EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801192

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801192

Supported by ACES Asian Chemical Editorial Society

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10.1002/ejoc.201801192

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The diverse one-pot reactions of 2-quinolylzincates: homologation, electrophilic trapping, hydroxylation, and arylation reactions

Hye Jin Jeong,[a] Suyeon Chae,[a] Keunhong Jeong [b] and Sung Keon Namgoong*[a]

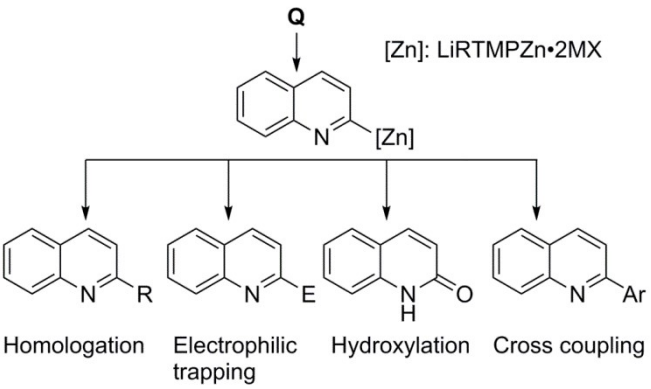
Abstract: 2-Quinolylzincates were efficiently produced from the regioselective metalation reactions of quinoline with various organozincates as key intermediates. The four different types of title reactions of these intermediates under the presented reaction conditions allowed for the facile formation of the corresponding C-2 functionalized quinolines which are not successfully accessed through typical zincation methods.

Introduction

2-Functionalized quinoline scaffolds are one of the most promising N-heterocyclic nuclei that occupy a crucial role in many bioactive compounds.[1] Consequently the directed C-2 metalation of quinolines are an important strategy for syntheses of regioselective functionalized quinolines. The use of highly active TMP (2,2,6,6-tetramethylpiperidyl) base for direct metalation can be a way to complete such a protocol.[2] Few examples for the functionalization of quinolines via C-2 metalation reaction have been previously reported: $Zr(TMP)_4/BF_3$-induced metalation and subsequent arylation[3]; transmetalated arylation and nucleophilic addition to active carbonyl compounds employing $TMPMgCl{\cdot}BF_3$.[4] In general, these arylation strategies of quinoline can be achieved by the Negishi cross-coupling reactions[5] of either commercially available expensive 2-haloquinoline or its derivative, 2-quinolylzinc halide with appropriate coupling partners. However, the other metalation strategy using Li*t*Bu$_2$TMPZn was not successful, resulting in the formation of ca 3:7 ratio for 2-:8-zincated quinoline (**Q**).[6]

We have widely studied the regioselective C-2 zincation for **Q** to obtain 2-quinolylzincate, a negatively charged ate-complex, as a key intermediate. In general, the reactivity of this zincate intermediate is very different from that of the neutral 2-quinolylzinc halide easily prepared by the reaction of 2-haloquinoline with activated zinc. It is a particularly useful molecule since various functionalized quinolines can be prepared from this single ate-intermediate via diverse one-pot reactions: homologation[7], electrophilic trapping[4b,6], hydroxylation[8], and cross-coupling reactions[6,9] (Scheme 1).

As a result, for a number of attempts for directed zincation reactions of **Q**, the use of Li*t*Bu$_2$TMPZn·2LiCl (2.2 equiv) derived from slightly hydrated $ZnCl_2$ (H_2O content: 5~20 mol%) afforded



Scheme 1. The diverse C-2 functionalization strategies of quinoline.

2-quinolylzincate as a sole intermediate at 45 ℃ in 80% yield, unlike the case employing anhydrous $ZnCl_2$. This initial finding is unknown and of particular interest, as there is no precedent for the regioselective formation of 2-quinolyzincate molecule, an ate-complex, in the field of organozincate chemistry. Therefore, we systematically examined the zincation reactions of **Q** with $LiR_2TMPZn{\cdot}2MX$ (R: alkyl or phenyl groups, MX: LiCl or $MgCl_2$) under various reaction conditions and herein report the subsequent results.

Results and Discussion

The present work is summarized in Table 1. The C-2 zincation strategy began with the deprotonation reactions of **Q** with various TMP-zincates (2.2 equiv). TMP-zincate is normally formed by the sequential reactions of $ZnCl_2$ with 2RLi (or 2RMgCl) and lithium 2,2,6,6-tetramethylpiperidinide (LiTMP). Consequently, TMP-zincate has two equiv of LiCl or $MgCl_2$. *N*-Heteroaryl compounds, such as quinoline and isoquinoline requires 2.2 equiv of TMP-zincates to completely deprotonate at specific positions of those compounds (see Experimental Section and Supporting Information).

