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“Naked” Lithium Cation:

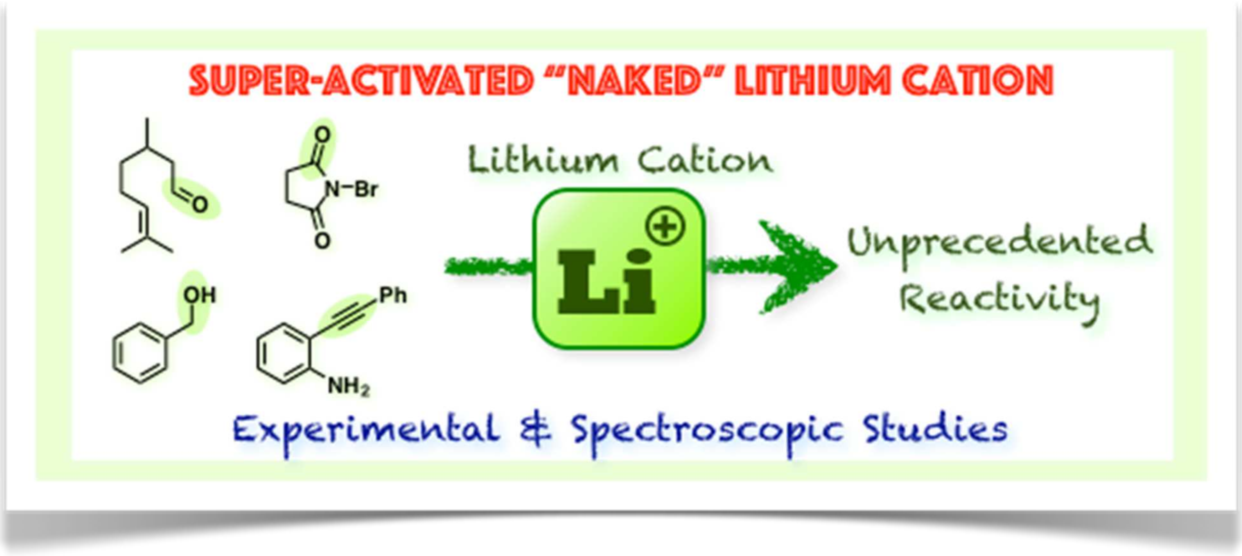
Strongly Activated Metal Cations Facilitated by Carborane Anions

Yu Kitazawa,[†] Ryo Takita,[*, ‡] Kengo Yoshida,[‡] Atsuya Muranaka,[‡] Seijiro Matsubara,[§] Masanobu Uchiyama[*, †, ‡]

† Graduate School of Pharmaceutical Sciences, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

‡ Elements Chemistry Laboratory, RIKEN, and Advanced Elements Chemistry Research Team, RIKEN Center for Sustainable Resource Science (CSRS)
2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan

§ Department of Material Chemistry, Graduate School of Engineering
Kyoto University
Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510 (Japan)



TOC Graphic

Abstract

Experimental and spectroscopic studies revealed unprecedented reactivity of “naked” lithium cation with very weakly coordinating anions including carborane anions. The super-activated lithium cation has greatly enhanced Lewis acidic character, and mediates various organic reactions, such as carbonyl-ene reaction, NBS-bromination of unactivated aromatics, and Friedel-Crafts alkylation, that are not promoted by conventional lithium salts. Chemical robustness of the counter anion also plays an important role in the chemistry of strongly activated lithium cation.

INTRODUCTION

Hydrogen and lithium are vertically adjacent elements in the periodic table, and are categorized as congeneric elements. However, they differ in many respects, including electronegativity (H 2.2 vs Li 1.0). This dissimilarity is reflected in their acid chemistry: for instance, trifluoromethanesulfonic acid (CF_3SO_3H: TfO^-H^+) and fluorosulfonic acid ($FSO_3^-H^+$) have been traditionally employed as superacids (super Brønsted acids), enabling a range of superacid-promoted synthetic transformations,[1] whereas Li^+OTf^- and $Li^+OSO_2F^-$ are essentially ineffective in most of these reactions because the potent electropositivity of lithium cation prevents complete dissociation of the counter anion. Indeed, the chemistry of “naked” metal cations (i.e., *super-activation of metal cations*) has not been well developed in general. Given that a wide variety of elements can be used in Lewis acid/metal cation chemistry, the development of super-activated metal cations should open up tremendous possibilities for enhanced or unprecedented reactivity. Here, we report a systematic study designed to generate “naked” Li^+. The key to success proved to be appropriate design/choice of counter anions. The formation of super-activated Li^+ was confirmed by ^7Li NMR and UV-vis spectroscopies. We found that super-activated lithium cation, which has greatly enhanced Lewis acidic character, mediates various reactions, such as carbonyl-ene reaction, NBS-bromination of unactivated aromatics, and Friedel-Crafts alkylation, that are not promoted by “conventional” lithium salts.

