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

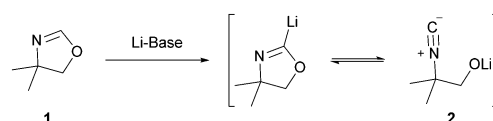
Diana Haas, Maximilian S. Hofmayer, Tomke Bresser and Paul Knochel*

The metalation of 4,4-dimethyloxazoline using TMPZnCl·LiCl provides a stable 2-zincated oxazolynyl 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.

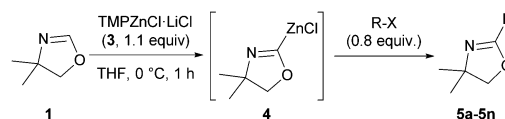
Oxazolines are an important class of heterocycles that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal properties,¹ but also possess high utility in organic synthesis² since this heterocycle was found to be an excellent *ortho*-directing group.³ However, the direct lithiation 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-dimethyloxazolynylzinc (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 oxazolynylzinc 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 oxazolynylzinc 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-dimethyloxazolynylzinc 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

Ludwig Maximilians-University Munich, Department of Chemistry, Butenandtstrasse 5-13, 81377 München, Germany. E-mail: paul.knochel@cup.uni-muenchen.de

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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

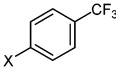
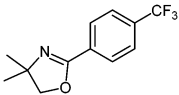
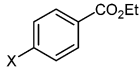
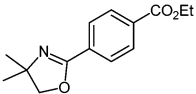
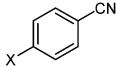
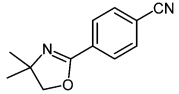
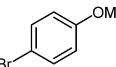
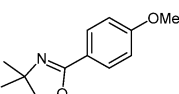
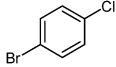
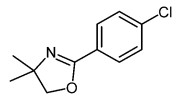
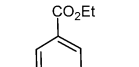
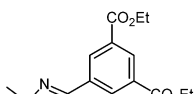
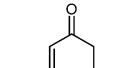
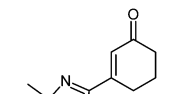
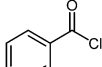
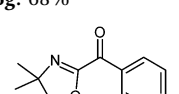
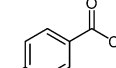
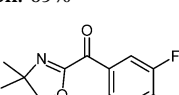
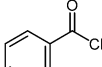
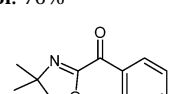
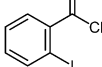
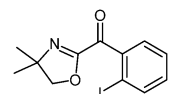
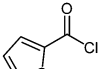
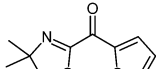

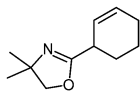
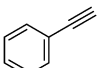
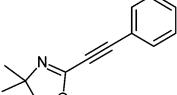
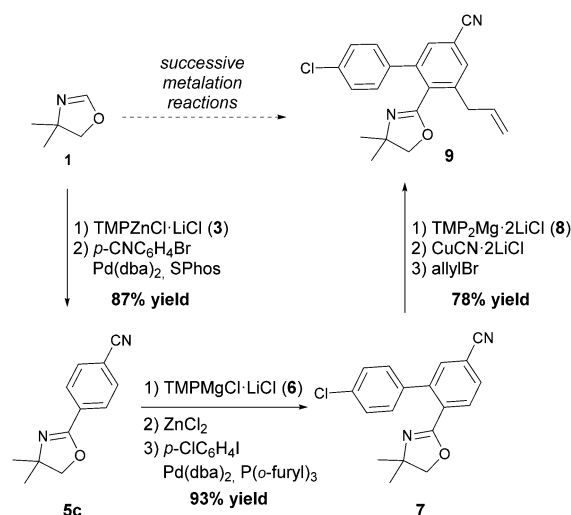
Entry	Electrophile/conditions	Product/yield ^a (%)
1	 50 °C, 4 h (X = I) 50 °C, 3 h (X = Br)	 5a : 79% ^b (X = I) 77% ^c (X = Br)
2	 50 °C, 4 h (X = I) 50 °C, 3 h (X = Br)	 5b : 78% ^b (X = I) 92% ^c (X = Br)
3	 50 °C, 4 h (X = I) 50 °C, 2 h (X = Br)	 5c : 80% ^b (X = I) 87% ^c (X = Br)
4	 50 °C, 4 h	 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 $\text{TMPZnCl} \cdot \text{LiCl}$ (**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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Notes and references