First of all, a zincation reaction employing slightly hydrated $ZnCl_2$ is not suitable as a scientific method due to the fact that the $ZnCl_2$ comes into contact with a variable amount of H_2O, meaning that it can fail to record reproducible yields. In fact, the water in $ZnCl_2$ reacts with RLi and is completely converted into LiOH in the preparation process of Li*t*Bu$_2$TMPZn. Therefore, LiOH may play an important role of showing high regioselectivity in the presented reaction. Indeed, an initial addition of LiOH (powder type, 5~20 mol% in THF) into the Li*t*Bu$_2$TMPZn·2LiCl solution and subsequent addition of **Q** proved to be effective and reproducible for the formation of 2-quinolylzincate, recorded 80% yield (Table 1, entry 1; MX: LiCl).

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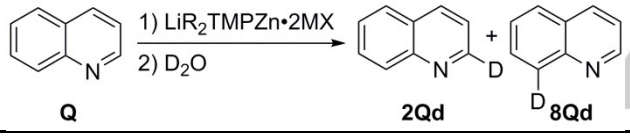
Supporting information for this article is given via a link at the end of the document.

The ^{1}H NMR study related with the deuterium labeling experiment in this application is displayed at Figures 1, S1 and S2. It indicated that the formation yields for 2- and 8-deuterioquinoline[10] were slowly varied from 33:66 to exactly 80:0 according to the increase in the reaction temperature from 25℃ to 45℃. The remaining 20% was recovered as **Q** (Figures 1(b), 1(d) and S1). The reaction time depends on the amount of LiOH added. It was 15 h and 18 h for the respective uses of 20 mol% and 5 mol% LiOH. Eventually, 20 mol% of LiOH was applied in this reaction for the optimum C-2 zincation of **Q** (Table 1). The amount of unreacted **Q** was gradually increased according to the addition of more than 20 mol% of LiOH to the reaction mixture. In the absence of LiOH, the zincation of **Q** was observed at 8- and 2-position with equal amounts (1:1) at 45 °C, even for a prolonged reaction time (72 h) (Figures 1(c)). These data do not reflect the thermodynamic correlation between 2- and 8-quinolylzincate. Therefore, the use of LiOH predominantly affects the regioselective C-2 zincation for **Q** under anhydrous reaction conditions.

Table 1. The regioselective formation of 2-deuterioquinoline (**2Qd**) via 2-quinolylzincates from quinoline.[a,b]



Q **2Qd** **8Qd**

Entry	R	MX (**2Qd**:**8Qd**, % yield)[c] LiCl/LiOH[d,e]	$MgCl_2$[f]
1	*t*Bu	80:0	99:0
2	*i*Pr	81:0	96:0[g]
3	Bu	80:0	96:0
4	Me	80:0	96:0
5	Ph	21:79	-

[a] Reaction conditions: **Q** (0.80 mmol), $LiR_2TMPZn{\cdot}2MX$ (1.8 mmol) and THF (10 mL) under N_2. [b] Quenching of 2-quinolylzincates with D_2O (1 mL). [c] Determined by ^{1}H NMR spectroscopic analyses. [d] Pre-addition of LiOH (0.16 mmol, 20 mol%) into **Q**/THF solution and subsequent addition of TMP-Zincate. [e] Reaction time: 15 h at 45 ℃. [f] Reaction time: 3 h at 25 ℃. [g] MX: $MgCl_2$ or $MgCl_2{\cdot}LiCl$.

The addition of the hydroxide ion into tri-coordinated 2- and 8-quinolylzincates in the presented reaction conditions may reversibly form tetra-coordinated quinolylzincate complexes.[11] The hydroxide group from these complexes can selectively transfer a proton to more basic 8-quinolyl ligand than 2-quinolyl ligand and facilitates the conversion of 8-quinolylzincate into 2-quinolylzincate through the repeated processes of C-8 reprotonation/C-2 deprotonation. It is still unclear why 20% of **Q** always remains unreactive following the reaction. A similar result was obtained in the other alkyl ligands-bearing zincation

