M. J. Geier et al.

Letter

Warming Up to Oxazole: Noncryogenic Oxazole Metalation and Negishi Coupling Development

Α

Michael J. Geier Xiaotian Wang Luke D. Humphreys Selcuk Calimsiz Mark E. Scott*



Department of Process Chemistry, Gilead Alberta ULC, 1021 Hayter Road NW, Edmonton, Alberta T6S 1A1, Canada mark.scott@gilead.com

Received: 14.05.2019 Accepted after revision: 27.07.2019 Published online: 19.08.2019 DOI: 10.1055/s-0037-1611909; Art ID: st-2019-v0272-l

Abstract This report details the development of several suitable noncryogenic metalation conditions for the synthesis of oxazole zincate. Subsequent rounds of high-throughput catalyst screening ultimately led to the identification of several suitable Pd sources that can be used for the Negishi coupling of unsubstituted oxazole. The scope and generality for one of the reported conditions is also presented.

Key words Negishi coupling, catalysis, cross-coupling, organozinc, oxazole, high-throughput screening

The oxazole functionality has found application in a variety of pharmaceuticals, ranging from antibacterial to anticancer agents.¹ While many approaches to the synthesis of diversely functionalized oxazoles have been reported,² methods for the installation of unsubstituted oxazole are lacking. In particular, transformation of unsubstituted oxazole into a suitable partner for cross-coupling reactions has proven challenging, a result of the inherent instability of oxazole. Attempts to form oxazole C2-organometallic species with organolithium or organomagnesium reagents such as *n*-BuLi³ or *i*-PrMgCl⁴ is complicated by the preferential formation of the ring-opened enolate isonitrile (Scheme 1).



In contrast, both the organotin and organozinc oxazole prepared from the organolithium exist primarily as the ring-closed C2-organometallic species (Scheme 2).⁵ For this reason, Stille⁶ and Negishi⁷ couplings remain the dominant approach towards the cross-coupling of unsubstituted oxazole despite their respective limitations. In both instances, process challenging cryogenic temperatures are required to prepare the thermally unstable organolithium intermediate, and in the case of the Stille coupling, this species is transmetalated to form a toxic organotin intermediate.⁸



Scheme 2 Formation of oxazole organometallics

Recently, we became interested in the synthesis of **2** via cross-coupling between oxazole and **1** (Scheme 3). While several methods for the direct arylation of oxazole have been reported,⁹ compound **2** could not be formed via conditions previously reported.^{9a} Next, we evaluated the use of Hauser bases¹⁰ such as TMPZnCl-LiCl to perform the C2 C-H zincation of oxazole as reported by Knochel,¹¹ thereby avoiding the intermediacy of the unstable organolithium species.



В

Initial efforts to metalate oxazole with TMPZnCl·LiCl and perform the subsequent Negishi coupling in the presence of Pd(PPh₃)₄ required elevated temperatures and long reaction times, delivering **2** with moderate crude purity (Scheme 3). Initially, we thought these issues could be addressed by selection of an alternative catalyst. A subsequent high-throughput catalyst screen using the precatalysts popularized by Buchwald was performed using THF and THF/NMP (2:1) with a focus on improving reaction efficiency. From this screening, several promising results were obtained in THF, including XPhos Pd G2, BrettPhos Pd G3, *t*-BuXPhos Pd G3, RuPhos Pd G2, and PEPPSI-IPent (Figure 1).



Figure 1 Catalyst screening with oxazole zincate derived from TMPZn-Cl-LiCl. Conditions: A stock solution was made by addition of TMPZn-Cl-LiCl (0.70 M in THF) to oxazole in THF at 0 °C. Separately, a slurry of 1 in the appropriate solvent was prepared at room temperature. Both stock solutions were sequentially dosed to wells containing a pre-weighed catalyst at room temperature and were heated to 65 °C for 18 hours. Each reaction contained 1 (0.01 mmol), oxazole (4.0 equiv), TMPZnCl-LiCl (4.8 equiv), catalyst (10 mol%), and the appropriate solvent (32 μ L) under argon. Conversion is based on area ratio of 2/[1+2] and %AN based on UPLC area normalization to 100%.