RESULTS AND DISCUSSION

To screen suitable counter anions to maximize the intrinsic character of Li^+, we systematically examined various anions, including traditional *w*eakly *c*oordinating *a*nions (WCAs: OTf^-, NTf_2^-,

BF_4^- and ClO_4^-),[2] borate-based anions ($BARF^-$ and $TFPB^-$),[3,4] and carborane anions ($CB_{11}H_{12}^-$ and $CB_{11}H_6Br_6^-$)[5] (Figure 1). Carborane anion is an icosahedral cluster molecule composed of 1 carbon and 11 boron atoms with exceptionally low basicity/nucleophilicity.[6] In addition, it can be flexibly functionalized,[5b,7] enabling precise tuning of its characteristics.

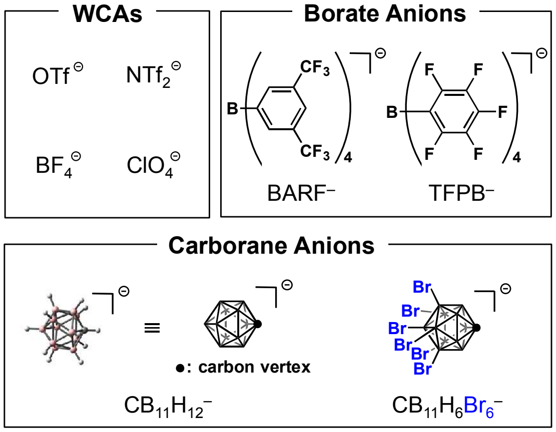


Figure 1. Counter Anions Investigated in This Work with Weak Coordinating Ability

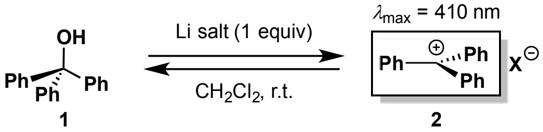
Table 1. ^7Li NMR Data of the Lithium Salts [a]

Entry	Li salt	$\Delta\delta(^7Li)$	Entry	Li salt	$\Delta\delta(^7Li)$
1	LiOTf	–1.56 ± 0.03	5	LiTFPB	–1.28 ± 0.02
2	$LiNTf_2$	–1.50 ± 0.02	6	LiBARF	–1.27 ± 0.04
3	$LiBF_4$	– [b]	7	$LiCB_{11}H_{12}$	–1.28 ± 0.01
4	$LiClO_4$	– [b]	8	$LiCB_{11}H_6Br_6$	–1.28 ± 0.02

[a] All spectra were recorded in liquid SO_2 at –20°C and referenced to external LiCl in acetone-d_6 (see Supporting Information for details). [b] These $\Delta\delta$ (^7Li) values were not determined because $LiBF_4$ and $LiClO_4$ were only sparingly soluble in liquid SO_2.

Firstly, we measured the ^7Li NMR spectra of the lithium salts in liquid SO_2 as a solvent[8] (Table 1). Although Brønsted acidity can be easily assessed using parameters such as acid dissociation constant (pK_a) and Hammett acidity function (H_0), evaluation of the Lewis acidity of metal cations is difficult due to the lack of a similar index. The ^{7}Li signals of Li$^+$OTf$^-$ and Li$^+$NTf$_2$$^-$ were observed as a sharp singlet at –1.56 and –1.50 ppm, respectively, under the conditions given in Table 1 (entries 1 and 2), while signals of Li$^+$BF$_4$$^-$ and Li$^+$ClO$_4$$^-$ could not be recorded because these salts did not dissolve under the NMR conditions. On the other hand, lithium salts of borate and carborane anions showed lower-field shifts to the observation limit (*ca.* –1.28 ppm),[9] which indicates that they have lower electron density (entries 5-8).

