text{o-furyl})_3$, 6 mol%), CuI (4 mol%) and Et_3N afforded the 2-substituted oxazoline (**5n**) in 79% yield (entry 14). As oxazolines serve as a useful directing group in directed metalations,¹⁹ magnesiation of the 2-arylated oxazolines is possible within 1.5 h at 0 °C using TMPMgCl-LiCl^{20} (**6**, Scheme 3).²¹ After transmetalation with ZnCl_2 and Pd-catalyzed cross-coupling, the biaryl **7** is afforded in 93% yield. Also, oxazoline **7** reacts in a second metalation step using $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}^{22}$ (**8**, −20 °C, 1.5 h). Transmetalation using $\text{CuCN}\cdot 2\text{LiCl}$, followed by addition of allyl bromide furnishes the desired oxazoline **9** in 78% yield. Since oxazolines can be readily converted to carboxylic acids, new *ortho*,*ortho*'-disubstituted benzoic acids can be obtained after deprotection using standard methods.²³

In summary, we have reported a simple, mild and efficient method for the zincation of 4,4-dimethyloxazoline in position 2 using $\text{TMPZnCl}\cdot\text{LiCl}$ (3). The resulting oxazolinylzinc reagents (4) were arylated *via Negishi* cross-couplings with various aryl iodides and bromides. Additionally, Cu-mediated acylation and allylation reactions proceed readily. Applications towards the synthesis of biologically active molecules are currently being investigated in our laboratories.

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