Subsequent scale-up reactions performed on a 2 gram scale of **1** with 5 mol% catalyst and 2 equivalents of oxazole afforded full conversion at 65 °C as expected (Table 1). However, analysis of the crude reactions revealed the presence of side products arising from regioisomeric metalation of oxazole at both the 4- and 5-position which proved chal-

lenging to purge. While metalation of oxazole at the 4- and 5-position with TMPZnCl-LiCl has been reported to occur only at elevated temperatures,¹¹ all attempts to improve regioselectivity by reducing reaction temperature failed to achieve full conversion (Table 1, entry 4).

Table 1 Catalyst Screening with TMPZnCl·LiCl^a

Entry	Catalyst	Temp (°C)	Conv. (%) ^b	2 (%AN) ^b	
1	RuPhos Pd G2	65	99	70	
2	BrettPhos Pd G3	65	100	67	
3	t-BuXPhos Pd G3	65	100	63	
4	t-BuXPhos Pd G3	40	22	16	
5	XPhos Pd G2	65	100	72	

^a Conditions: TMPZnCl·LiCl in THF (2.4 equiv) was added to a solution of oxazole (2.0 equiv) in THF (5 mL) at 0 °C. In a separate flask, TMPZnCl·LiCl (1.2 equiv) was added to a slurry of **1** (2.0 g, 5.0 mmol) in THF (16 mL) at 0 °C, followed by catalyst (5 mol%) and the organozinc solution. The mixture was heated to the required temperature for 2 hours under nitrogen. ^b Conversion is based on area ratio of **2**/[**1**+**2**] and %AN based on UPLC area normalization to 100%.

In search of a more regioselective metalation strategy, a variety of different reagents were screened to generate the organozinc coupling partner prior to the subsequent Negishi coupling with *t*-BuXPhos Pd G3 (Table 2). As anticipated, generation of the intermediate organolithium at -78 °C with *n*-BuLi followed by transmetalation^{7a} was effective, despite the need for cryogenic temperatures below -40 °C due to the instability of the intermediate organolithium. Given this limitation, a wider range of bases was further evaluated in order to assess the formation of the oxazole organozinc at non-cryogenic temperatures (Table 2). From this screening, one notably effective base was *i*-PrMgCl, which has been used previously to acylate oxazole at C2 with Weinreb amides.^{4b} We hypothesized that transmetalation of the intermediate magnesiated oxazole with either solid ZnCl₂ or a solution of ZnCl₂ in MeTHF or a comparable solvent would allow access to the desired organozinc reagent. This approach proved successful using *i*-PrMgCl, *i*-PrMgCl·LiCl, and TMPMgCl·LiCl as the organomagnesium base (Table 2).

Table 2 Base Screening for Deprotonation of Oxazole and Subsequent

 Negishi Coupling

Entry	Base	Metalation (°C)	Conv. (%) ^c	2 (%AN) ^c	
1	n-BuLi ^a	-78	100	76	
2	i-PrMgCl ^a	-15	100	76	
3	i-PrMgCl·LiCl ^a	-15	100	61	
4	TMPMgCl·LiCl ^a	-15	100	76	
5	LiHMDS ^b	-15	100	74	
6	NaHMDS ^b	-15	32	24	
7	KHMDS^b	-15	49	39	
8	LiN(Cy)2 ^b	-15	100	76	
9	LiN(<i>i</i> -Pr) ₂ ^b	-15	100	75	
10	LiTMP ^b	-15	100	73	
11	LiOt-Bu ^b	-15	0	0	
12	NaOt-Bu ^b	-15	0	0	
13	KOt-Bu ^b	-15	4	3	

^a A solution of oxazole (3.0 equiv) in THF (16 mL) was cooled to the specified temperature, and the base (3.2 equiv) was charged over 30 minutes. A solution of $ZnCl_2$ (6.0 equiv) in MeTHF (14 mL) was then added over 30 minutes and the mixture warmed to 22 °C. **1** (2.0 g, 5.0 mmol) and *t*-BuX-Phos Pd G3 (5 mol%) were added and the mixture warmed to 65 °C for 6 hours under nitrogen.

