Tetrahedron Letters 53 (2012) 3594–3598

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Trimethyl borate/magnesium halide complex-induced one-pot homologation reactions of isoquinoline with dialkyl-TMP-zincate

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ARTICLE INFO

Article history:
Received 2 April 2012
Revised 24 April 2012
Accepted 2 May 2012
Available online 7 May 2012

Keywords:
Trimethyl borate
Magnesium halide
Isoquinoline
Dialkyl-TMP-zincate
Homologation

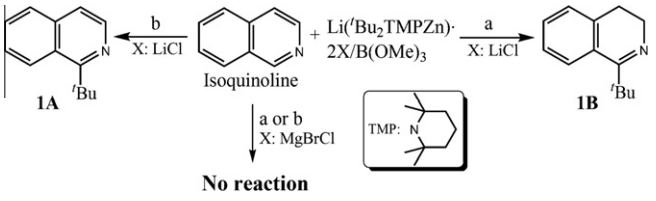
ABSTRACT

Novel one-pot homologation reactions of isoquinoline with lithium dialkyl-TMP-zincate·2MgBrCl/trimethyl borate are described. 1-Alkylisoquinolines (**2**, **3A**, **4A**, **5A**, **6**, and **7**) and 1-alkyl-3,4-dihydroisoquinolines (**3B**, **4B**, and **5B**) are easily prepared under the presented reaction conditions. The role of the $B(OMe)_3$/MgBrCl complex is examined in these homologation reactions. The specific reaction mechanisms, including 1,2-migration of the alkyl ligands from 1-isoquinolylzincates, are proposed. The migratory aptitudes of ligands of 1-isoquinolylzincates are also discussed.

Di-*tert*-butyl(2,2,6,6-tetramethylpiperidino)zincate (TMP-zincate) is a useful deprotonating agent for the directed *ortho* metalation (DoM) reaction of isoquinoline and other heteroaryl compounds.[1] It is also an efficient *t*-butylating agent for the homologation reactions of benzophenone[2] and isoquinoline.[3]

TMP-zincate is normally formed by the sequential reactions of $ZnCl_2$ with $2\,^tBuLi$ (or $2\,^tBuMgBr$) and lithium 2,2,6,6-tetramethylpiperidinide (LiTMP). Consequently, TMP-zincate has two equivalents of LiCl or MgBrCl. Our previous study on trimethyl borate-induced one-pot homologation reactions of isoquinoline (**Iq**) with TMP-zincate·2LiCl showed that 1-*t*-butylisoquinoline **1A**[4] and 1-*t*-butyl-3,4-dihydroisoquinoline **1B**[5] were selectively prepared according to the choice of two separate work-up methods under the identical reaction condition (Scheme 1).[3] The reaction mechanisms for the formation of **1A** and **1B** proceeded through 5- and 6-step processes, involving 1,2-migratory addition of a ^{t}Bu ligand from 1-isoquinolylzincate.[3] Recently, the corresponding reactions of TMP-zincate·2MgBrCl did not afford the products **1A** and **1B** at all. Instead, the reactant, **Iq** was quantitatively isolated.[6] The simple replacement of LiCl with MgBrCl in this application demonstrated a remarkable difference in the 1,2-migratory ability of the ^{t}Bu ligand. On the other hand, this tendency is completely reversed in the results obtained for several different alkyl ligand-bearing zincate reactions (R: Et and ^{i}Pr) of LiCl versus MgBrCl.[6]

The homologation strategy employing zincate·2LiCl/$B(OMe)_3$ is limited to the preparation of 1-*t*-butylisoquinoline derivatives,



Scheme 1. Result for the reactions of isoquinoline with Li(^{t}Bu$_2$TMPZn)·2X and $B(OMe)_3$ in THF. Reagents and conditions: (a) excess H_2O, 30 min, 96%; (b) ventilation, 1 h, 94%.

whereas the other strategy using zincate·2MgBrCl/$B(OMe)_3$ can be generally applied to synthetic methods for most of the other 1-alkylisoquinoline derivatives.