Table 2. Effects of Counter Anions on the Lewis Acidity of Lithium Cation in Trityl Cation (**2**) Formation



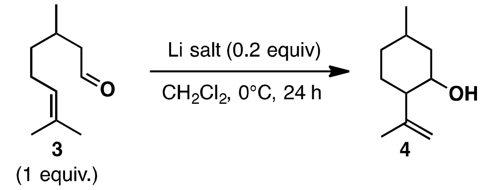
Entry	Li salt	Abs (λ = 410 nm)	Entry	Li salt	Abs (λ = 410 nm)
1	LiOTf	ND	5	LiTFPB	1.14
2	LiNTf$_2$	ND	6	LiBARF	0.28^a
3	LiBF$_4$	ND	7	LiCB$_{11}$H$_{12}$	0.16^a
4	LiClO$_4$	ND	8	LiCB$_{11}$H$_6$Br$_6$	1.24

[a] Decrease of the peak intensity at 410 nm was observed during the course of measurement.

We then performed a UV-vis spectral study to evaluate the generation of trityl cation (**2**) (at 410 nm) *via* Lewis acidic activation of trityl alcohol (**1**), as reported by Kobayashi and co-workers.[10] The lithium salts of borate and carborane anions, Li$^+$TFPB$^-$, Li$^+$BARF$^-$, Li$^+$CB$_{11}$H$_{12}$$^-$, and Li$^+CB_{11}H_6Br_6$$^-$, were sufficiently reactive to generate **2** (Table 2, entries 5-8), whereas Li$^+$OTf$^-$, Li$^+$NTf$_2$$^-$, Li$^+BF_4$$^-$, and Li$^+ClO_4$$^-$ produced no spectral change (entries 1-4). This indicates that there is a distinct difference of Lewis/metal acidity between them, which is in accordance with the ^{7}Li NMR results. Note that in the cases of Li$^+$BARF$^-$ and Li$^+$CB$_{11}$H$_{12}$$^-$, the absorbance of **2** diminished during the course of measurements, implying that side reactions or decomposition of

2 occur in the presence of these counter anions.[11] These results suggest that not only counter anion stability (i.e., extremely low nucleophilicity), but also chemical robustness, that is, tolerance to side reactions/decomposition, would be necessary to enable super-activation of the Li^+ center.

Table 3. Carbonyl-Ene Reaction of Citronellal (**3**)

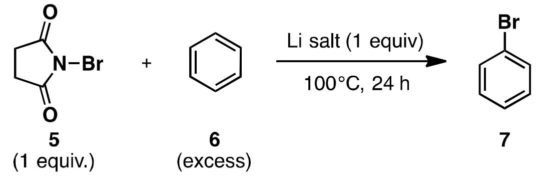


Entry	Li salt	Yield (%)[a]	Entry	Li salt	Yield (%)[a]
1	LiOTf	0	5	LiTFPB	75
2	$LiNTf_2$	0	6	LiBARF	60
3	$LiBF_4$	0	7	$LiCB_{11}H_{12}$	63
4	$LiClO_4$	0	8	$LiCB_{11}H_6Br_6$	69

[a] Yields were determined by GC analysis using tridecane as an internal standard.

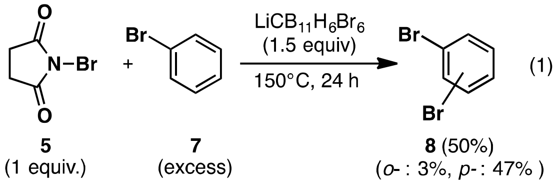
With the spectroscopic results in hand, we next examined whether super-activated lithium could promote various fundamental reactions that do not proceed in the presence of ordinary lithium salts. Carbonyl activation is a key step for organic transformation. For example, carbonyl-ene reaction generally requires strong Lewis acids to activate the carbonyl group.[12] When Li^+OTf^-, $Li^+NTf_2^-$, $Li^+BF_4^-$, or $Li^+ClO_4^-$ was employed for the carbonyl-ene reaction of citronellal (**3**) in dichloromethane at 0°C, the desired product **4** was not obtained at all and only the starting **3** was recovered (Table 3, entries 1-4). In contrast, the desired cyclization proceeded under the same conditions in the presence of a catalytic amount of Li^+TFPB^-, Li^+BARF^-, $Li^+CB_{11}H_{12}^-$, or $Li^+CB_{11}H_6Br_6^-$ (entries 5-8).

