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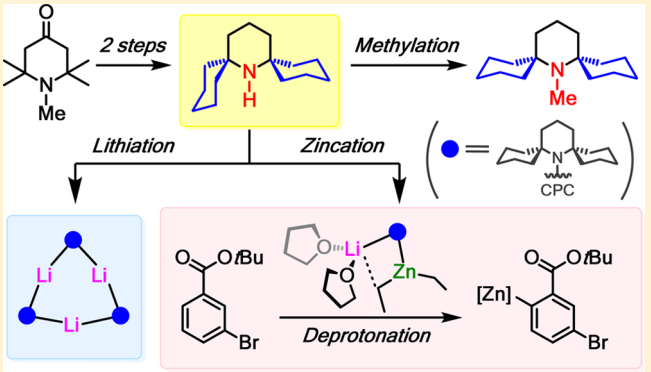
Synthesis of a Sterically Demanding Dispiropiperidine and Its Application in Monoamidodialkyl Zincate Complexes

Shogo Morisako, Rong Shang, and Yohsuke Yamamoto*

Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan

Supporting Information

ABSTRACT: The new sterically hindered piperidine analog, dispiro[cyclohexane-2,2′-piperidine-6′,2″-cyclohexane] (CPC-(H), **2**), and its *N*-methylated derivative CPC(Me) (**3**) were synthesized from commercially available starting materials in short steps. The *N*-lithiated amide LiCPC (**4**) was also isolated from **2** as a cyclictrimer in single crystals and showed slightly larger steric hindrance than that of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in the competitive methylation reaction with methyl trifluoromethanesulfonate. In addition, the heterobimetallic heteroleptic zincate complexes [Li(μ-NR_2)(μ-Et)Zn(Et)] (NR_2 = CPC, **5**, and NR_2 = TMP, **6**) were obtained as THF- and TMEDA-coordinated monomer **5**·$(THF)_2$, **6**·$(THF)_2$, **5**·**TMEDA**, and **6**·**TMEDA** (THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine). These molecular structures bearing different amido ligands in single crystals showed little structural differences from crystallographic studies. Diffusion-ordered spectroscopy (DOSY) revealed that the solution structures of the zincate complexes **5**·$(THF)_2$ and **6**·$(THF)_2$ only differ in the number of coordination THF molecules. In the deprotonation reactions with *tert*-butyl 3-bromobenzoate, the zincate complexes containing the CPC ligand [Li(μ-CPC)(μ-R)Zn(R)] (R = Et (**5**), *t*Bu) showed moderately improved regioselectivity for the 6 position in comparison to those containing the TMP ligand [Li(μ-TMP)(μ-R)Zn(R)] (R = Et (**6**), *t*Bu).



INTRODUCTION

Direct C−H metalation is a powerful tool for synthesizing highly functionalized aromatics in fields of functional materials and pharmaceuticals.[1] Besides common deprotonation methods that include the employment of strong Brønsted bases such as alkyllithium and lithium amides,[2] heterobimetallic heteroleptic ate compounds have attracted attention in recent years.[3] In particular, the lithium dialkyl(amido)zincate reagents such as [Li(TMP)Zn(tBu)$_2$] (TMP = 2,2,6,6-tetramethylpiperidino), first reported by Kondo and Uchiyama et al.,[4] offer complementary reactivity and improved regio- and chemoselectivity with high functional group tolerance in certain cases.[5,6] The steric bulk of amido ligands used in these zincate reagents have been recently shown to play a decisive role in the reactivity and regioselectivity of C−H metalation (Figure 1).[7,8]

Despite of their crucial role and wide applications in synthetic organic chemistry, the library of sterically hindered secondary amides remains rather small, with diisopropylamide (DA), 1,1,1,3,3,3-hexamethyldisilazide (HMDS), and TMP being the mostly used amides (Figure 2).[9] Among these reagents, TMP is preferred as it offers higher stability,[10,11] larger steric bulk,[9,12] and the highest basicity as the lithium amide.[9]

This work aims to synthesize new sterically demanding secondary amide, dispiro[cyclohexane-2,2′-piperidine-6′,2″-cyclohexane]-1′-ide (CPC), which may offer comparable or additional steric bulk than that from TMP as alternatives for direct deprotonation reactions (Figure 2). Herein, the synthesis

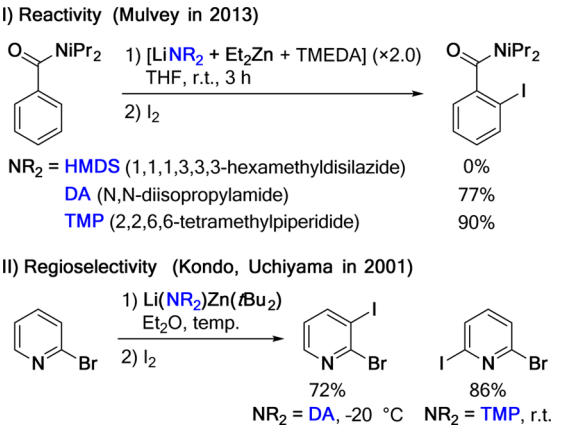


Figure 1. Selected examples demonstrating the effect of different amido ligands on reactivity and regioselectivity of C−H activation: Iodination of (I) *N*,*N*-diisopropylbenzamide and (II) 2-bromopyridine.