As key structural units in many important natural products[7] and pharmaceuticals,[8,9] isoquinoline derivatives such as 1-alkylisoquinoline and 1-alkyl-3,4-dihydroisoquinoline are typically obtained through Pomeranz–Fritsch reaction[10] and Bischler–Napieralski reaction.[11] These types of reactions normally require more than a single step to prepare the expected products, together with drastic reaction conditions. In contrast, the zincate reactions described herein offer the advantage of successfully achieving the homologations of **Iq** through one-pot reaction under mild condition. Furthermore, this method allows the production of each 1-alkylisoquinoline and its 3,4-reduced derivative under the identical reaction condition and selective control of work-up methods when an alkyl ligand is the *sec*-alkyl group. This result is of particular interest as there is no precedent for a generally applicable

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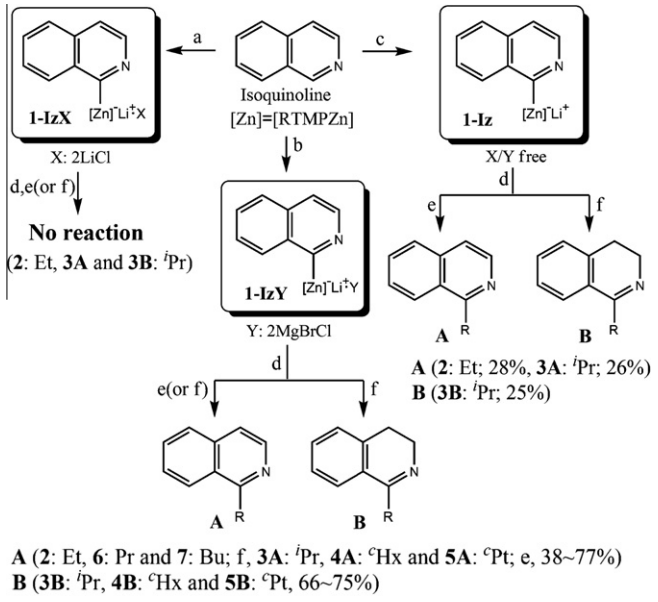
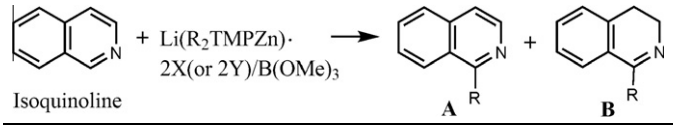
http://dx.doi.org/10.1016/j.tetlet.2012.05.002



Scheme 2. Synthetic scheme for 1-alkylisoquinoline derivatives. Reagents and conditions: (a) Li(R_2TMPZn)·2LiCl (2.2 equiv), THF, rt, 3 h; (b) Li(R_2TMPZn)·2MgBrCl (2.2 equiv), THF, rt, 3 h; (c) Li(R_2TMPZn) (2.2 equiv), THF, rt, 3 h; (d) $B(OMe)_3$ (1.2 equiv), 3 h; (e) ventilation, 1 h; (f) excess H_2O, 5–30 min.

Table 1
The conversion of isoquinoline into products **A** and **B**[a]



Entry/ product	R	Work-up condition[b]	Yield[c] (A:B, %)		
			X: LiCl	Y: MgBrCl	X/Y free[d]
1/**1A**	^{t}Bu	V	**94**:0[3]	NR[e]	–
2/**1B**	^{t}Bu	W	0:**96**[3]	NR	–
3/**2**	Et	W or V	NR	**64**:0	**28**:0
4/**3A**	^{i}Pr	V	NR	**77**:8	**26**:10
5/**3B**	^{i}Pr	W	NR	10:**75**	8:**25**
6/**4A**	^{c}Hx[f]	V	–	**72**:6	–
7/**4B**	^{c}Hx	W	–	10:**75**	–
8/**5A**	^{c}Pt[g]	V	–	**67**:4	–
9/**5B**	^{c}Pt	W	–	5:**66**	–
10/**6**	Pr	W or V	–	**42**(**52**)[h]:0	–
11/**7**	Bu	W or V	**37**:0[3,i]	**38**:0	–
12/**8**	Me	W or V	NR	NR	–

[a] Reactions carried out in anhydrous THF at rt.
[b] W: rapid work-up of the reaction mixture with excess water; V: ventilation of the reaction mixture by removal of a sealing septum from the reaction flask.
[c] The isolated yield of **A** and **B** after purification by column chromatography.
[d] The reaction yield in the absence of LiCl and MgBrCl.
[e] NR: No reaction occurred.
[f] ^{c}Hx: Cyclohexyl.
[g] ^{c}Pt: Cyclopentyl.
[h] The yield for the reaction of the Iq·BF_3 complex with Li(Pr_2TMPZn)·2Y.
[i] The overall yield for the butylzincate reaction before/after addition of $B(OMe)_3$.

one-pot homologation method of **Iq** in organozincate chemistry. Therefore, we specially examined the $B(OMe)_3$-induced homologation reactions of isoquinoline with various Li(R_2TMPZn)·2MgBrCl compounds and herein report the subsequent results.