^b A solution of oxazole (3.0 equiv) and ZnCl₂ (6.0 equiv) in MeTHF (14 mL) was cooled to the specified temperature, the base was charged over 30 minutes and the mixture warmed to 22 °C. **1** (2.0 g, 5.0 mmol) and *t*-BuXPhos Pd G3 (5 mol%) were added and the mixture warmed to 65 °C for 6 hours under nitrogen.

^c Conversion is based on area ratio of **2**/[**1**+**2**] and %AN based on UPLC area normalization to 100%.

Webb et al. recently disclosed the formation of a substituted oxazole organozinc by deprotonation of the parent oxazole at C2 with LiHMDS in the presence of ZnCl₂ at -10 °C.^{2e} This was followed by Negishi coupling to generate an intermediate in the synthesis of a phosphatidinylinositol-3kinase delta inhibitor. Inspired by these findings, we also opted to evaluate a series of amide bases for the ability to generate the oxazole organozinc by deprotonation of oxazole in the presence of ZnCl₂. From these efforts, a variety of different lithium amide bases including LiHMDS, LiN(*i*-Pr)₂ $LiN(Cy)_2$ and LiTMP were found to be effective, while both NaHMDS and KHMDS provided only partial conversion. In contrast to direct zincation with the amide base TMPZnCl·Li-Cl, no products arising from regioisomeric metalation of oxazole were observed using these bases. While the use of amide bases was effective, attempts to metalate using t-butoxide bases were less successful.

A high-throughput catalyst screen was subsequently performed using *i*-PrMgCl in THF as the base with 24 different catalysts in THF (Figure 2). Full conversion was achieved with XPhos Pd G2, BrettPhos Pd G3, and *t*-BuXPhos Pd G3, while less than 50% conversion was noted for the remaining catalysts under the screening conditions.



Figure 2 Catalyst screening with *i*-PrMgCl. Conditions: A stock solution was made by addition of *i*-PrMgCl to oxazole in THF at –15 °C, followed by addition of a solution of ZnCl₂ in MeTHF, warming to 22 °C, and addition of 1. This stock solution was dosed to wells with pre-weighed catalyst and heated to 65 °C for 18 hours. Each reaction contained 1 (0.02 mmol), oxazole (3.0 equiv), catalyst (5 mol%), *i*-PrMgCl (2 M in THF, 3.2 equiv), ZnCl₂ (6.0 equiv), THF (60 µL), MeTHF (60 µL) under argon. Conversion is based on area ratio of 2/[1+2] and %AN based on UPLC area normalization to 100%.

An additional follow-up screen of Pd sources was performed for the *t*-BuXPhos and XPhos ligands (Figure 4). In addition to several of the available Buchwald precatalysts, generation of the active catalyst was performed by combining free ligand with dimeric Pd(II) precatalysts ($\mathbf{3}$,¹² $\mathbf{4}$ ¹³) as well as a recently reported pre-complexed *t*-BuXPhos π -allyl complex $\mathbf{5}$.¹⁴



Figure 3 Pd sources used in catalyst screening

For *t*-BuXPhos, full conversion was achieved with *t*-BuXPhos Pd G3, *t*-BuXPhos Pd G3·MTBE, **5**, and the combination of $Pd_2(dba)_3$ and *t*-BuXPhos, while 74% and 90% conversion were observed with combinations of **3** + *t*-BuXPhos and $[(allyl)PdCl]_2 + t$ -BuXPhos, respectively (Figure 4). In the case of XPhos, only XPhos Pd G2 provided full conversion, while partial conversion was achieved using XPhos Pd G3, or alternatively, $Pd_2(dba)_3$, and $[(allyl)PdCl]_2$ in combination with XPhos ligand.