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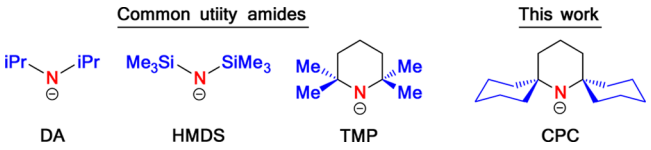


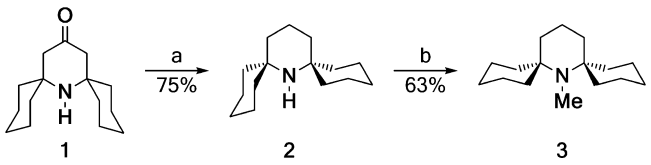
Figure 2. Chemical structures of large sterically hindered secondary amides.

of CPC and its application in C−H metalation with zincates are reported.

RESULTS AND DISCUSSION

The parent amine dispiro[cyclohexane-2,2′-piperidine-6′,2″-cyclohexane] (CPC(H), **2**) was synthesized from the previously reported ketone **1**.[13] A Wolff−Kishner−Huang reduction[14] of ketone **1** afforded **2** in 75% yield (Scheme 1).

Scheme 1. Synthesis of Dispiropiperidine Derivatives CPC(H) 2 and CPC(Me) 3



[a]Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, DMSO, 60 °C, 1 h; then KOH, 130 °C, 2 h; then reflux, 8 h. (b) $HO(CH_2O)_nH$, HCO_2H, toluene, 130 °C, 12 h; then NaOH, rt, 1 h. DMSO = dimethyl sulfoxide. $HO(CH_2O)_nH$ = paraformaldehyde.

The amine **2** can be methylated by treatment with paraformaldehyde and formic acid[15] to provide 1′-methyldispiro-[cyclohexane-2,2′-piperidine-6′,2″-cyclohexane] (CPC(Me), **3**) in 63% yield.

The ^1H and $^{13}C\{^1H\}$ NMR spectra of **2** and **3** are unremarkable, with all signals lying within the expected range. Their structures were confirmed by X-ray crystal structure analyses. Their solid-state molecular structures are shown in Figure 3a and 3b. In both structures, all cyclohexyl groups assume the chair conformation. The parent amine **2** has an asymmetric structure, with one cyclohexyl ring equatorial and the other axial with respect to the C−N bond. The methyl derivative **3** has a symmetric structure in the solid state, with both cyclohexyl rings folded back, assuming equatorial positions. This might be due to the repulsions between the *N*-methyl and the cyclohexyl hydrogen atoms. Results from variable-temperature (VT) NMR experiments and preliminary DFT calculation on the energy gaps of possible conformational isomers of **2** and **3** suggested fluxional behaviors of **2** and nonfluxional behavior of **3** below room temperature (see SI, S16, S17, S26, and S27).

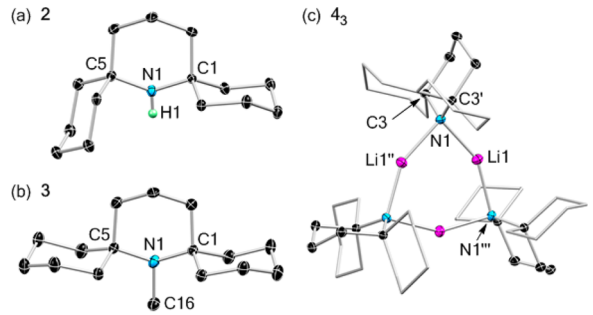


Figure 3. Molecular structures of (a) **2**, (b) **3**, and (c) **4** obtained from single-crystal X-ray diffraction analyses. Thermal ellipsoids are displayed at 30% probability. Hydrogen atoms except N−H are omitted for clarity. Selected bond angles (degrees) for CPC(H) (**2**): C1−N1−C5 121.5(2), C1−N1−H1 111(2), C5−N1−H1 118(3). Selected bond angles (degrees) for CPC(Me) (**3**): C1−N1−C5 120.0(2), C1−N1−C16 112.8(2), C5−N1−C16 113.5(2). Selected bond lengths (Angstroms) and angles (degrees) for $(LiCPC)_3$ (**4**): N1−Li1 2.003(3), N1−Li1″ 2.064(3); C3−N1−C3′ 116.2(2), Li1−N1−Li1″ 88.7(2), N1−Li1−N1‴ 151.3(2). There are two independent molecules in the asymmetric unit of **3**, and one of these is shown.

In order to compare the steric effects of the methyl- and cyclohexyl-substituted derivatives, a competitive methylation reaction between TMP(H) and CPC(H) (**2**) was carried out (Scheme 2). A 1:1 mixture of both amines was lithiated completely at 0 °C with a slight excess of *n*BuLi (2.01 equiv). Then 0.95 equiv of MeOTf was added at 0 °C. The reaction mixture was stirred at the same temperature for 12 h before being quenched with *i*PrOH. The product mixture contained 56% 1,2,2,6,6-pentamethylpiperidine (PMP) and 44% **3** (results from repetition reactions are shown in Table S1, S-5). This suggested that LiCPC reacted only slightly more slowly than LiTMP, most likely due to the larger and more flexible cyclohexyl groups of **4**.

Before carrying out C−H metalations with substrates, we isolated and structurally characterized the lithium dialkyl(amido)zincate using both CPC and TMP for a detailed comparison. The zincates $[Li(\mu\text{-}NR_2)(\mu\text{-}Et)Zn(Et)]$ (NR_2 = CPC, **5** and NR_2 = TMP, **6**) were obtained by addition of the commercially available $ZnEt_2$ to a freshly prepared lithium amide suspension ($LiNR_2$, NR_2 = CPC and TMP; Scheme 3). Recrystallization from a THF/hexane solution mixture afforded the respective solvated monomeric zincates, $[(THF)_2Li(\mu\text{-}NR_2)(\mu\text{-}Et)Zn(Et)]$ (NR_2 = CPC, **5**·$(THF)_2$ and NR_2 = TMP, **6**·$(THF)_2$) as colorless crystals in moderate yields (Scheme 3).