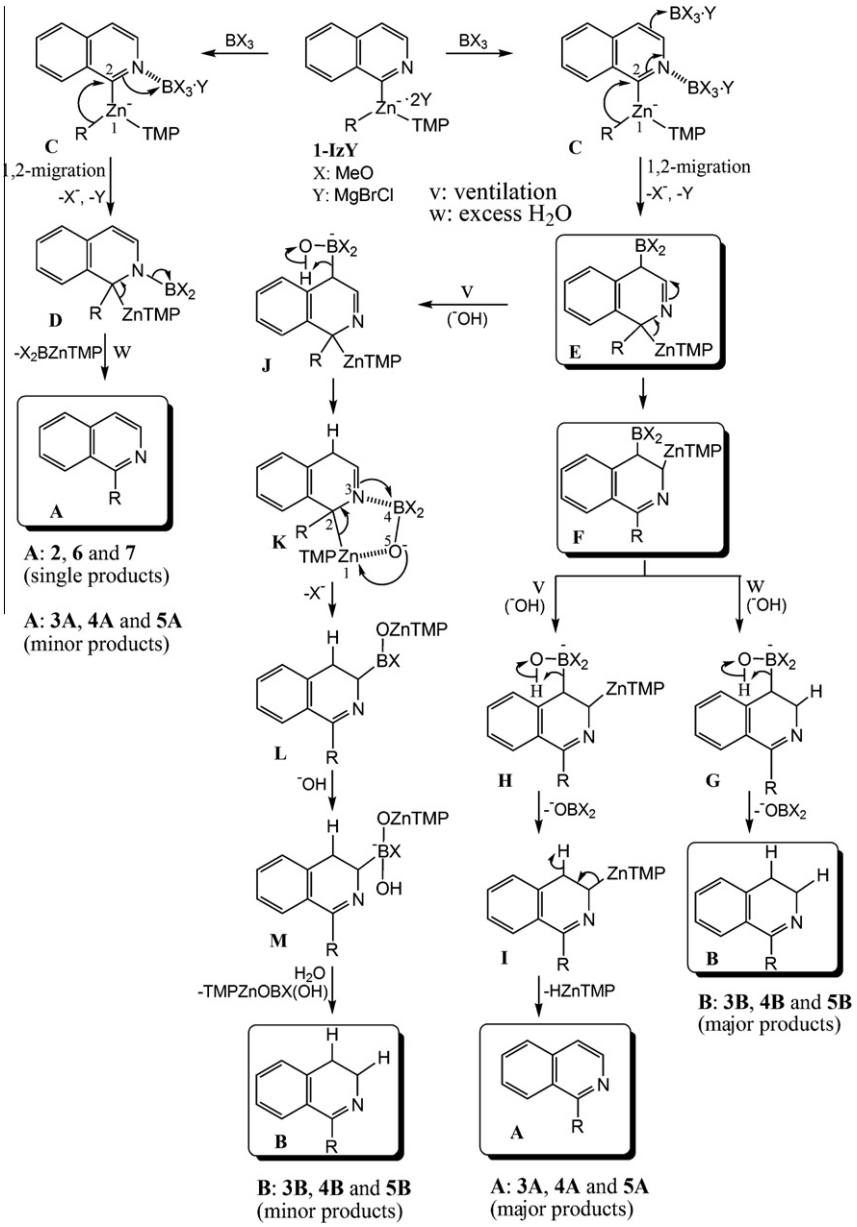
The present work is outlined in Scheme 2 and summarized in Table 1. The one-pot homologation strategy began with the DoM reaction of **Iq** with various lithium dialkyl-TMP-zincates (2.2 equiv). Regioselective metalation reactions quantitatively produced the lithium 1-isoquinolylzincate intermediates (**1-IzX**, **1-IzY**, and **1-Iz**) in THF within 3 h as shown in Scheme 2. Subsequent trimethyl borate-induced reactions of **1-IzX** (R: Et and ^{i}Pr, X: 2LiCl) were unsuccessful, leading to the sole recovery of **Iq**.