Letter

Syn lett

M. J. Geier et al.

D



Figure 4 Screen of Pd sources with *t*-BuXPhos and XPhos for *i*-PrMgCl. Conditions: A stock solution was made by addition of *i*-PrMgCl to oxazole in THF at –15 °C, followed by addition of a solution of ZnCl₂ in MeTHF, warming to 22 °C, and addition of **1**. This stock solution was dosed to reaction vessels with pre-weighed catalyst and warmed to 65 °C for 6 hours under nitrogen. Each reaction contained **1** (2.50 mmol), oxazole (3.0 equiv), catalyst (5 mol%), *i*-PrMgCl (2 M in THF, 3.2 equiv), ZnCl₂ (6.0 equiv), THF (7 mL), MeTHF (6 mL). Conversion is based on area ratio of **2**/[**1**+**2**] and %AN based on UPLC area normalization to 100%.

A subsequent catalyst screen was also performed using LiHMDS as the base, and in this case, only the *t*-BuXPhoscatalyzed reaction reached completion (Figure 5), while both XPhos Pd G2 and BrettPhos Pd G3 displayed modest conversion under the conditions employed in the screen.



Figure 5 Catalyst screening with LiHMDS. Conditions: A stock solution was made by addition of LiHMDS to a solution of oxazole and $ZnCl_2$ in MeTHF at -15 °C, warming to 22 °C, addition of **1**, and dosing to wells with pre-weighed catalyst and warming to 65 °C for 18 hours under nitrogen. Each reaction contained **1** (0.02 mmol), catalyst (5 mol%), LiHMDS (1.3 M in THF, 3.2 equiv), oxazole (3.0 equiv), $ZnCl_2$ (6.0 equiv), and MeTHF (80 μ L). Conversion is based on area ratio of **2**/[**1**+**2**] and %AN based on UPLC area normalization to 100%.

Finally, a screen of Pd sources was performed using LiHMDS as the base (Figure 6). Full conversion was achieved with *t*-BuXPhos Pd G1, *t*-BuXPhos Pd G3, *t*-BuXPhos Pd G4, t -BuXPhos Pd G4, t -BuXPhos Pd G4, t -BuXPhos Pd G4, t -BuXPhos Pd

G3·MTBE, and **5**. The improved activity of pre-ligated catalyst sources under LiHMDS-mediated conditions is note-worthy in comparison to that observed for *i*-PrMgCl conditions.



Figure 6 Screen of Pd sources with *t*-BuXPhos in LiHMDS. Conditions: A stock solution was made by addition of LiHMDS to a solution of oxazole and ZnCl₂ in MeTHF at –15 °C, warming to 22 °C, addition of 1, and dosing to reaction tubes with pre-weighed catalyst and heating to 65 °C for 6 hours under nitrogen. Each reaction contained 1 (2.50 mmol), oxazole (3.0 equiv), catalyst (5 mol%), LiHMDS (1 M in THF, 3.2 equiv), ZnCl₂ (6.0 equiv), and MeTHF (80 μ L). Conversion is based on area ratio of 2/[1+2] and %AN based on UPLC area normalization to 100%.

Finally, the generality of this method was evaluated for a range of aryl and heteroaryl bromides using *i*-PrMgCl as the base and *t*-BuXPhos Pd G3 as the catalyst (Scheme 4). In addition to the ester, thiophene and N–H uracil functionality present in **1**, nitrile, fluoro, trifluoromethyl, and sulfone groups were also well tolerated under the coupling conditions.