The bonding parameters of **5**·$(THF)_2$ and **6**·$(THF)_2$ in the solid state are very similar (Figure 4a and 4c). Their structures resemble those previously reported lithium dialkyl(amido)-zincates.[17] The amide coordinates to both metal centers. The lithium cation is stabilized by an α-(CH_2) group of the diethyl zinc and two THF molecules, forming a planar four-membered Li−N−Zn−C cyclic structure. The N−Zn distance of 2.062(2) Å in **5**·$(THF)_2$ is longer than that of **6**·$(THF)_2$ [2.041(2) Å], while the N−Li distances in **5**·$(THF)_2$ [2.022(3) Å] and **6**·$(THF)_2$ [2.018(5) Å] are X-ray crystallographically indistinguishable.

The *N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) coordinated lithium dialkyl(amido)zincates $[(TMEDA)Li(\mu\text{-}NR_2)(\mu\text{-}Et)Zn(Et)]$ were also isolated for structural comparison. A recrystallization of the THF solvated zincate in neat

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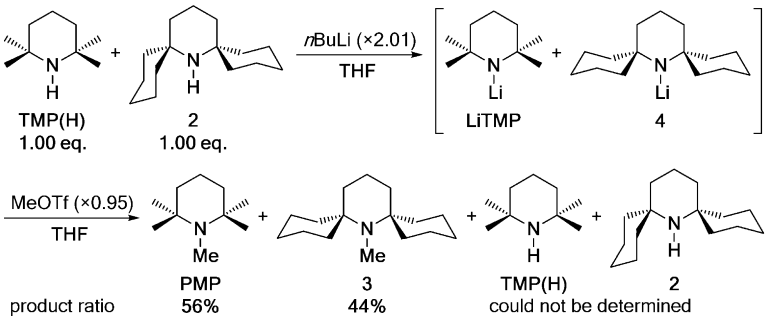
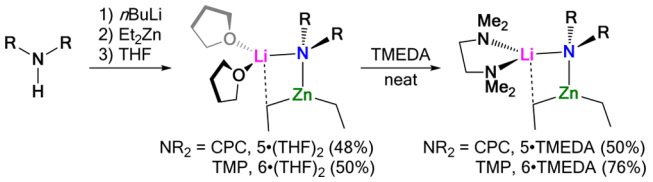
Scheme 2. Competitive Methylation Reaction



[a]The product ratio of PMP to **3** was determined from the ^{1}H NMR spectrum of the crude product mixture. The product ratio of TMP(H) to **2** could not be determined by ^{1}H NMR of the crude product mixture because of the overlapping of the signals corresponding to both compounds. Reagents and conditions: (lithiation) *n*BuLi × 2.01 equiv of THF, 0 °C, 1 h; (methylation) MeOTf × 0.95 equiv of THF, 0 °C, 12 h; then *i*PrOH. OTf = trifluoromethanesulfonate.

Scheme 3. Preparation of THF-Solvated Monomeric Zincates 5·(THF)$_2$ and 6·(THF)$_2$



TMEDA afforded [(TMEDA)Li(μ-NR$_2$)(μ-Et)Zn(Et)] (NR$_2$ CPC, **5·TMEDA** and NR$_2$ = TMP, **6·TMEDA**) as needle-shaped colorless crystals (Figure 4b and 4d). In these TMEDA-coordinated structures, the N−Li and N−Zn distances of **5·TMEDA** and **6·TMEDA** are crystallographically identical. However, in comparison to the THF-solvated analogues, the N−Li distances in **5·TMEDA**, [2.058(5) Å] and **6·TMEDA** [2.042(5) Å] are marginally longer. The N−Zn distance of 2.066(2) Å in **6·TMEDA** is only slightly longer than that of **6·(THF)$_2$** [2.041(2) Å], while the N−Zn distance in **5·TMEDA** [2.067(2)] is identical to that observed in **5·(THF)$_2$**.

The ^{1}H and ^{13}C{^{1}H} spectra of **5·(THF)$_2$** and **6·(THF)$_2$** are generally unremarkable. At room temperature, only one set of signals was observed from the two ethyl moieties. The ^{7}Li NMR chemical shifts of **5·(THF)$_2$** and **6·(THF)$_2$** in C_6D_6 were observed at 1.42 and 1.03 ppm, respectively, lying in higher fields than those observed for the lithium amide complexes (**4**, 2.75 ppm; (LiTMP)$_n$, 2.47 ppm).[16a]

To gain a better understanding of the solution behavior in the reaction solvent THF, DOSY ^{1}H NMR studies of **5·(THF)$_2$** and **6·(THF)$_2$** were carried out in THF-d_8.[7,18] The NMR spectrum shows that in solution, **5·(THF)$_2$** loses one THF on average, while **6·(THF)$_2$** frees both of its coordinating THF molecules from the Li atom in the zincate **6** (see SI, S20−S25).

As shown in Figure 1, there have been examples of C−H metalation reactions that are dependent on the zincate amido ligand. As the steric environment of the amido ligand affects the pK_a and the structure of the intermediates involved in the reaction sequence, we investigated how the newly prepared zincate **5** influenced the reactivity and/or regioselectivity of C−H metalation reactions in comparison to previously reported analogues.