On the other hand, the corresponding reactions of **1-IzY** (R: Et and ^{i}Pr, Y: 2MgBrCl) produced the desired products **2, 3A**, and **3B** in good yields (Scheme 2 and Table 1, entries 3–5). Those reactions were completed within 3 h and did not produce any products without adding $B(OMe)_3$ to the reaction mixture of **1-IzY**. A minimum requirement (1.2 equiv) of $B(OMe)_3$ was necessary to complete the reaction. As for the zincate reactions including sterically less hindered primary alkyl ligands, such as ethyl (Et), propyl (Pr), and butyl (Bu) groups, 1-alkylisoquinolines (**A**) were only observed and no reductive alkylation products (**B**) were detected, regardless of the choice of the two separate work-up procedures. The following two experimental work-up conditions can be recommended based on these results: quickly quench the reaction and work-up the reaction mixture with an excess of H_2O comparable to the solvent (THF) volume (W in Table 1), and slowly supply moisture for the reaction mixture through ventilation for 1 hour (V in Table 1).The reaction mixture is ventilated by removal of a sealing septum from the reaction flask. The reaction of **1-IzY** (R: Et) with $B(OMe)_3$ generated **2**[12] as the single major product (Scheme 2 and Table 1, entry 3).

As for the cases concerned with sterically more hindered secondary alkyl and cycloalkyl ligands, such as isopropyl (^{i}Pr), cyclohexyl (^{c}Hx), and cyclopentyl (^{c}Pt) groups, **A** and **B** can be selectively formed as the major products according to the adopted work-up method. This pattern is very similar to that of the case for the ^{t}Bu ligand as illustrated in Scheme 1 (Table 1, entries 1 and 2, X: LiCl).[3] Thus, the respective work-up methods for the isopropylzincate reaction facilitated the generation of each of **3A**[13] and **3B**[14] (Scheme 2 and Table 1, entries 4 and 5; Y: MgBrCl). The **1-IzY** reactions possessing *sec*-alkyl ligands always produced **A** or **B** as the minor products below 10% yields under the respective work-up conditions (Table 1, entries 4–9), unlike the case of the ^{t}Bu ligand.

The presented results of the **1-IzY** reactions contrast with those of the **1-IzX** reactions in Scheme 2 and Table 1 (entries 1–5). These results pose two curious questions: what are the functions of LiCl and MgBrCl in the reactions of **1-IzX** and **1-IzY** with $B(OMe)_3$; and how are **A** and **B** formed together under each different work-up condition? The latter question is addressed later by the reaction mechanism illustrated in Scheme 3.

To elucidate the functions of such inorganic salts in this application, the following experiments were carried out. First, the salt-free reactions of **1-Iz** with $B(OMe)_3$ were investigated (Scheme 2 and Table 1, entries 3–5). **1-Iz** was prepared by the deprotonation reaction of **Iq** with Li(R_2TMPZn) which can be obtained from the reaction of the commercially available R_2Zn (R: Et and ^{i}Pr) with LiTMP. These salt-free reactions were partially successful, leading to the production of **2**–**3B** in 25–28% yields, whereas the corresponding reactions of **1-IzX** (X: LiCl) were not at all. These poor yields of **2**–**3B** were attributed to the predominant nucleophilic addition of R from excess Li(R_2TMPZn) (1.2 equiv) to $B(OMe)_3$ over the 1,2-migration of R from **1-Iz**. The results for the **1-IzX** reactions, however, showed that the 1,2-migration of alkyl ligands was completely inhibited in the presence of LiCl. LiCl initially forms the coordinative complex with $B(OMe)_3$ prior to the coordination of $B(OMe)_3$ with the sp^2-nitrogen of **1-IzX**. This complex, possibly $B(OMe)_3{\cdot}(LiCl)_n$ (n = 1 or 2), is extremely electrophilic and hence predominantly undergoes nucleophilic attack by the labile alkyl ligands (Et and ^{i}Pr) from excess Li(R_2TMPZn). Therefore, the formation reactions of products **2**–**3B** could not proceed at all. Nonetheless, the excellent results for the ^{t}Bu ligand (Table 1, entries 1 and 2; X: LiCl) is unusual. The ^{t}Bu ligand proved to be the powerful 1,2-migrating group in the formation reactions of **1A** and **1B**. The ^{t}Bu ligand is not labile, so that it cannot undergo nucleophilic addition to the $B(OMe)_3$·LiCl complex.