In summary, we have identified a series of new, regioselective, and noncryogenic metalations of unsubstituted oxazole for the Negishi coupling and synthesis of **2**. Several rounds of catalyst and palladium source screening have been performed, identifying several suitable catalysts and metal-ligand combinations yielding a broadly applicable transformation. Additionally, a range of aryl and heteroaryl bromides were found to be competent coupling partners under these conditions, highlighting the generality of the method.¹⁵

Acknowledgment

The authors thank Richard Yu, Anna Chiu, Kevin Allan, Josh Dunetz, Darren Bykowski, and Jeff Ng for helpful discussions during preparation of the manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611909.

Letter

Synlett

M. I. Geier et al.

Letter



Ε

Scheme 4 Substrate scope of oxazole Negishi coupling. Conditions: A stock solution was prepared by addition of *i*-PrMgCl to oxazole in THF at -15 °C, followed by addition of a solution of ZnCl₂ in MeTHF, and then warming the solution to 22 °C. A portion of this stock solution was dosed to reaction vessels with the substrate (2.5 mmol), followed by addition of *t*-BuXPhos Pd G3 (5 mol%), and warmed to 65 °C for 18 hours under nitrogen. Each reaction contained substrate (2.5 mmol), oxazole (3.0 equiv), *t*-BuXPhos Pd G3 (5 mol%), *i*-PrMgCl (2 M in THF, 3.2 equiv), ZnCl₂ (6.0 equiv), THF (7 mL), and MeTHF (6 mL).

References and Notes

- (1) Zhang, H. Z.; Zhao, Z. L.; Zhou, C. H. Eur. J. Med. Chem. 2018, 144, 444.
- (2) (a) Lakhan, R.; Ternai, B. In Advances in Heterocyclic Chemistry, Vol. 17; Katritzky, A. R.; Boulton, A. J., Eds.; Academic Press: New York, **1974**, 99. (b) Wiley, R. H. Chem. Rev. **1945**, 37, 401. (c) Vinay, Kumar. K. S.; Swaroop, T. R.; Rajeev, N.; Vinayaka, A. C.; Lingaraju, G. S.; Rangappa, K. S.; Sadashiva, M. P. Synlett **2016**, 27, 1363. (d) Cheung, C. W.; Buchwald, S. L. J. Org. Chem. **2012**, 77, 7526. (e) Edney, D.; Hulcoop, D. G.; Leahy, J. H.; Vernon, L. E.; Wipperman, M. D.; Bream, R. N.; Webb, M. R. Org. Process Res. Dev. **2018**, 22, 368. (f) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. J. Org. Chem. **2000**, 65, 1516.
- (3) (a) Hodges, J. C.; Patt, W. C.; Connolly, C. J. J. Org. Chem. 1991, 56, 449. (b) Crowe, E.; Hossner, F.; Hughes, M. J. Tetrahedron 1995, 51, 8889. (c) Boche, G.; Bosold, F.; Hermann, H.; Marsch, M.; Harms, K.; Lohrenz, J. C. W. Chem. Eur. J. 1998, 4, 814.
- (4) (a) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. J. Org. Chem. 2005, 70, 5190. (b) Pippel, D. J.; Mapes, C. M.; Mani, N. S. J. Org. Chem. 2007, 72, 5828.
- (5) Fu, L. In Metalation of Azoles and Related Five-Membered Ring Heterocycles; Gribble, G. W., Ed.; Springer: Berlin/Heidelberg, 2012, 103.
- (6) (a) Krebs, O.; Taylor, R. J. K. Org. Lett. 2005, 7, 1063. (b) Dowlut, M.; Mallik, D.; Organ, M. G. Chem. Eur. J. 2010, 16, 4279. (c) Ferrer Flegeau, E.; Popkin, M. E.; Greaney, M. F. J. Org. Chem. 2008, 73, 3303.