We carried out the deprotonative metalation and iodination of the *tert*-butyl 3-bromobenzoate (**7**) using **5** and **6**. In

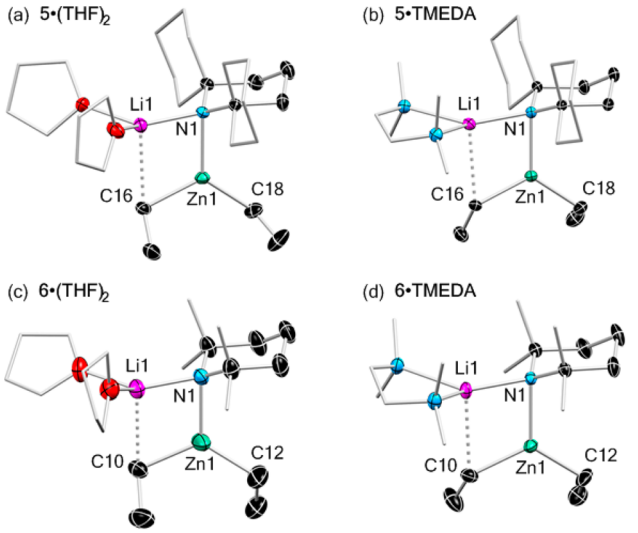


Figure 4. Molecular structures of (a) **5·(THF)$_2$**, (b) **5·TMEDA**, (c) **6·(THF)$_2$**, and (d) **6·TMEDA** obtained from single-crystal X-ray diffraction analyses. Thermal ellipsoids are displayed at 30% probability. Hydrogen atoms and some carbon atoms are omitted for clarity. Structural disorders were observed in THF and TMEDA moieties in all structures as well as in ethyl moieties of **6·(THF)$_2$**. Selected bond lengths (Angstroms) and angles (degrees) for **5·(THF)$_2$**: N1−Li1 2.022(3), N1−Zn1 2.062(2), Li1−C16 2.635(4), Zn1−C16 2.048(2), Zn1−C18 2.009(2); C1−N1−C5 116.5(2), Σ_{LiNZnC} = 360.1. Selected bond lengths (Angstroms) and angles (degrees) for **5·TMEDA**: N1−Li1 2.058(5), N1−Zn1 2.067(2), Li1−C16 2.652(6), Zn1−C16 2.036(3), Zn1−C18 2.004(3); C1−N1−C5 117.0(2), Σ_{LiNZnC} = 360.0. Selected bond lengths (Angstroms) and angles (degrees) for **6·(THF)$_2$**: N1−Li1 2.018(5), N1−Zn1 2.041(2); C1−N1−C5 114.7(2). Selected bond lengths (Angstroms) and angles (degrees) for **6·TMEDA**: N1−Li1 2.042(5), N1−Zn1 2.066(2), Li1−C10 2.649(7), Zn1−C10 2.034(4), Zn1−C12 2.005(4); C1−N1−C5 115.4(2), Σ_{LiNZnC} = 360.0;. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

compound **7**, the 2-hydrogen situated between two electron-withdrawing groups (EWG) has the highest acidity. Thus, the derivations of **7** at the 2 position are thermodynamically favored (Figure 5, Path A). With the bromine atom at the 3 position, we hypothesized that a bulky amido ligand would cast steric hindrance over the halogen, as illustrated in Figure 5 Path B, forcing the alternative facial coordination to favor the deprotonation at the 6 position.

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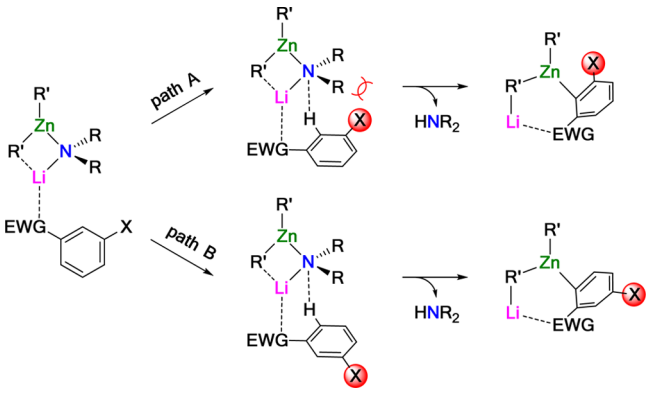


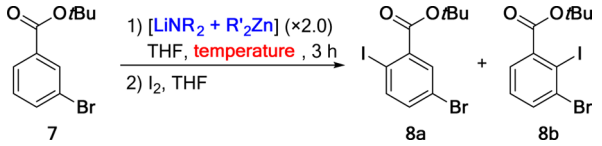
Figure 5. Proposed mechanism for deprotonative metalation of the 1,3-disubstituted benzene.[19] Path A: deprotonation at the 2 position with steric repulsion between the halogen and the amido ligand. Path B: deprotonation at the 6 position without steric repulsion. EWG = electron-withdrawing groups, X = halide.

Previously, this substrate (**7**) has been used in Uchiyama's studies on alkyl ligand-dependent selectivity and reactivity of TMP−zincates.[5a] Their study showed that the methyl−zincate favored benzyne formation (at reflux temperature), while the *tert*-butyl zincate provided the 6-iodinated product **8a** and the 2-iodinated product **8b** at room temperature in 67% and 31% yields, respectively. We carried out the same iodinating reactions to see if the newly developed amide would further promote the formation of **8a**.