Scheme 3. Proposed mechanisms for the formation of **2**–**7** from **1**-**IzY**.

The other experiment was to investigate the substitution effect of MgBrCl with $MgCl_2$ and $MgBr_2$ under the identical reaction condition. Both $MgCl_2$ and $MgBr_2$ (2.2 equiv for **Iq**) were generated by the reactions of $ZnCl_2$/2RMgCl and $ZnBr_2$/2RMgBr, respectively. When MgBrCl was replaced by $MgCl_2$, this method failed to produce reproducible yields of **3A** and **3B** due to the limited solubility of $MgCl_2$ in THF. A considerable amount of precipitated $MgCl_2$ was observed during the preparation of $^{i}Pr_2Zn$. It was gradually dissolved in the THF as the amount of $B(OMe)_3$ added to the reaction mixture was increased. This indicated that a coordinative complex was formed between the insoluble $MgCl_2$ and $B(OMe)_3$ and that this complex became soluble in THF. In this regard, a similar result is observed in the literature method for preparing the complex, $Mg(OEt)_2{\cdot}B(OMe)_3$.[15] $Mg(OEt)_2$ was practically insoluble in alcohol solvents and most of $Mg(OEt)_2$ became soluble in alcohols after the addition of $B(OMe)_3$ to the reaction mixture, resulting in the formation of the 1:1 complex. This complex formation reaction was noticeably exothermic. However, the use of $B(OMe)_3$ (1.2 equiv) was not effective for the formation of **3A** and **3B**, and recorded yields of only ca 5–10%. These yields were slightly improved to ca 30–40% when 8 equiv of $B(OMe)_3$ were used in this application. The homologation strategy employing $MgCl_2$ required the use of a large amount of $B(OMe)_3$/THF and therefore, was not efficient. Its precipitation was not observed in THF when MgBrCl was substituted with $MgBr_2$. Its **1**-**IzY** reaction (R: Et) produced **2** in 45% yield, which was lower than that of the MgBrCl reaction (Table 1, entry 3). In general, the corresponding reactions of $MgBr_2$ need $ZnBr_2$, which is relatively expensive as compared to $ZnCl_2$. Based on the combined experimental results of **1**-**IzY**, the homologation strategy employing MgBrCl was demonstrated to be the best among the three strategies described above.

The coordination pattern of MgBrCl with $B(OMe)_3$ is expected to be different from the case of LiCl even though the exact structures of these coordinative complexes are not clear. The metal ion of MgBrCl coordinates with the oxygen atom(s) of $B(OMe)_3$ in a similar manner to that of LiCl. At the same time, one of its halide ions presumably coordinates with the electrophilic boron atom, unlike the case of LiCl. The dual coordination between MgBrCl and

$B(OMe)_3$ may lead to the production of the 1:1 complex like the complex, $Mg(OEt)_2{\cdot}B(OMe)_3$.[15] This complex is not only less electrophilic but also more sterically hindered than the LiCl complex, and is presumably not susceptible to nucleophilic attack by alkyl ligands from excess zincates, leading to stable formation of the subsequent complex between **1-IzY** and $MgBrCl{\cdot}B(OMe)_3$. In this application of the ^{t}Bu ligand, the steric hindrance between the borate complex and 1-(^{t}BuTMPZn) group of **1-IzY** is too large to allow access of this complex to the ring nitrogen atom, which prevents any production of **1A** or **1B** (entries 1 and 2).

