



Cite this: *Chem. Commun.*, 2015, 51, 6415

Received 6th February 2015,
Accepted 2nd March 2015

DOI: 10.1039/c5cc01144b

www.rsc.org/chemcomm

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

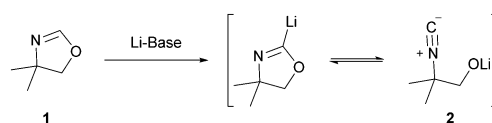
Diana Haas, Maximilian S. Hofmayer, Tomke Bresser and Paul Knochel*

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

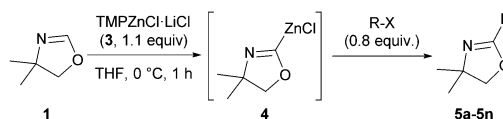
Oxazolines are an important class of heterocycles that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal properties,¹ but also possess high utility in organic synthesis² since this heterocycle was found to be an excellent *ortho*-directing group.³ However, the direct lithiation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

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

† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra of all products. See DOI: 10.1039/c5cc01144b



Table 1 2-Substituted 4,4-dimethyloxazolines of type **5** Obtained by zincation using TMPZnCl·LiCl (**3**) and Reaction with electrophiles

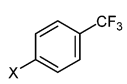
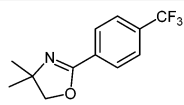
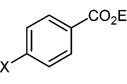
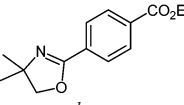
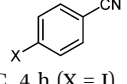
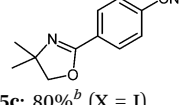
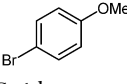
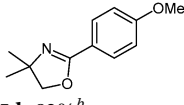
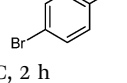
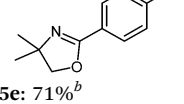
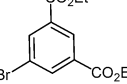
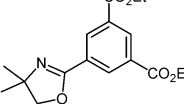
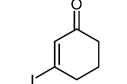
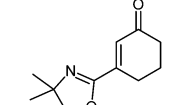
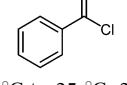
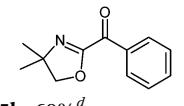
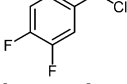
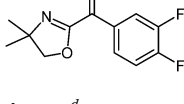
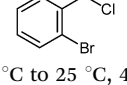
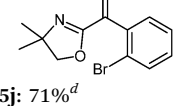
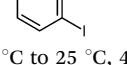
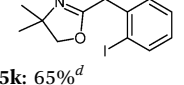
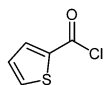
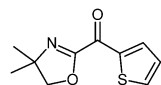

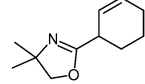
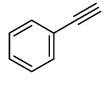
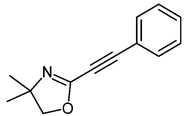
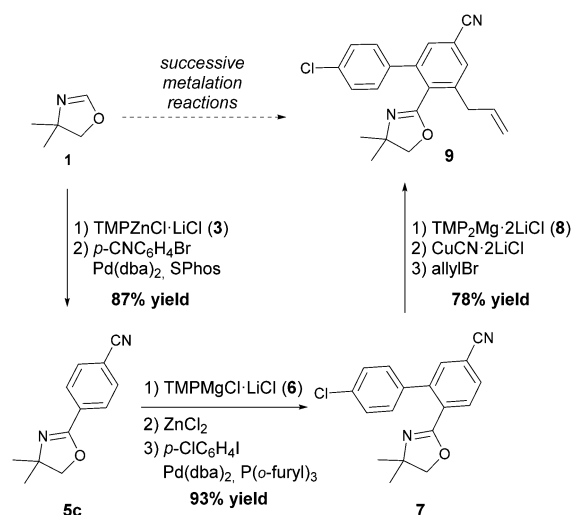
Entry	Electrophile/conditions	Product/yield ^a (%)
1	 50 °C, 4 h (X = I) 50 °C, 3 h (X = Br)	 5a : 79% ^b (X = I) 77% ^c (X = Br)
2	 50 °C, 4 h (X = I) 50 °C, 3 h (X = Br)	 5b : 78% ^b (X = I) 92% ^c (X = Br)
3	 50 °C, 4 h (X = I) 50 °C, 2 h (X = Br)	 5c : 80% ^b (X = I) 87% ^c (X = Br)
4	 50 °C, 4 h	 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 oxazolinyzinc 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.

We thank the European Research Council under the European Community's Seventh Framework Programme (FP7/2007–2013; ERC grant agreement no. 227763) and the Deutsche Forschungsgemeinschaft (DFG) for financial support. We also thank BASF SE (Ludwigshafen), W. C. Heraeus GmbH (Hanau) and Rockwood Lithium GmbH (Frankfurt) for the generous gift of chemicals.

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; C₁₄H₃₀ 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. Queguiner 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.