- (7) (a) Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, R. J.; Pangborn, J. J. Org. Process Res. Dev. 2003, 7, 696. (b) Albaneze-Walker, J.; Raju, R.; Vance, J. A.; Goodman, A. J.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P. A.; Espino, P.; Andrews, D. R. Org. Lett. 2009, 11, 1463. (c) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. Chem. Commun. 2008, 1241.
- (8) (a) Magano, J.; Dunetz, J. R. Chem. Rev. 2011, 111, 2177.
 (b) Magano, J.; Dunetz, J. R. In New Trends in Cross-Coupling: Theory and Applications; Colacot, T. J., Ed.; The Royal Society of Chemistry: Cambridge, 2015, 697. (c) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. ACS Catal. 2016, 6, 1540.
- (9) (a) Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Wilson, J. E.
 Org. Lett. **2010**, *12*, 3578. (b) Besselièvre, F.; Lebrequier, S.; Mahuteau-Betzer, F.; Piguel, S. *Synthesis* **2009**, 3511.
- (10) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. Angew. Chem. Int. Ed. **2011**, *50*, 9794.
- (11) Haas, D.; Mosrin, M.; Knochel, P. Org. Lett. 2013, 15, 6162.
- (12) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Chem. Sci. 2013, 4, 916.
- (13) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. J. Org. Chem. 2014, 79, 4161.
- (14) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. J. Org. Chem. 2015, 80, 6794.
- (15) Typical Procedure for the Synthesis of tert-Butyl 2-Methyl-2-{5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,4dihydrothieno[2,3-d]pyrimidin-3(2H)-yl}propanoate (2) A stock solution was prepared by addition of *i*-PrMgCl (60 mL, 120 mmol) to oxazole (7.3 mL, 112 mmol) in THF (120 mL) at -15 °C, followed by addition of a solution of ZnCl₂ (30.5 g, 224 mmol) in MeTHF (105 mL) and warming to 22 °C. To a reaction

M. J. Geier et al.

vial, under nitrogen, was added the aryl halide 1 (2.50 mmol), followed by the oxazole zincate solution (20 mL, 7.50 mmol, 3.0 equiv) and t-BuXPhos Pd G3 (105 mg, 5 mol%). The vial was warmed to 65 °C for 18 hours under nitrogen. The reaction was then cooled and quenched by addition of 1 M HCl (20 mL). Compound 2 was obtained by filtration. ¹H NMR (400 MHz, DMSO d_6): $\delta = 1.36$ (s, 9 H), 1.64 (s, 6 H), 2.72 (s, 3 H), 8.20 (s, 1 H), 7.36 (s, 1 H), 12.31 (s, 1 H) ppm. ¹³C NMR (100 MHz DMSO- d_6): δ = 14.2, 24.2, 27.4, 62.5, 79.9, 113.6, 114.2, 128.2, 136.2, 139.4, 150.1, 151.6, 156.7, 159.9, 171.2 ppm. Compounds 6-15 were obtained following the general procedure above, using the appropriate aryl halide starting material, however, following the addition of 1 M HCl (20 mL), ethyl acetate (20 mL) was added, and the layers separated. The aqueous layer was again extracted with ethyl acetate (20 mL), and the combined ethyl acetate layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with 4:1 heptanes/ethyl acetate (compounds **7–10**) or dichloromethane (compounds **6**, **11–15**). The characterization data for examples **8** and **10** below was found to be in agreement with that previously reported.¹¹

2-(4-Methoxyphenyl)oxazole (8)

¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.96 (m, 2 H), 7.64 (s, 1 H), 7.18 (s, 1 H), 6.97–6.95 (m, 2 H), 3.84 (s, 3 H) ppm. ¹³C NMR (100 MHz CDCl₃): δ = 162.0, 161.3, 138.0, 128.2, 128.0, 120.3, 114.2, 55.3 ppm.

4-(Oxazol-2-yl)benzonitrile (10)

¹H NMR (400 MHz, CDCl₃): δ = 8.16 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H), 7.75 (s, 1 H), 7.32 (s, 1 H) ppm. ¹³C NMR (100 MHz CDCl₃): δ = 160.1, 139.8, 132.7, 131.2, 129.2, 126.8, 118.3, 113.7 ppm.