The iodination reaction using **4** was carried out with Et_2Zn and tBu_2Zn independently at both elevated and reduced temperatures to optimize the yields. Parallel reactions using TMP were also performed for comparison (see Experimental Section).

In all reactions, both **8a** and **8b** were isolated. The optimized reaction conditions and results are summarized in Table 1. In combination with the Et_2Zn (Table 1, entries 1−4), the iodination of **7** at 0 °C employing Li(CPC)$ZnEt_2$ (**5**) afforded **8a** and **8b** in 64% and 11% yields, respectively (entry 2). Although this **8a**/**8b** ratio was better than that observed in the parallel reaction using LiTMP (**8a**, 45%; **8b**, 21%, entry 1), the difference in regioselectivity is not conclusive due to the low total yields (entries (1) LiTMP, 66%; (2) **4**, 75%) of the products. This is likely due to the benzyne formation, which has been observed from the reaction of **7** with Li(TMP)$ZnMe_2$ by Uchiyama et al.[5,20]

Table 1. Direct C−H Metalation of *tert*-Butyl 3-Bromobenzoate 7 with Zincates



entry	$LiNR_2 + R'_2Zn$	temp. (°C)	yield (%)[a] **8a**, **8b**	ratio[b] **8a**/**8b**
1	LiTMP + Et_2Zn	0	45, 21	2.1
2	LiCPC (**4**) + Et_2Zn	0	64, 11	5.8
3	LiTMP + Et_2Zn	−30	49,[c] 46[c]	1.1
4	**LiCPC (4) + Et_2Zn**	**−30**	**72,[c] 22[c]**	**3.3**
5	LiTMP + tBu_2Zn	0	66,[c] 30[c]	2.2
6	**LiCPC (4) + tBu_2Zn**	**0**	**77,[c] 20[c]**	**3.9**
7	LiTMP + tBu_2Zn	−30	64, 32	2.0
8[d]	LiCPC (**4**) + tBu_2Zn	−30	60, 17	2.4

[a]Isolated yield. [b]The ratio was calculated from isolated yield. [c]Average value of two times. [d]Reaction time was 12 h, and *tert*-butyl 3-bromobenzoate **7** was recovered in 17% yield. A shorter reaction time provided the higher yield of **7**.

The yield improved significantly when the iodination of **7** was repeated at −30 °C. In reactions employing Li(CPC)$ZnEt_2$ (entry 4), **8a** and **8b** were obtained in 72% and 22% yields (total yield, 94%), showing a higher regioselectivity for the 6 position. By comparison, the parallel reactions employing Li(TMP)$ZnEt_2$ afforded **8a** and **8b** in close to equal amounts, 49% and 46%, respectively (total yield, 95%). In the case of using $LiNR_2$ and Et_2Zn, the metalated intermediate, generated by C−H metalation at the 2 position on the aromatic ring, might decompose through the benzyne formation. This decomposition can be suppressed at lower temperatures or by using tBu_2Zn. Uchiyama et al. observed this benzyne formation from the reaction of **7** with Li(TMP)$ZnMe_2$ but no benzyne formation with Li(TMP)Zn$(tBu)_2$.[5a] Therefore, the yields of **8b** were higher at −30 °C (entry 3, 46%; entry 4, 22%) than those at 0 °C (entry 1, 21%; entry 2, 11%), and the ratios **8a**/**8b** were apparently lower at −30 °C (entry 3, 1.1; entry 4, 3.3) than those at 0 °C (entry 1, 2.1; entry 2, 5.8).

Similar regioselectivity can be achieved using Li(CPC)Zn$(tBu)_2$ at 0 °C (**8a**, 77%; **8b**, 20%, entry 6), moderately improved from the reaction with Li(TMP)Zn$(tBu)_2$, (**8a**, 66%; **8b**, 30%, entry 5). The regioselectivity is more affected by the alkyl ligands of zinc in the TMP zincates than in the CPC zincates. With both alkyl zinc agents, the CPC zincates consistently offered higher regioselectivity for the 6 position (kinetic product) in comparison to the TMP zincates.

CONCLUSIONS

In conclusion, we developed a convenient synthetic procedure for a new dispiropiperidine analogue, CPC(H) (**2**), from the commercially available starting materials. A direct *N*-lithiation provides the corresponding bulky amide (**4**), which may be a useful addition to the currently rather small library of sterically hindered secondary amide reagents. A preliminary reaction study on the iodination of the *tert*-butyl 3-bromobenzoate (**7**) with Li(CPC)ZnR_2 showed a moderately improved regioselectivity for the 6 position in comparison to that with the Li(TMP)ZnR_2, which suggested a slightly larger (at least comparable) steric bulk of CPC in comparison to the TMP. Applications of the bulky CPC amines in other fields as well as preparations of additional sterically hindered bases are currently in progress.