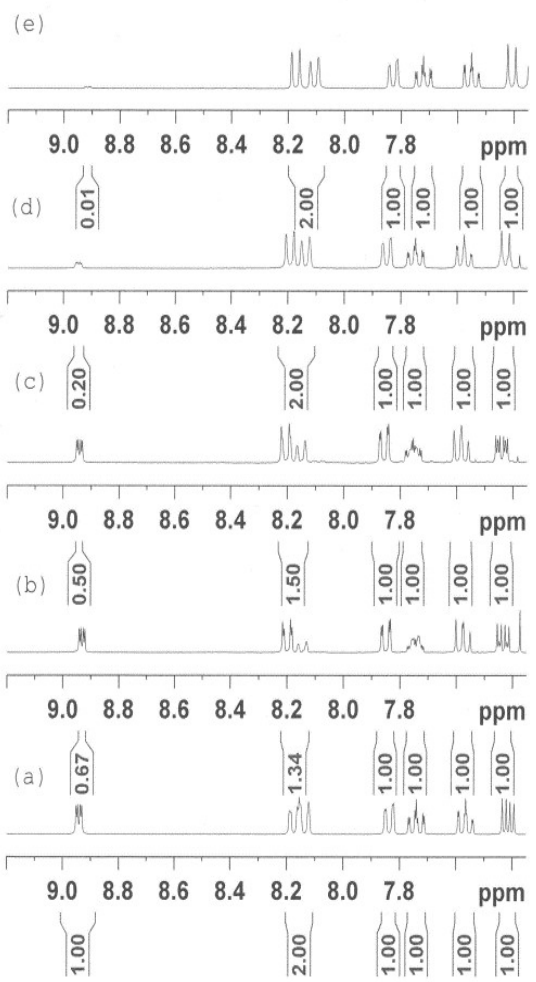


Figure 1. Deuterium labelling experiments of 2- and 8-quinolylzincates (Li*t*Bu**Q**TMPZn·2MX) under various reaction conditions: (a) **Q** as a reference molecule (300 Hz, δ, H-2: 8.95 and H-8: 8.13 ppm); (b) MX: LiCl, 3 h at 25 ℃, (**2Qd**:**8Qd**, % yield), 33:66; (c) MX: LiCl, 72 h at 45 ℃, (**2Qd**:**8Qd**, % yield), 50:50; (d) LiOH (20 mol%) added, MX: LiCl, 15 h at 45 ℃, (**2Qd**:**8Qd**, % yield), 80:0; (e) MX: $MgCl_2$, 3 h at 25 ℃, (**2Qd**:**8Qd**, % yield), 99:0.

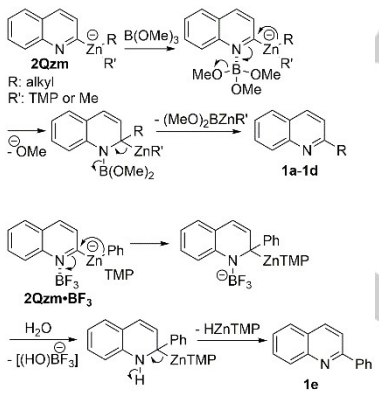
reactions (R: *i*Pr, Bu, and Me, Table 1, entries 2-4; MX: LiCl, Figure S1). However, this C-2 zincation strategy was unsuccessful in the case of a Ph ligand, resulting in the preferential formation for C-8 zincated **Q** (Table 1, entry 5; MX: LiCl, Figure S1).

A continuous effort was then initiated to determine an optimum condition for improving the limited yields of 2-quinolylzincates. As a result, the selection of $LiR_2TMPZn{\cdot}2MgCl_2$ (2.2 equiv, R: *t*Bu, *i*Pr, Bu, and Me) were successful in almost quantitatively producing 2-quinolylzincates without the use of LiOH (Table 1, entries 1-4; MX: $MgCl_2$, Figures 1(e) and S2). As for the case concerned with *i*Pr ligand, the use of $Li{i}Pr_2TMPZn$ including either $MgCl_2$ or $MgCl_2{\cdot}LiCl$ was also effective for the C-2 zincation. Surprisingly, the zincations in this series occurred at the C-2 position only, even at initial stages and were completed

within 3 h at 25℃. It was quite remarkable that the simple replacement of LiCl with $MgCl_2$ in this application demonstrated a perfect C-2 regioselectivity even though the mode of deprotonative metalation is unclear.

2-Quinolylzincates to apply for the following title reactions are divided into two different ate-complexes. The first one is 2-quinolylzincates·2LiCl·LiOH (LiR**Q**TMPZn·2LiCl·LiOH, R: alkyl, **2QzI**). **2QzI** contains 2 equiv of LiCl and 20 mol% of LiOH as an additive. The other one is 2-quinolylzincates·2$MgCl_2$ (LiR**Q**TMPZn·2$MgCl_2$, R: alkyl, **2Qzm**). On the other hand, **2Qzm** includes only 2 equiv of $MgCl_2$. These two zincates, **2QzI** or **2Qzm**, were prepared by the deprotonation reactions of **Q** with the prepared TMP-zincates containing either LiCl or $MgCl_2$ in the presence or absence of 20 mol% LiOH (see Experimental Section and Supporting Information).

The first application strategy employing 2-quinolylzincates is to prepare 2-homologated quinolines. This preparation method normally includes the following two-step reactions: nucleophilic addition of alkyl or aryl anion to **Q** and an additional oxidation of 2-substituted-1,2-dihydroquinoline.[12] On the basis of the excellent C-2 zincation results of **Q** and our previous homologation results for isoquinoline (**Iq**) [7a], the one-pot homologation strategy started from the $B(OMe)_3$-induced reactions of 2-quinolylzincates·2$MgCl_2$ (**2Qzm**) (for *i*Pr ligand: 2$MgCl_2$·2LiCl) under anhydrous condition. The corresponding homologation reactions described here can avoid such required two-step reactions. The formation mechanisms[7b] for **1a-1e**[12,13] are illustrated (Scheme 2) and the present work is summarized (Table 2).



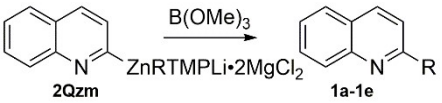
Scheme 2. The proposed formation mechanisms for **1a-1e**.