Table 4. Bromination of Benzene (**6**) with NBS (**5**)



Entry	Li salt	Yield (%)[a]	Entry	Li salt	Yield (%)[a]
1	LiOTf	0	5	LiTFPB	35
2	$LiNTf_2$	0	6	LiBARF	34
3	$LiBF_4$	0	7	$LiCB_{11}H_{12}$	0
4	$LiClO_4$	0	8	$LiCB_{11}H_6Br_6$	84

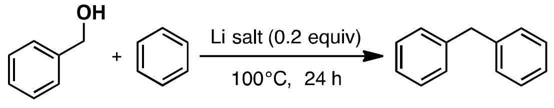
[a] Yields were determined by GC analysis using tridecane as an internal standard.



(1)

Inspired by the success of the first carbonyl-ene reaction catalyzed by lithium salts (i.e., intramolecular C–C bond formation *via* carbonyl activation), we then examined the bromination of benzene (**6**) by activation of *N*-bromosuccinimide (NBS) (**5**) (Table 4). With non-activated benzenes, this reaction requires super-electrophilic reagents, such as (multiply) protonated NBS reagents in superacid.[13] Again, ordinary lithium salts such as Li^+OTf^-, $Li^+NTf_2^-$, $Li^+BF_4^-$, or $Li^+ClO_4^-$ did not mediate the bromination reaction at all (entries 1-4). On the other hand, the combination of NBS with 1 equivalent of $Li^+CB_{11}H_6Br_6^-$ successfully brominated benzene (**7**) in 84% yield at 100°C for 24 h (entry 8). Moreover, even bromobenzene (**7**), a deactivated benzene substrate, could be brominated in the presence of 1.5 equivalents of $Li^+CB_{11}H_6Br_6^-$ to give the product **8** in 50% yield (eq. 1). With Li^+TFPB^-, Li^+BARF^-, or $Li^+CB_{11}H_{12}^-$, the reaction was sluggish and bromination of carborane anion or decomposition of the borate scaffold occurred preferentially (entries 5-7).[14] These results indicate that the reaction requires 1) an extremely acidic lithium cation that strongly activates NBS to give super-electrophilic brominating reagents, and 2) a robust anion skeleton compatible with the generated super-electrophilic species.

Table 5. Friedel-Crafts Alkylation of Benzene (**6**) with Benzyl Alcohol (**9**)



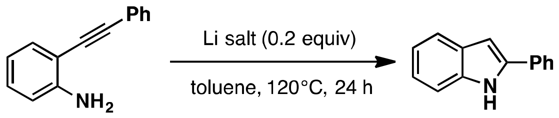
9 (1 equiv.) **6** (excess) **10**

Entry	Li salt	Yield (%)^a	Entry	Li salt	Yield (%)^a
1	LiOTf	0	5	LiTFPB	95
2	$LiNTf_2$	0	6	LiBARF	trace
3	$LiBF_4$	0	7	$LiCB_{11}H_{12}$	0
4	$LiClO_4$	0	8	$LiCB_{11}H_6Br_6$	94

^{a} Yields were determined by GC analysis using tridecane as an internal standard

Intermolecular Friedel-Crafts (FC) alkylation reaction of benzene was next investigated (Table 5). For the success of FC reactions using alcohols (OH is a poor leaving group) as the electrophile, the use of superacid or strong Lewis acid is generally required.[15] Indeed, no reaction of **9** took place in the presence of Li^+OTf^-, $Li^+NTf_2^-$, $Li^+BF_4^-$, or $Li^+ClO_4^-$. However, we found that the use of Li^+TFPB^- or $Li^+CB_{11}H_6Br_6^-$ gave the desired FC product **10** in 95% or 94% yield, respectively (entries 5 and 8). On the other hand, decomposition/side reactions of the anion moiety prior to the FC reaction were observed when Li^+BARF^- or $Li^+CB_{11}H_{12}^-$ was employed.

Table 6. Intramolecular Cyclization of 2-Phenylethynylaniline (**11**) to Afford 2-Phenylindole (**12**)



11 **12**

Entry	Li salt	Yield (%)^a	Entry	Li salt	Yield (%)^a
1	LiOTf	5	5	LiTFPB	25
2	$LiNTf_2$	9	6	LiBARF	7
3	$LiBF_4$	6	7	$LiCB_{11}H_{12}$	84
4	$LiClO_4$	19	8	$LiCB_{11}H_6Br_6$	50

^{a} Yields were determined by GC analysis using tridecane as an internal standard