This MgBrCl complex was exclusively applied to other homologation reactions as shown in Table 1 (entries 6–12). The results for the ^{c}Hx and ^{c}Pt ligands were analogous to that of the ^{i}Pr ligand and also showed the expected products **4A**[16], **4B**[17], **5A**,[18] and **5B**[19] in good yields (entries 6–9). Although compound **5A** was specified in the literature,[18] its spectral data remain unknown.[20] The yields for the Pr and Bu ligands (42% and 38% yields, entries 10 and 11, respectively) were relatively lower than that of **2** (entry 3). As they are probably more labile than the Et ligand, these ligands undergo an easier nucleophilic addition to the $B(OMe)_3$ complex. The reactions for the Pr and Bu ligands required a rapid work-up within 5 min, unlike the reactions for the other ligands. Otherwise, an inseparable mixture of products was formed for the prolonged work-up time (30 min). The alternative preparation method[3] employing the **Iq**$\cdot BF_3$ complex and $Li(Pr_2TMPZn){\cdot}2MgBrCl$ improved the yield of **6**[21] (52%, entry 10), even though the yields of the corresponding reactions for the other ligands were still low in the range of 18–41%. However, this method afforded only the single major product **6** and was not sensitive to the prolonged work-up time. Especially, product **7**[22] was initially formed from the reaction for Bu ligand/LiCl[3] in ca 20% yield, even without $B(OMe)_3$.On the other hand, this product was not generated in the corresponding reaction of MgBrCl without the presence of $B(OMe)_3$ (entry 11). This result indicates that MgBrCl acts to restrict direct addition of the labile Bu ligand from excess $Li(Bu_2TMPZn)$ into isoquinoline.

Finally, this homologation strategy was unsuccessful in the reactions for methyl and aryl ligands. **1-IzY** possessing the methyl ligand demonstrated inactivity for the 1,2-migratory addition and, therefore, was not converted into product **8**[22] at all (entry 12; X and Y). The Me ligand does not seem to be sufficiently nucleophilic to facilitate 1,2-migratory addition. Although the results are not shown in Table 1, the aryl (Ph and 4-Cl-Ph, Y) ligands also proved extremely labile as in the previously reported example (Ph, X).[3] Such arylzincate reactions gave the 1:1 **Iq**·triarylborane complexes as the major products instead of the desired products. All the spectral data of the prepared compounds (**2**–**4B** and **5B**–**7**) were identical to those in the reference data.[12–14,16–19,21,22] The structure of compound **5A** was also confirmed by IR, NMR, and high resolution mass spectroscopic analyses.[20]

This present evaluation of the 1,2-migratory ability of the ligands in **1-IzY** revealed a migratory aptitude in the following order: *sec*-R (alkyl group) > *pri*-R >> Me. The order of a migratory aptitude for *tert*-alkyl (^{t}Bu) ligand could not be defined in this series because its inactive nature was attributed to the steric hindrance of $MgBrCl{\cdot}B(OMe)_3$ complex, unlike the case of Me ligand. The ^{t}Bu group was the most effective 1,2-migrating group in a series of ligands in **1-IzX**. These two ligands, ^{i}Pr and Et, were extremely labile in this series, and hence predominantly underwent nucleophilic addition to the $B(OMe)_3{\cdot}LiCl$ complex. In addition, the Me ligand was the most non-transferring alkyl group for the 1,2-migratory addition and the nucleophilic addition to $B(OMe)_3$ in both series.

The reaction mechanisms for the formation of **2**–**7** are proposed in Scheme 3, and proceed through 3- to 7-step processes from **1-IzY**. The following mechanism is for the major production of **A** (**2**, **6**, and **7**) possessing primary alkyl groups: (1) coordination of $B(OMe)_3{\cdot}Y$ (Y: MgBrCl) with the sp^2-nitrogen of **1-IzY**, (2) 1,2-migratory addition of the alkyl ligand from **C**, and (3) subsequent reformation of the aromatic ring through loss of the $(MeO)_2BZnTMP$ group from **D**. The $B(OMe)_3{\cdot}Y$ complex plays an important role in enhancing electrophilicity at the 1-carbon, and stimulating movement of the nucleophilic alkyl ligand to the corresponding position of **1-IzY**. The elimination pattern of $(MeO)_2BZnTMP$ is similarly observed in the formation mechanisms of 1-butylisoquinoline and 2-*t*-butylquinoline, as previously reported.[3] **1-IzY** possessing *sec*-alkyl ligands can be partially converted into **A** type of minor products (**3A**, **4A**, and **5A**) due to the insufficient steric hindrance between R (^{i}Pr, ^{c}Hx, and ^{c}Pt) and ZnTMP groups of **D**, even under the work-up condition (W) applied for excess H_2O.