The following formation mechanism for **1a-1d** is proposed, proceeding through a three-step process: (1) coordination of $B(OMe)_3$ with the sp^2-nitrogen of **2Qzm**, (2) 1,2-migratory addition of the alkyl ligand from **2Qzm**·$B(OMe)_3$ complex and subsequent cleavage of B-OMe bond, and (3) reformation of the aromatic ring through loss of $(MeO)_2$BZnTMP at 1,2-position from precursor.[7b] The $B(OMe)_3$ plays an important role in enhancing electrophilicity at the 2-carbon, stimulating movement of the nucleophilic alkyl ligand to the 2-position of **2Qzm**·$B(OMe)_3$ complex. Moreover, the steric hindrance between the alkyl and TMP-Zn groups caused by 1,2-migration facilitated further elimination of $(MeO)_2$BZnTMP to quickly produce **1a-1d**. For the formation mechanism of **1e**[13], it was very similar to that of **1a-1d**, except for the elimination of HZnTMP/BF_3 through the aqueous work-up process (Scheme2).[7b]

All of the reactions were completed within an hour after the addition of $B(OMe)_3$ (5 equiv) in this series. The metal ion of $MgCl_2$ coordinates with the oxygen atom of $B(OMe)_3$. At the same time, one of its chloride ions presumably coordinates with the electrophilic boron atom. The double dual coordination between $MgCl_2$ and $B(OMe)_3$ may lead to the production of the 1:2 complex (2$MgCl_2$:4$B(OMe)_3$), unlike the previous 1:1 dual coordination complex in the case of **Iq** series.[7a] This bulky 1:2 complex cannot coordinate to the nitrogen atom of **2Qzm**, so the additional 1 equiv of $B(OMe)_3$ (total 5 equiv) was necessary to complete the reaction. On the other hand, a 1.2 equivalent of $B(OMe)_3$ was sufficient for a successful homologation in **Iq** series. Therefore, it is indicated that the interactive functions of MgX_2 (X: Cl or Br) with $B(OMe)_3$ in 2-quinolyl and 1-isoquinolyl zincate series are considerably different.

The present evaluation of the 1,2-migratory ability of the alkyl ligands in **2Qzm** revealed that most alkyl ligands were the effective 1,2-migrating groups in this series (Table 2, entries 1-3).

Table 2. The $B(OMe)_3$-induced homologation reactions of **2Qzm**.[a]



Entry	Product/R	Yield(%)[b]
1	**1a**/*t*Bu	94
2	**1b**/*i*Pr	75[c]
3	**1c**/Bu	85
4[d]	**1d**/Me	50
5	**1e**/Ph	63[e]

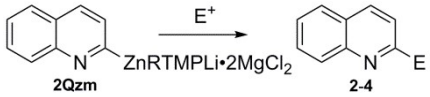
[a] Reaction conditions: $B(OMe)_3$ (4.0 mmol), **2Qzm** (0.80 mmol) and THF (10 mL) under N_2 for 1 h at 25 ℃. [b] Isolated yield by column chromatography. [c] $B(OMe)_3$ (5.6 mmol) used. [d] **2Qzm** possessing Me ligand instead of TMP ligand. [e] Reaction conditions: **Q**·BF_3 pre-complex (0.80 mmol), $LiPh_2TMPZn$·2LiCl (1.8 mmol) and THF (10 mL) under N_2 for 1 h at 25 ℃.

For the case of *i*Pr ligand, it is noted that **2Qzm** containing 2$MgCl_2$·2LiCl, instead of 2$MgCl_2$, was only effective for 1,2-migratory addition. However, this homologation strategy was partially successful in the reaction for methyl ligand, probably

due to its weak nucleophilic nature (Table 2, entry 4). As for the case of Ph ligand, the alternative preparation method employing the reaction of **Q**·BF_3 pre-complex[7a] with $LiPh_2TMPZn$ (2.2 equiv) was only successful in the generation of **1e** (Table 2, entry 5). However, the 1,2-migratory ability of the alkyl ligands in 1-isoquinolyl zincate was also quite different from that in **2Qzm**. The corresponding homologation reactions (R: Me and Ph) of **Iq** did not work at all due to both the inactive nature of the Me ligand and its preferential attack to $B(OMe)_3$ prior to 1,2-migratory addition of Ph ligand. The butylation of **Iq** recorded only 37% yield.[7a]

The second application strategy employing **2Qzm** aims to synthesize another functionalized quinolines (**2-4**) by electrophilic trapping reactions (Table 3, R: *t*Bu).

Table 3. The electrophilic trapping reactions of **2Qzm**.[a]



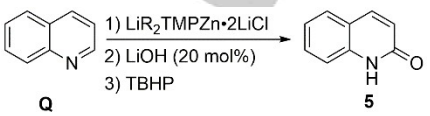
Entry	R	E^+	Product/E	Yield(%)[b]
1	*t*Bu	D_2O	**2**/D	99[c]
2	*i*Pr	D_2O	**2**/D	96[c]
3	*t*Bu	I_2	**3**/I	98
4	*i*Pr	I_2	**3**/I	94
5	*t*Bu	PhCHO	**4**/PhCHOH	86
6	*i*Pr	PhCHO	**4**/PhCHOH	80

[a] Reaction conditions: E^+ (4.0 mmol), **2Qzm** (0.80 mmol) and THF (10 mL) under N_2 for 1 h at 25 ℃. [b] Isolated yield by column chromatography. [c] Product **2** obtained as an inseparable mixture with unreacted **Q** after purification by column chromatography.