EXPERIMENTAL SECTION

General Considerations. All syntheses were carried out under inert atmosphere with standard Schlenk and glovebox techniques unless otherwise stated. Tetrahydrofuran (THF), diethyl ether (Et_2O), hexane, and toluene were freshly distilled from Na/benzophenone prior to use. Hexane was distilled from sodium followed by drying over potassium mirror and degassed three times using freeze−pump−thaw cycling and stored in an argon-filled glovebox for washing and recrystallization of **5**·$(THF)_2$ and **6**·$(THF)_2$. Dimethyl sulfoxide (DMSO) and 2,2,6,6-tetramethylpiperidine (TMP(H)) were distilled from CaH_2 and stored over 4 Å molecular sieves. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled from CaH_2. Cyclohexanone was dried over 4 Å molecular sieves. MeOTf was freshly distilled prior to use. $ZnCl_2$ was dried by heating in vacuo. 1-Phenylnaphthalene (PhN) was distilled from sodium. C_6D_6 and

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C_4D_8O (THF-d_8) were distilled from sodium followed by drying over potassium mirror and degassed three times using freeze−pump−thaw cycling and stored in an argon-filled glovebox for NMR measurements of **4**, **5**·$(THF)_2$, **6**·$(THF)_2$, **5**·**TMEDA**, **6**·**TMEDA**, and tBu_2Zn. Other chemicals were used as supplied. Column chromatography was carried out using Kanto silica gel 60N (spherical, neutral) or Merck KGaA aluminum oxide 90 acc. to Brockmann (activity II−III).

General Measurements. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^7Li NMR (155 MHz) spectra were recorded using a JEOL EX-400 or AL-400 NMR spectrometer. The ^1H and ^{13}C NMR chemical shifts (δ scale) are determined by residual protons of the solvent (^1H, CDCl3, δ = 7.26 ppm; C_6D_6, δ = 7.20 ppm; C_4D_8O, δ = 3.58 ppm) or the solvent itself (^{13}C, $CDCl_3$, δ = 77.0 ppm; C_6D_6, δ = 128.0 ppm; C_4D_8O, δ = 67.4 ppm). The ^7Li NMR chemical shifts are referenced to LiCl in D_2O at 0 ppm. Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The elemental analyses were performed using a PerkinElmer 2400CHNS elemental analyzer.

Preparation and Characterization. *CPC(H) (2).* The DMSO used in this step was not dried. Hydrazine monohydrate (0.360 mL, 7.40 mmol) was added to a solution of 7-azadispiro[5.1.5.3]hexadecan-15-one (**1**) (64.1 g, 271 mmol) in DMSO (180 mL) at 60 °C. The solution was stirred at 80 °C for 1 h before KOH (186 mg, 3.33 mmol) was added at the same temperature. The resulting mixture was heated to 130 °C for 6 h before being heated to 190 °C to remove water azeotropically (over 12 h). The resulting solution was cooled to ambient temperature before water (120 mL) and toluene (75 mL) were added. The mixture was stirred at room temperature for 1 h and acidified with aqueous HCl solution (10%, pH 1−2). The precipitate was filtered and washed with ether. The filtrate was adjusted to pH 9 using an aqueous K_2CO_3 solution and then extracted with AcOEt (4 × 400 mL). The combined organic layer was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. The filtered precipitate was added to water (ca. 1 L), and the suspension was also adjusted to pH 9 using aqueous K_2CO_3 solution and then extracted with AcOEt (4 × 400 mL). The combined organic layer was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. All AcOEt extracts were combined and concentrated under reduced pressure. The residual brown oil was preliminarily purified by column chromatography (aluminum) with AcOEt as the eluent. The resultant orange oil was further purified by distillation under reduced pressure (ca. 62 °C/0.2 mmHg) to give CPC(H) (**2**) (44.9 g, 203 mmol, 75%) as a colorless oil. After this oil was cooled at −30 °C, the oil solidified into a white solid. Recrystallization of this solid from CH_2Cl_2 at −30 °C afforded crystals suitable for X-ray crystallographic analysis. Mp 34−35 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.13−2.00 ppm (26H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.24 (C), 40.30 (CH_2), 36.08 (CH_2), 26.28 (CH_2), 22.52 (CH_2), 17.03 ppm (CH_2). Anal. Calcd for $C_{15}H_{27}N$: C, 81.38; H, 12.29; N, 6.33. Found: C, 81.77; H, 12.22; N, 6.61.

CPC(Me) (3). Formic acid (0.190 mL, 5.00 mmol) was added dropwise to a toluene (20 mL) solution of **2** (1.00 g, 4.52 mmol) and paraformaldehyde (190 mg, 6.34 mmol) at 90 °C. The reaction mixture was heated to 130 °C for 18 h with stirring followed by another hour at 100 °C before being cooled to ambient temperature, to which NaOH (108 mg, 2.70 mmol) was added as a solid. The mixture was stirred for 1 h, and the sodium hydroxide was filtered off. The solvent was concentrated, and the residual solid was purified by column chromatography (silica gel) with AcOEt as the eluent to give CPC(Me) (**3**) (155 mg, 0.698 mmol, 70%) as a white solid (R_f = 0.07). Recrystallization from CH_3CN at ambient temperature gave crystals suitable for X-ray crystallographic analysis. Mp 58−59 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (3H, s), 1.80−1.18 (24H, m), 1.10−0.91 ppm (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 56.95 (C), 33.81 (CH_2), 33.28 (CH_2), 27.10 (CH_3), 25.95 (CH_2), 23.23 (CH_2), 16.28 ppm (CH_2). Anal. Calcd for $C_{16}H_{29}N$: C, 81.63; H, 12.42; N, 5.95. Found: C, 81.81; H, 12.80; N, 6.03.