- (a) S. Yamamoto, N. Okujo, Y. Fujita, M. Saito, T. Yoshida and S. J. Shinoda, *J. Biochem.*, 1993, **113**, 538; (b) H. Shitakawa, S. Nakajima, M. Hirayama, H. Kondo and K. Kojiri, *Chem. Abstr.*, 2000, **132**, 150670; (c) M. R. Prinsep, R. E. Moore, I. A. Levine and G. M. L. Patterson, *J. Nat. Prod.*, 1992, **55**, 140.
- (a) M. Reuman and A. I. Meyers, *Tetrahedron*, 1985, **41**, 837; (b) A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed.*, 1976, **15**, 270; (c) J. A. Frump, *Chem. Rev.*, 1971, **71**, 483.
- (a) S. Oi, E. Aizawa, Y. Ogino and Y. Inoue, *J. Org. Chem.*, 2005, **70**, 3113; (b) P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34; (c) P. Beak, A. Tse, J. Hawkins, C. Chen and S. Mills, *Tetrahedron*, 1983, **39**, 1983; (d) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; (e) Y. Zhao and V. Snieckus, *J. Am. Chem. Soc.*, 2014, **136**, 11224; (f) K. Groom, S. M. S. Hussain, J. Morin, C. Nilewski, T. Rantanen and V. Snieckus, *Org. Lett.*, 2014, **16**, 2378.
- L. Degennaro, V. Capriati, C. Carlucci, S. Florio, R. Luisi, I. Nuzzo and C. Cuocci, *Tetrahedron*, 2009, **65**, 8745.
- (a) A. I. Meyers and E. W. Collington, *J. Am. Chem. Soc.*, 1970, **92**, 6676; (b) F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 1968, **9**, 6231; (c) S. R. Neal, A. Ellern and A. D. Sadow, *J. Organomet. Chem.*, 2011, **696**, 228.
- (a) G. A. Molander, W. Febo-Ayala and L. Jean-Gérard, *Org. Lett.*, 2009, **11**, 3830; (b) P. Garg, S. Chaudhary and M. D. Milton, *J. Org. Chem.*, 2014, **79**, 8668; (c) I. Mohammadpoor-Baltork, A. R. Khosropour and S. F. Hojati, *Synlett*, 2005, 2747; (d) M. Brandstätter, F. Roth and N. W. Luedtke, *J. Org. Chem.*, 2015, **80**, 40.
- (a) X.-F. Wu, H. Neumann, S. Neumann and M. Beller, *Chem. – Eur. J.*, 2012, **18**, 13619; (b) L. Fan, E. Lobkovsky and B. Ganem, *Org. Lett.*, 2007, **9**, 2015.
- (a) S. H. Kim and S. Chang, *Org. Lett.*, 2010, **12**, 1868; (b) L. Ackermann, S. Barfüsser, C. Kornhaass and A. R. Kapdi, *Org. Lett.*, 2011, **13**, 3082; (c) S. H. Wiedemann, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2004, **6**, 1685.
- For examples, see: (a) V. Padmavathi, K. Mahesh, G. D. Reddy and A. Padmaja, *Eur. J. Med. Chem.*, 2010, **45**, 3178; (b) M. Tsuda, M. Yamakawa, S. Oka, Y. Tanaka, Y. Hoshino, Y. Mikami, A. Sato, H. Fujiwara, Y. Ohizumi and J. Kobayashi, *J. Nat. Prod.*, 2005, **68**, 462; (c) Q. Li, K. W. Woods, A. Claireborne, S. L. Gwanlley, K. J. Barr, G. Liu, L. Gehrke, R. B. Credo, Y. Hua Hui, J. Lee, R. B. Warner, P. Kovar, M. A. Nukla, N. A. Zielinski, S. K. Tahir, M. Fitzgerald, K. H. Kim, K. Marsh, D. Frost, S.-C. Ng, S. Rosenberg and H. L. Sham, *Bioorg. Med. Chem.*, 2002, **12**, 465.
- (a) M. Mosrin and P. Knochel, *Org. Lett.*, 2009, **11**, 1837; (b) S. Duez, A. K. Steib, S. M. Manolikakes and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 7686; (c) A. Unsinn, M. J. Ford and P. Knochel, *Org. Lett.*, 2013, **15**, 1128; (d) D. Haas, M. Mosrin and P. Knochel, *Org. Lett.*, 2013, **15**, 6162.