Quenching the **2Qzm** formation reaction with D_2O almost quantitatively produced 2-deuterioquinoline[14] (**2**) as an inseparable mixture with unreacted **Q** (Table 3, entry 1). The yield of **2** was determined via ^1H NMR spectroscopic analysis. When **2Qzm** was treated with I_2, 2-iodoquinoline (**3**)[6] was obtained in 98% yield (Table 3, entry 3). Treatment of **2Qzm** with PhCHO gave the addition product, α-phenyl-2-quinolylmethanol (**4**)[15] in 86% yield (Table 3, entry 5). The employment of *i*Pr ligand, instead of *t*Bu ligand, in this application also showed similar results (Table 3, entries 2, 4 and 6).

In general, zincate complex is not susceptible to oxidation, unlike cuprate complex.[8] Nonetheless, 2-quinolylzincate·2LiCl·LiOH (**2Qzl**, R: *t*Bu, *i*Pr and Bu, LiOH: 20 mol% as an additive) was partially converted into carbostyril (**5**)[16] (2-hydroxyquinoline as a tautomer) under O_2 atmospheric condition in 39% yield. The third application strategy employing **2Qzl** aims to develop an efficient C-2 hydroxylation method. As a result of this study, the reactions of **2Qzl** with TBHP (*tert*-butyl hydroperoxide, 2.5 equiv)[8] resulted in the better formation of **5**. Product **5** was almost quantitatively generated by the hydroxylation reactions including these three kinds of alkyl ligands when the limited conversion yields of **Q** into **2Qzl** (Table 1, entries 1-3, ca 80%) are considered (Table 4, entries 1-3 for **5**). Of particular note is that the corresponding reactions of

Table 4. The synthesis of **5** from **Q** via **2Qzl**.



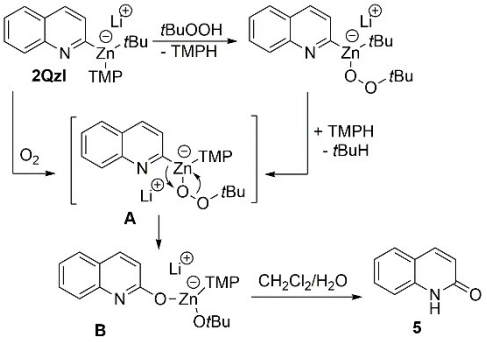
Entry	R	Yield(%)[a,b]
1	*t*Bu	80
2	*i*Pr	77
3	Bu	80

[a] Isolated yield by column chromatography. [b] Reaction conditions: $LiR_2TMPZn·2LiCl$ (1.8 mmol), LiOH (0.16 mmol), **Q** (0.80 mmol) and THF (10 mL) under N_2 for 15 h at 45 ℃; TBHP (2.0 mmol) for 1 h at 25 ℃.

2Qzm did not work at all. Although the role of $MgCl_2$ is unclear, its presence is a critical factor in unsuccessful hydroxylation reactions. Similar results were also observed in the production reactions of isocarbostyril[8] (1-hydroxyisoquinoline as a tautomer) proceeding in the same manner as mentioned above from **Iq** even if these data are not described here.

According to previously published results[8] not including **Q**, the directed hydroxylations for a couple of aryl cuprates/zincates should proceed in the presence of stoichiometric/catalytic amount of CuCN, whereas those in this application did not require the use of CuCN. Moreover, the C-2 hydroxylation of **Q** is yet to be reported because its regioselective C-2 zincation was unsuccessful.

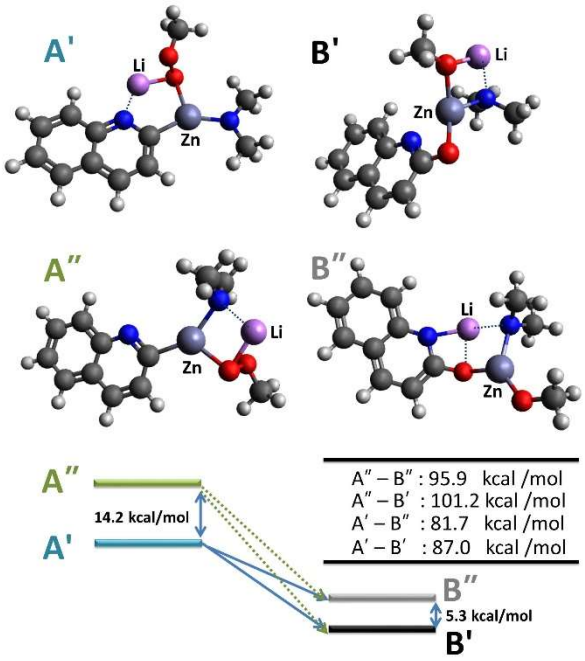
The proposed reaction mechanism for the formation of **5** proceeds through a three-step process from **2Qzl** (R: *t*Bu): (1) production of **A** by the addition of TBHP anion to *t*BuZn**Q** and the subsequent reformation of TMP-zincate, (2) 1,2-migration of 2-quinolyl group to an oxygen atom of $tBuO_2$ ligand followed by the addition of resulting *t*BuO group to a Zn atom, and (3) final rapid hydrolytic cleavage of **Q**O–Zn bond from **B** (Scheme 3).