LiCPC (4). *n*-Butyllithium (1.60 M in hexane, 0.35 mL, 0.56 mmol) was added dropwise to a hexane (5.0 mL) solution of **2** (125 mg, 0.562 mmol) at 0 °C with no stirring. The still reaction mixture stood at ambient temperature for 1 h, from which colorless crystals were obtained. The reaction mixture was centrifuged at 20 °C for 2 min at a speed of 3000 rpm. The supernatant was removed by syringe. The remaining crystals were washed with hexane (5 mL), and the washing was separated and removed as described above. The remaining solid in a small amount of hexane was filtered under argon atmosphere to give LiCPC (**4**) (118 mg, 0.517 mmol, 92%) as colorless crystals suitable for X-ray crystallographic analysis. ^1H NMR (C_6D_6, 400 MHz): δ = 2.09−1.98 (2H, m), 1.80−1.13 (20H, m), 1.00−0.83 ppm (4H, m). ^{13}C NMR (C_4D_8O, 100 MHz): δ = 54.26 (C), 45.80 (CH_2), 39.70 (CH_2), 32.54 (CH_2), 28.69 (CH_2), 23.53 (CH_2), 20.29 (CH_2), 14.44 ppm (CH_2). ^7Li NMR (C_6D_6, 155 MHz, LiCl in D_2O): δ = 2.75 ppm.

THF-Coordinated Zincate Complexes, ***5**·$(THF)_2$ and **6**·$(THF)_2$.* *n*-Butyllithium (1.63 M in hexane, 1.25 mL, 2.04 mmol for **5**·$(THF)_2$, or 1.85 mL, 3.02 mmol for **6**·$(THF)_2$) was added dropwise to **2** (neat, 443 mg, 2.00 mmol for **5**·$(THF)_2$) or TMP(H) (neat, 0.500 mL, 2.96 mmol for **6**·$(THF)_2$) at −78 °C. After stirring at −78 °C for 1 h, diethyl zinc (1.06 M in hexane, 2.00 mL, 2.12 mmol for **5**·$(THF)_2$, or 3.00 mL, 3.18 mmol for **6**·$(THF)_2$) was added and the resultant slurry was warmed to ambient temperature. THF (3.0 mL for **5**·$(THF)_2$, or 2.0 mL for **6**·$(THF)_2$) was then added to the reaction mixture to give a homogeneous solution and concentrated under reduced pressure. The resultant solution was stored at −80 °C for 1 day, from which two phases formed. The top layer is a solvent mixture of THF and hexane, which is removed using a syringe. The bottom phase is frozen **5**·$(THF)_2$ or **6**·$(THF)_2$ in THF, which was stored at −30 °C for 1 day under argon atmosphere to afford **5**·$(THF)_2$ or **6**·$(THF)_2$ as a white solid. This was filtered and washed with hexane (3 × 2 mL) to afford pure **5**·$(THF)_2$ (473 mg, 0.955 mmol, 48%) or **6**·$(THF)_2$ (620 mg, 1.49 mmol, 50%). Recrystallization from hexane at −30 °C gave crystals suitable for X-ray crystallographic analysis.

5·$(THF)_2$. ^1H NMR (C_6D_6, 400 MHz): δ = 3.46 (8H, m), 2.35 (2H, d, J = 12 Hz), 2.13 (2H, m), 1.91 (6H, t, J = 8 Hz), 1.84−1.00 (30H, m), 0.58 ppm (4H, q, J = 8 Hz). ^{13}C NMR (C_6D_6, 100 MHz): δ = 68.27 (CH_2), 55.47 (C), 46.23 (CH_2), 41.69 (CH_2), 35.71 (CH_2), 26.93 (CH_2), 25.40 (CH_2), 24.42 (CH_2), 24.04 (CH_2), 18.64 (CH_2), 13.80 (CH_3), 5.81 ppm (CH_2). ^7Li NMR (C_6D_6, 155 MHz, LiCl in D_2O): δ = 1.42 ppm.

6·$(THF)_2$. ^1H NMR (C_6D_6, 400 MHz): δ = 3.42 (8H, m), 2.08−1.65 (10H, m), 1.48 (6H, s), 1.38−1.02 (16H, m), 0.51 ppm (4H, q, J = 8 Hz). ^{13}C NMR (C_6D_6, 100 MHz): δ = 68.27 (CH_2), 52.79 (C), 41.04 (CH_2), 36.19 (CH_3), 32.01 (CH_3), 25.32 (CH_2), 20.05 (CH_2), 13.56 (CH_3), 5.24 ppm (CH_2). ^7Li NMR (C_6D_6, 155 MHz, LiCl in D_2O): δ = 1.03 ppm.

TMEDA-Coordinated Zincate Complexes, ***5**·**TMEDA** and **6**·**TMEDA**.* Recrystallization of **5**·$(THF)_2$ (175 mg, 0.354 mmol) or **6**·$(THF)_2$ (154 mg, 0.370 mmol) from neat TMEDA afforded **5**·**TMEDA** (82.3 mg, 0.176 mmol, 50%) or **6**·**TMEDA** (109 mg, 0.282 mmol, 76%) as colorless crystals suitable for X-ray crystallographic analysis.

5·**TMEDA**. ^1H NMR (C_6D_6, 400 MHz): δ = 2.36−0.83 (48H, m), 0.41 ppm (4H, q, ^3J = 7.8 Hz). ^{13}C NMR (C_6D_6, 100 MHz): δ = 57.17 (CH_2), 55.46 (C), 46.84 (CH_3), 43.49 (CH_2), 43.14 (CH_2), 33.03 (CH_2), 26.36 (CH_2), 24.23 (CH_2), 23.62 (CH_2), 18.63 (CH_2), 14.34 (CH_3), 6.27 ppm (CH_2). ^7Li NMR (C_6D_6, 155 MHz, LiCl in D_2O): δ = 0.75 ppm.