- For general reviews on the metalation of aromatics and heterocycles see: (a) M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206; (b) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802; (c) F. Chevallier and F. Mongin, *Chem. Soc. Rev.*, 2008, **37**, 595; (d) B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794.
- Compare Table 1, entry 13; $\text{C}_{14}\text{H}_{30}$ was used as an internal standard.
- (a) E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821; (b) E. Negishi, L. F. Valente and M. Kobayashi, *J. Am. Chem. Soc.*, 1980, **102**, 3298; (c) E. Negishi and M. Kobayashi, *J. Org. Chem.*, 1980, **45**, 5223; (d) E. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340; (e) E. Negishi, *Angew. Chem., Int. Ed.*, 2011, **50**, 6738.
- T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685.
- P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.
- (a) V. Capriati, S. Florio, R. Luisi, V. Russo and A. Salomone, *Tetrahedron Lett.*, 2000, **41**, 8835; (b) V. Capriati, S. Florio, R. Luisi, V. Russo and A. Salomone, *Tetrahedron Lett.*, 2000, **41**, 8835.
- (a) K. Sonogashira, Y. M. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; (b) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; (c) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834; (d) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084; (e) K. Sonogashira, in *Metal-catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 1998.
- (a) V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585; (b) V. Farina, S. R. Baker, D. A. Benigni and C. Sapino Jr., *Tetrahedron Lett.*, 1988, **29**, 5739.
- (a) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, 1975, **40**, 3158; (b) H. A. Chiong, Q.-N. Pham and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 9879; (c) X. Chen, J.-J. Li, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 78; (d) S. T. Chadwick, A. Ramirez, L. Gupta and D. B. Collum, *J. Am. Chem. Soc.*, 2007, **129**, 2259.
- (a) A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 2958; (b) W. Lin, O. Baron and P. Knochel, *Org. Lett.*, 2006, **8**, 5673; (c) P. Garcia-Alvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara and S. Weatherstone, *Angew. Chem., Int. Ed.*, 2008, **47**, 8079; (d) R. E. Mulvey, *Organometallics*, 2006, **25**, 1060; (e) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802.
- (a) J. H. C. Batista, F. M. dos Santos, L. A. Bozzini, R. Vessecchi, A. R. M. Oliveira and G. C. Clososki, *Eur. J. Org. Chem.*, 2015, 967; (b) E. Bellamy, O. Bayh, C. Hoarau, F. Trécourt, G. Quéguiner and F. Marsais, *Chem. Commun.*, 2010, **46**, 7043.
- (a) G. C. Clososki, C. J. Rohbogner and P. Knochel, *Angew. Chem., Int. Ed.*, 2007, **46**, 7681; (b) C. J. Rohbogner, G. C. Clososki and P. Knochel, *Angew. Chem., Int. Ed.*, 2008, **47**, 1503; (c) B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794; (d) A. Unsinn, C. J. Rohbogner and P. Knochel, *Adv. Synth. Catal.*, 2013, **355**, 1553.
- (a) P. J. Kocienski, *Protecting Groups*, Georg Thieme Verlag, Stuttgart, 3rd edn, 2005, pp. 107–110; (b) K. J. Edgar and C. K. Bradsher, *J. Org. Chem.*, 1982, **47**, 1585; (c) J. I. Levin and S. M. Weinreb, *Tetrahedron Lett.*, 1982, **23**, 2347; (d) C. A. Boulet and G. A. Poulton, *Heterocycles*, 1989, **28**, 405.