Scheme 3. The proposed formation mechanism for **5** from **2Qzl.**

In addition, the hydroxylation mechanism applying O_2 gas involves an additional single-step process for the generation of the identical intermediate **A**: Zn-O bond formation through the insertion of O_2 between Zn-*t*Bu bond of **2Qzl** (Scheme 3).[17]

A DFT calculation (see Supporting Information, p11-14) with thermodynamic properties was performed to examine the stable structures of **A** and **B**, as shown in Scheme 3. Both TMP and *t*BuO_2 ligands were replaced by Me_2N and MeO_2 groups as the chemical models, respectively. After investigating the four possible intermediate structures with Li^+ (**A', A'', B',** and **B''**), the 5-membered ring complex for **A'** and 4-membered ring complex for **B'** showed the most stable structures, which were more stable than the other possible structures, 4-membered ring complex (**A''**) and skewed 6-membered ring complex (**B''**) by as much as 14.2 kcal/mol and 5.3 kcal/mol, respectively (Scheme 4). Therefore, the migration reaction in Scheme 3 would be processed from **A** to **B** by being thermodynamically stabilized as much as 87.0 kcal/mol.



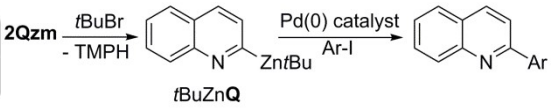
Scheme 4. Optimized stable intermediates (**A** and **B** in Scheme 3) and their energy differences between proposed intermediates including possible Li^+ coordination in the structures.

Finally, the Pd-catalyzed cross-coupling reactions of arylzincates[6,9] with aryl halides normally failed to record good yields even under harsh reaction conditions. This is presumably attributable to the side reactions of aryl halides under the given reaction conditions such as those dehalogenation reactions caused by *t*Bu ligand and deprotonative zincation reactions induced by TMP base from zincates. As an alternative method, the Suzuki-Miyaura cross-coupling reactions including very expensive 2-haloquinolines as coupling partners were applied for C-2 arylations of **Q** in the presence of specific catalysts.[1b,18]

Our previous C-2 arylation results employing **2Qzm** (R: *t*Bu) were similar to those of the above described arylations. Accordingly, the conversion of the ate-complex, **2Qzm**, into the neutral *tert*-butylquinolylzinc (*t*BuZn**Q**) is necessary to avoid such side reactions. The use of *tert*-butyl bromide (*t*BuBr, 2.2 equiv) entirely converted **2Qzm** to *t*BuZn**Q** and offered excellent arylation results in this application. It is noted that the E2 reaction of *t*BuBr with TMP base from **2Qzm** can quickly afford *t*BuZn**Q** within 5 min. The C-2 arylations of **Q** are successfully achieved by the present method under mild conditions without specific catalysts and the resulting work is summarized in Table 4.

All of the Pd(0)-catalyzed one-pot C-2 arylation reactions of **Q** via *t*BuZn**Q** with various aryl iodides gave the corresponding products, **1e**[1b] and **6a-6d**[19] within 1 h in excellent yields (Table 5, entries 1-5).

Table 5. The Pd(0)-catalyzed arylation reactions of **2Qzm** via *t*BuZn**Q**.[a]



Entry	ArI	Product	Yield(%)[b]
1		**1e**	93
2		**6a**	90
3		**6b**	96
4		**6c**	84
5		**6d**	93[c]
6		**6e**	82[d]

[a] Reaction conditions: **2Qzm** (R: *t*Bu, 0.80 mmol), *t*BuBr (1.8 mmol) and THF (10 mL) under N_2 for 5 min at 25 ℃; ArI (0.96 mmol) and $(Ph_3P)_4Pd$ (0.04 mmol) for 1 h at 25 ℃. [b] Isolated yield by column chromatography. [c] $Pd(dba)_2$ (0.04 mmol) used as a Pd(0) catalyst. [d] Syringe pump injection of corresponding ArI (0.96 mmol) to a mixture of *t*BuZn**Q** (0.80 mmol), THF (10 mL) and $(Ph_3P)_4Pd$ (0.08 mmol) for 12 h at 25 ℃.