6·**TMEDA**. ^1H NMR (C_6D_6, 400 MHz): δ = 2.16−1.71 (26H, m), 1.65−1.46 (2H, m), 1.25 (12H, s), 0.32 ppm (4H, q, ^3J = 7.8 Hz). ^{13}C NMR (C_6D_6, 100 MHz): δ = 57.19 (CH_2), 52.91 (C), 46.79 (CH_3), 38.66 (CH_2), 35.99 (CH_3), 33.70 (CH_3), 20.00 (CH_2), 14.24 (CH_3), 5.59 ppm (CH_2). ^7Li NMR (C_6D_6, 155 MHz, LiCl in D_2O): δ = 0.70 ppm.

Competitive Methylation Reaction. *n*-Butyllithium (1.60 M in hexane, 3.50 mL, 5.60 mmol) was added to a THF solution (28.0 mL) of TMP(H) (393 mg, 2.78 mmol) and **2** (616 mg, 2.78 mmol) dropwise at −78 °C. After addition, the reaction mixture was slowly warmed to 0 °C and stirred at 0 °C for 1 h. MeOTf (0.300 mL, 2.65 mmol) was added to the resulting suspension, and the reaction mixture was stirred at 0 °C for 12 h. The residual lithium amides were quenched by addition of *i*PrOH at 0 °C. Afterward, the solution was

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adjusted to pH 10 with aqueous HCl solution (10%) before being extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The product ratio was determined by ^1H NMR of this crude product mixture and is summarized in Scheme 2.

Deprotonative Metalation of 7. *General Procedure A with [Li(NR$_2$)ZnEt$_2$].*[7] For each 4 mmol of [Li(NR$_2$)ZnEt$_2$] (NR$_2$= CPC, **5** and NR$_2$= TMP, **6**) prepared, *n*-butyllithium (1.54 M in hexane, 2.65 mL, 4.08 mmol) was added to R$_2$N(H) (neat, 4.03 mmol) dropwise at room temperature. The resulting pale yellow suspension was stirred at room temperature for 15 min, and then THF (10 mL) was added, followed by Et$_2$Zn (1.06 M in hexane, 3.85 mL, 4.08 mmol). The resulting pale orange solution was stirred for 15 min at room temperature. After addition of *tert*-butyl 3-bromobenzoate (**7**) (514 mg, 2.00 mmol) at the reaction temperature (from −30 °C to room temperature), the reaction mixture solution was stirred for 3 h, during which the color of the solution changed to dark orange. To trap the metalated intermediate, iodine (4.09 g, 16.1 mmol) in THF (16.1 mL) was added slowly to the reaction solution at the reaction temperature. After stirring for 8 h, the reaction solution was quenched by addition of $Na_2S_2O_3$ (satd aq.) and a small amount of NH_4Cl (satd aq.) and then extracted with AcOEt (× 4). (In some cases, solids were generated which were removed by filtration before extraction.) The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and dried under reduced pressure. The residue was purified by column chromatography (silica gel) with hexane/AcOEt (15:1) as the eluent to separate *tert*-butyl 5-bromo-2-iodobenzoate (**8a**) (pale yellow oil, R_f = 0.59) and *tert*-butyl 3-bromo-2-iodobenzoate (**8b**) (pale yellow oil, R_f = 0.42). For **8a**, ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (1H, d, ^4J = 0.8 Hz), 7.77 (1H, d, ^3J = 5.1 Hz), 7.23 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz), 1.61 ppm (9H, s). For **8b**, ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (1H, dd, ^3J = 8.1 Hz, ^4J = 1.7 Hz), 7.35 (1H, dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz), 7.23 (1H, t, ^3J = 8.0 Hz), 1.61 ppm (9H, s).

General Procedure B with [Li(NR$_2$)Zn(tBu)$_2$].[5a] For each 4 mmol of [Li(NR$_2$)Zn(*t*Bu)$_2$] (NR$_2$= CPC, TMP) prepared, *n*-butyllithium (1.54 M in hexane, 2.65 mL, 4.08 mmol) was added dropwise to R$_2$N(H) (4.03 mmol) in THF (10 mL) at −78 °C. The resulting pale orange solution was stirred at room temperature for 30 min before a THF solution (10 mL) of *t*Bu$_2$Zn (790 mg, 4.40 mmol) was added at −78 °C. The resulting pale orange solution was stirred for 30 min at 0 °C. After addition of *tert*-butyl 3-bromobenzoate (**7**) (514 mg, 2.00 mmol) at the reaction temperature (from −30 °C to room temperature), the reaction mixture solution was stirred for the reaction time (3−36 h), during which the color of the solution changed to dark orange. To trap the metalated intermediate, iodine (3.55 g, 14.0 mmol) in THF (14.0 mL) was added slowly to the reaction solution at the reaction temperature. After stirring for 12 h, the reaction solution was quenched by addition of $Na_2S_2O_3$ (satd aq.) and a small amount of NH_4Cl (satd aq.) and then extracted with $CHCl_3$ (×4). (In some cases, solids were generated which were removed by filtration before extraction.) The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and dried under reduced pressure. The residue was purified as described for general procedure A to give **8a** and **8b**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.6b01965.

Preparation of reported compounds, NMR spectra, crystallographic data, DOSY NMR analyses, DFT calculations (PDF)

Crystallographic data for **2**, **3**, **4**, **5**·(THF)$_2$, **6**·(THF)$_2$, **5**·**TMEDA**, and **6**·**TMEDA** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yyama@sci.hiroshima-u.ac.jp.

Notes

The authors declare no competing financial interest.

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