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Zincation of 4,4-dimethyloxazoline using TMPZnCl·LiCl. A new preparation of 2-aryloxazolines†

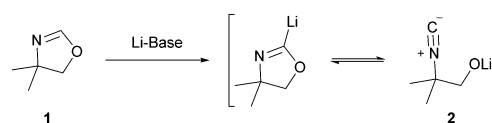
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The metalation of 4,4-dimethyloxazoline using TMPZnCl·LiCl provides a stable 2-zincated oxazolanyl reagent which readily undergoes palladium-catalyzed Negishi cross-couplings allowing a new access to 2-aryloxazolines. Cu-mediated acylation and allylation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

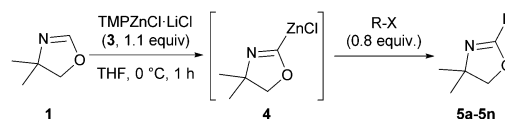
Oxazolines are an important class of heterocycles that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal properties,¹ but also possess high utility in organic synthesis² since this heterocycle was found to be an excellent *ortho*-directing group.³ However, the direct lithiation 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 zincation 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 TMPZnCl·LiCl¹⁰ (**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 zincation of 4,4-dimethyloxazoline (**1**) using TMPZnCl·LiCl (**3**) and a subsequent quenching of the resulting zinc species with various electrophiles. Thus, treatment of 4,4-dimethyloxazoline (**1**) with TMPZnCl·LiCl (**3**, 1.1 equiv.) leads smoothly to the formation of the corresponding 4,4-dimethyloxazolanylzinc (**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



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



Scheme 2 Zincation of 4,4-dimethyloxazoline (**1**) using TMPZnCl·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 oxazolanylzinc 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 oxazolanylzinc species (**4**) reacts with the disubstituted diethyl 5-bromoisophthalate 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-dimethyloxazolanylzinc 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 zincated 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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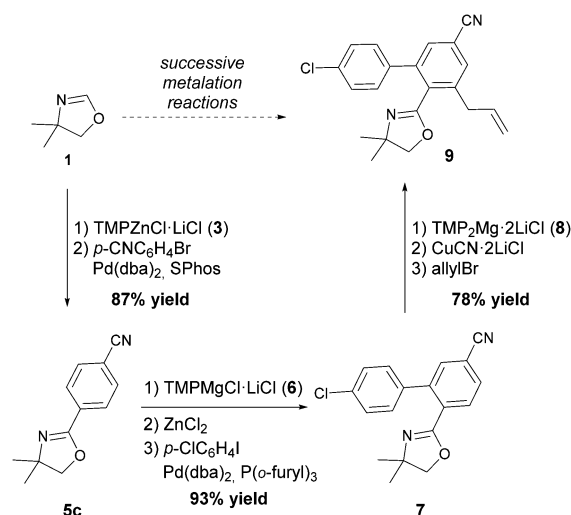
Table 1 2-Substituted 4,4-dimethyloxazolines of type **5** Obtained by zincation using TMPZnCl·LiCl (**3**) and Reaction with electrophiles

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% Pd(OAc)₂ and 6 mol% SPhos. ^c Pd-catalyzed cross-coupling using 3 mol% Pd(dba)₂ and 6 mol% SPhos. ^d A transmetalation with CuCN·2LiCl (1.2 equiv.) was performed. ^e Pd-catalyzed cross-coupling using 3 mol% Pd(dba)₂ and 6 mol% P(*o*-furyl)₃, 4 mol% CuI and NEt₃ (1.2 equiv.).

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

the presence of Pd(dba)₂ (3 mol%), Farina's ligand¹⁸ P(*o*-furyl)₃, 6 mol%), CuI (4 mol%) and Et₃N 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·LiCl²⁰ (**6**, Scheme 3).²¹ After transmetalation with ZnCl₂ and Pd-catalyzed cross-coupling, the biaryl **7** is afforded in 93% yield. Also, oxazoline **7** reacts in a second metalation step using TMP₂Mg·2LiCl²² (**8**, -20 °C, 1.5 h). Transmetalation using CuCN·2LiCl, 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 TMPZnCl-LiCl (**3**). The resulting oxazoliny zinc 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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