The *t*Bu group of *t*BuZn**Q** probably enhances the nucleophilicity[20] of **Q** ligand, such that it can undergo rapid arylation reactions. Especially, the chemoselective arylation of **Q** was successful in the formation of **6a**[1b] under the presented reaction condition (Table 5, entry 2). The other arylation reaction to afford the bioactive haplophyllum alkaloid, dubamine (**6e**)[1c,4a] required prolonged injection time of the corresponding aryl iodide (1.2 equiv) to the reaction mixture by syringe pump for 12

h, mainly due to the formation of homo-coupling side product (Table 5, entry 6). Although the C-1 arylation results for **Iq** are not described here, these were comparable to the results of **Q**.

Conclusions

In conclusion, the diverse C-2 functionalized quinolines were efficiently produced from the key intermediates, either **2Qzm** or **2QzI** via one-pot homologation, electrophilic trapping, hydroxylation and cross-coupling reactions under the presented reaction conditions. These types of reactions were generally applicable to the synthetic methods for 2-functionalized quinolines in the field of organozincate chemistry. Such synthetic methods can be also applicable to the preparation of other functionalized *N*-heterocycles. The specific formation mechanisms for compounds **1a**–**1e** and **5** were proposed in detail. In addition, The DFT calculation study also suggested the stable structures of the intermediates **A** and **B** formed in the process of hydroxylation reaction of quinoline.

Experimental Section

General: All of the reagents used in this work were purchased from Sigma-Aldrich, Tokyo chemical industry and Alfa aesar companies. The reactions were performed under anhydrous conditions. All the reaction glassware was flame-dried for at least 1 h and purged with N_2. The THF solvent was distilled from sodium/benzophenone under N_2 atmospheric condition. All the synthetic compounds were characterized by ^1H and ^{13}C NMR spectroscopic analyses. The NMR spectra were recorded on Brucker AvanceⅢ 300. The $CDCl_3$ was used as solvent unless otherwise stated ($CDCl_3$ peak ^1H NMR: δ 7.28 ppm, ^{13}C NMR: δ 77.0 ppm). All coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used: brs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet, spt = septet, and m = multiplet. Thin layer chromatography was performed with Silica gel 60 F_{254} and compounds were visualized under UV light at 254 nm. All of the products were isolated by flash column chromatography (Silica gel 60, 0.063-0.200 mm). The representative procedures for the prepared compounds are as follows; the synthetic procedures and corresponding spectral data for all of the compounds prepared in this work are described in the supporting information, p7-10.

Lithium 2,2,6,6-tetramethylpiperidinide (LiTMP).
BuLi (2.0M in cyclohexane, 0.90 mL, 1.8 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.31 mL, 1.8 mmol) in THF (2 mL) at -78 ℃ under N_2 atmosphere. The mixture was stirred for 30 min at 0 ℃ to give LiTMP (1.8 mmol).

Lithium *tert*-butyl(quinolin-2-yl)(2,2,6,6-tetramethylpiperidin-1-yl)zincate·2LiCl·LiOH (2Qzl, R: *t*Bu, LiOH: 20 mol% as an additive).
*t*BuLi (1.7M in pentane, 2.2 mL, 3.6 mmol) was added to a solution of $ZnCl_2$ (0.26 g, 1.8 mmol) in THF (5 mL) at -78 ℃ under N_2. The mixture was stirred at 25 ℃ for 30 min to give $tBu_2Zn{\cdot}2LiCl$. The prepared LiTMP solution (3.2 mL, 1.8 mmol) was added to the solution of $tBu_2Zn{\cdot}2LiCl$ at -78 ℃. The reaction mixture was stirred for 30 min at 25 ℃ to generate $LitBu_2TMPZn{\cdot}2LiCl$. Lithium hydroxide (4.0 mg, 0.16 mmol) in THF (1 mL) was added to the corresponding $LitBu_2TMPZn{\cdot}2LiCl$ solution at 25 ℃. Finally, quinoline (0.1 mL, 0.80 mmol) was added to the resulting mixture and then stirred for 15 h at 45 ℃ to afford **2QzI** (0.80 mmol).

Lithium *tert*-butyl(quinolin-2-yl)(2,2,6,6-tetramethylpiperidin-1-yl)zincate·2MgCl$_2$ (2Qzm, R: *t*Bu).
*t*BuMgCl (1.0M in THF, 3.6 mL, 3.6 mmol) was added to a solution of $ZnCl_2$ (0.26 g, 1.8 mmol) in THF (3 mL) at -78 ℃ under N_2. The mixture was stirred for 30 min at 25 ℃ to give the solution of $tBu_2Zn{\cdot}2MgCl_2$. The prepared LiTMP solution (3.2 mL, 1.8 mmol) was added to the corresponding $tBu_2Zn{\cdot}2MgCl_2$ solution at -78 ℃. The reaction mixture was stirred for 30 min at 25 ℃ to generate $LitBu_2TMPZn{\cdot}2MgCl_2$. Finally, quinoline (0.1 mL, 0.80 mmol) was added to the $LitBu_2TMPZn{\cdot}2MgCl_2$ solution under N_2 atmosphere. The resulting mixture was then stirred for 3 h at 25 ℃ to produce **2Qzm** (0.80 mmol).