As for both reductive alkylation and alkylation mechanisms for the major production of **B** (**3B**, **4B**, and **5B**) and **A** (**3A**, **4A**, and **5A**), these mechanisms involve the same pathways as those previously reported for the formation of compounds **1A** and **1B**.[3] The production mechanism for **B** proceeds through a 4-step process from **C**: (1) 1,2-migratory addition of R from **C**, (2) further migration of the ZnTMP group to a 3-carbon, (3) rapid hydrolytic cleavage (W) of C-Zn bond, and (4) final C-B bond cleavage at the 4-position of intermediate **G**. The steric repulsion between the *sec*-alkyl and ZnTMP groups caused by 1,2-migration facilitated further migration of the ZnTMP group to quickly produce **F**.

The following mechanism for major formation of **A** involves a 3-step process from **F**: (1) production of **H** by nucleophilic addition of hydroxide ion to a boron atom, (2) preferential benzylic C—B bond cleavage via internal electrophilic substitution (S_Ei),[23] and (3) subsequent re-aromatization through elimination of HZnTMP from **I**. The ventilation work-up method (V) allowed the production of the hydroxide ion derived from H_2O and predominated the preferential hydroxide ion-promoted C—B bond cleavage at a 4-carbon prior to C—Zn bond cleavage at a 3-carbon of **H**, thereby generating the precursor **I**.[3,23]

Finally, the mechanism for minor formation of **B** (**3B**, **4B**, and **5B**) is proposed in Scheme 3, proceeding through a 5-step process from **E**: (1) production of **J** by nucleophilic addition of hydroxide ion to a boron atom, (2) preferential C—B bond cleavage followed by re-coordination of borate moiety with sp^2-nitrogen, (3) rearrangement of the ZnTMP group to an oxide ion of borate moiety through cyclic transition state from **K**, (4) repeated nucleophilic addition of hydroxide ion to a boron atom of **L**, and (5) final hydrolytic cleavage of the C-B bond of **M**. The species **E** is not completely transformed into **F** due to the limited steric hindrance between the *sec*-R and ZnTMP groups. Thus, the remaining species **E** is converted into **K** via **J** under ventilation condition (V). A re-coordination of borate moiety with **K** followed by formation of a 5-membered cyclic structure possibly facilitates intramolecular rearrangement of the ZnTMP group, which is then transformed into the more stable conjugated species **L**. The hydrolytic cleavage of the C—B bond from **M** leads to the formation of reductive alkylation products **B** (**3B**, **4B**, and **5B**) as minor products in 5–10% yields, even under ventilation condition. Consequently, each of the two separate work-up methods allowed minor production of **A** or **B** in this application, as illustrated in Scheme 3.

In conclusion, one-pot homologation reactions of isoquinoline were efficiently achieved in the presence of the trimethyl borate/MgBrCl complex via directed *ortho* metalation and a 1,2-migratory addition reaction. The role of the $B(OMe)_3$/MgBrCl complex in the presented reactions was explained by the selected experimental results. These types of homologation reactions were generally applicable to the synthetic method for 1-alkylisoquinoline derivatives in the field of zincate chemistry. The migratory aptitude of the ligands was clearly determined by evaluating the 1,2-migratory ability of the ligands in **1-IzY**. The specific formation mechanisms for compounds **2**–**7** were also suggested.

Acknowledgments

The authors are very grateful to the Molecular Imaging Research Center (Korea Institute of Radiological & Medical Sciences, Seoul 139–706) for the kind support of their NMR facilities. This work was supported by a special research grant from Seoul Women's University (2012).

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20. *Spectral data of* ***5A****:* pale yellow oil; IR ($CHCl_3$) 3020, 2958, 1624, 1589, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49–8.47 (d, J = 5.7 Hz, 1H, Ph), 8.28–8.25 (d, J = 8.2 Hz, 1H, Ph), 7.84–7.81 (m, 1H, Ph), 7.70–7.65 (m, 1H, Ph), 7.63–7.57 (m, 1H, Ph), 7.50–7.49 (d, J = 5.4 Hz, 1H, Ph), 4.10–4.00 (qt, J = 8.3 Hz, 1H, CH), 2.20–2.04 (m, 4H, $2CH_2$), 1.98–1.76 (m, 4H, $2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 141.8, 136.2, 129.6, 127.4, 127.2, 126.8, 125.2 118.9, 43.0, 32.8, 26.1 ppm; HRMS (CI) m/z calcd for $C_{14}H_{16}N$ (MH^+): 198.1283; found: 198.1284.
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