2-*tert*-Butylquinoline (1a).
$B(OMe)_3$ (0.46 mL, 4.0 mmol) was added to the solution of **2Qzm** (R: *t*Bu, 9.9 mL, 0.80 mmol) and stirred for 1 h at 25 ℃. The reaction was quenched with distilled water (6 mL) at 0 ℃. THF was evaporated under reduced pressure and the resulting mixture was diluted with CH_2Cl_2 (6 mL). The organic layer was washed with H_2O (6 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (ethyl acetate:hexane, 1:4) to afford **1a** as a pale-yellow oil. Yield 94% (140 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 2 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.73-7.67 (m, 1 H), 7.57-7.47 (m, 2 H), 1.50 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.25, 147.39, 135.89, 129.37, 129.00, 127.22, 126.44, 125.63, 118.23, 38.13, 30.15 ppm.

2-Iodoquinoline (3).
I_2 (1.0 g, 4.0 mmol) was added to the solution of **2Qzm** (R: *t*Bu, 9.9 mL, 0.8 mmol) and stirred for 1 h at 25 ℃. The reaction was quenched with distilled water (6 mL) at 0 ℃. THF was evaporated under reduced pressure and CH_2Cl_2 (6 mL) was added to the resulting mixture. The organic layer was washed with H_2O (6 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (ethyl acetate:hexane, 1:2) to give **3** as a yellow solid. Yield 98% (201 mg). (m.p. 52 ℃; lit. m.p. 52-53 ℃). ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 1 H), 7.74-7.65 (m, 4 H), 7.55-7.52 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.51, 137.11, 131.94, 130.31, 128.76, 127.87, 127.16, 127.09, 119.12 ppm.

Carbostyril (5).
tert-Butyl hydroperoxide (0.40 mL, 2.0 mmol) was added to the solution of **2QzI** (R: *t*Bu, 11mL, 0.80 mmol) at 25 ℃ and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and then quenched with distilled water (4 mL) at 0 ℃. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (ethyl acetate:hexane, 4:1) to give **5** as a white solid. Yield 80% (93 mg). (m.p. 188-190 ℃; lit. m.p. 192-194 ℃). ^1H NMR (300 MHz, $CDCl_3$) δ 11.8 (brs, 1 H), 7.84 (d, *J* = 9.6 Hz, 1 H), 7.61-7.40 (m, 3 H), 7.28-7.23 (m, 1 H), 6.73 (d, *J* = 9.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.64, 141.14, 138.53, 130.70, 127.70, 122.73, 121.28, 119.92, 116.38 ppm.

2-(4-Bromophenyl)quinoline (6a).
tert-Butyl bromide (0.21 mL, 1.8 mmol) was added to the solution of **2Qzm** (R: *t*Bu, 9.9 mL, 0.80 mmol). The mixture was stirred for 5 min at 25 ℃. $(Ph_3P)_4Pd$ (5.0 mg, 0.04 mmol) in THF (1 mL), and 1-bromo-4-iodobenzene (0.28 g, 0.96 mmol) in THF (1 mL) was added to the reaction mixture. The reaction mixture was stirred for 1 h at 25 ℃. The reaction was quenched with saturated aqueous NH_4Cl (6 mL) at 0 ℃. THF was evaporated under reduced pressure and CH_2Cl_2 (6 mL) was added to the resulting mixture. The organic layer was washed with H_2O (6 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (ethyl acetate:hexane,1:10) to produce **6a** as a yellow solid. Yield 90% (206 mg). (m.p. 115 ℃; lit. m.p. 117-119 ℃). ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d *J* = 8.7 Hz, 1 H), 8.18 (d, *J* = 8.7 Hz, 1 H), 8.10-8.06 (m, 2 H), 7.88-7.84 (m, 2 H), 7.79-7.76 (m, 1 H), 7.70-7.66 (m, 2 H), 7.59-7.54 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.07, 148.24, 138.51, 137.03, 132.00, 129.89, 129.70, 129.12, 127.52, 127.25, 126.55, 123.94, 118.55 ppm.

Acknowledgements

This work was supported by a research grant from Seoul Women's University (2018).

Keywords: Nitrogen heterocycles • Regioselectivity • Zincates• Quinoline • Regioselective C-2 zincations • One-pot reactions • Functionalized quinolines

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10.1002/ejoc.201801192

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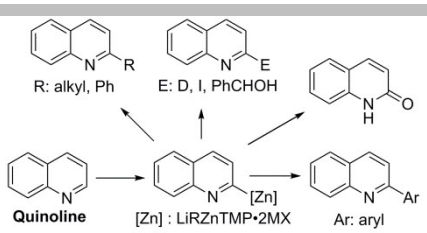
FULL PAPER

The diverse C-2 functionalizations of quinoline are successfully achieved via 2-quinolylzincate intermediates by the four different types of title reactions.



Functionalized quinolines

Hye Jin Jeong, Suyeon Chae, Keunhong Jeong and Sung Keon Namgoong[a]*

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The diverse one-pot reactions of 2-quinolylzincates: homologation, electrophilic trapping, hydroxylation, and arylation reactions