Finally, to characterize the behavior of lithium cation compared with normal superacids such as TfO$^-$H$^+$, we focused on activation of a less-polar alkyne triple bond. Indole synthesis from *o*-alkynylanilines (Table 6) was selected because "soft" metals are generally required to activate the C–C π bond,[16] and superacids are ineffective for the annulation, presumably due to preferential protonation of the aniline nitrogen in superacid media.[17] When ordinary lithium salt, Li$^+$OTf$^-$, Li$^+$NTf$_2^-$, Li$^+$BF$_4^-$, or Li$^+$ClO$_4^-$, was employed, the desired indole annulation proceeded, albeit in low yield, probably due to the low acidity (entries 1-4). In sharp contrast, the use of Li$^+$CB$_{11}$H$_{12}^-$ promoted the desired annulation reaction to give **12** in 84% yield. Other lithium salts with borate anions and Li$^+$CB$_{11}$H$_6$Br$_6^-$ seemed to favor strong coordination to nitrogen, which disturbed the indole cyclization.

In summary, combined spectroscopic and experimental studies demonstrated that the Lewis acidity and character of lithium cation can be finely-tuned by means of an appropriate choice of counter anion. In particular, carborane anions strongly activated lithium cation to achieve unprecedented reactivity, and the super-activated lithium cation mediated various reactions (carbonyl-ene reaction, NBS-bromination of unactivated aromatics, Friedel-Crafts alkylation) that are not promoted by conventional lithium salts. Counter anion stability and chemical robustness are both crucial to prevent side reactions. Given that the carborane anion is readily customizable,[5b] including carborane-based multivalent anions,[7a] we anticipate that carborane anions will be an excellent platform for *the flexible design of super-activated metal centers in periodic table-wide chemistry*. We believe the concept/methods described herein offer a toolkit that will be of general use for exploration of a range of super-activated metal cations.

Experimental Section

General Remarks

$Me_3NHCB_{11}H_{12}$ and $CsCB_{11}H_{12}$ were purchased from commercial suppliers. Bromobenzene, citronellal, *N*-bromosuccinimide, and benzyl alcohol were used after appropriate purification (distillation or recrystallization). 2-Phenylethynylaniline was prepared as described previously.[18] Lithium Tetrakis(3,5-trifluoromethyl)phenylborate, LiBARF, was prepared as described previously.[19] Lithium trifluoromethanesulfonate, lithium bis(trifluoromethanesulfonimide), lithium tetrafluoroborate, and lithium perchlorate were used after drying under vacuum (1.0×10^{-1} hPa/80ºC overnight). All other chemicals were of reagent grade and used as received. Air- and moisture-sensitive manipulations were performed with standard Schlenk techniques or in a glove box under argon atmosphere. Normal-phase column chromatography was performed with silica gel 60 (230-400 mesh) and thin-layer chromatography was carried out on 0.25 mm silica gel plates. The NMR spectral measurements were performed on a 500 MHz spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). ^1H, ^{13}C NMR spectra were referenced to tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet.

***Synthesis of Trimethylammonium 7,8,9,10,11,12-hexabromo-1-carba-closo-dodecaborate, (NMe$_3$H)CB$_{11}$H$_6$Br$_6$.* [442549-75-9]**

$CsCB_{11}H_6Br_6$ (2.5 g, 3.35 mmol) was dissolved in an aqueous solution of HCl (10%, 100 mL) and extracted with Et_2O three times. The combined Et_2O extracts were evaporated to dryness. The solid residue was treated with water. The product was precipitated by addition of $NHMe_3Cl$ (960 mg, 10.05 mmol). The white solid was filtered off, washed with water, and dried under vacuum (1.0×10^{-1} hPa/100ºC, overnight) to give the title compound as white powder in 85% yield (1900 mg). This compound was previously reported.[20a, b] $^1H\{^{11}B\}$ NMR (500 MHz, acetone-d_6): 2.33 (bs, 5H), 3.04 (bs, 1H), 3.23 (s, 9H); HRMS (ESI-TOF) *m*/*z* calcd. for $CH_6B_{11}Br_6$ ([M]$^-$): 616.6605, found: 616.6601.

***Synthesis of Lithium 7,8,9,10,11,12-hexabromo-1-carba-closo-dodecaborate, LiCB$_{11}$H$_6$Br$_6$.* [225797-12-6]**

Typical Procedure A: To the aqueous solution (200 mL) of $(NMe_3H)CB_{11}H_6Br_6$ (2.0 g, 2.97 mmol) was added $LiOH\cdot H_2O$ (374 mg, 8.92 mmol). This solution was stirred for 60 min at room temperature and then evaporated to dryness. The solid was treated with water again and extracted with Et_2O three times. The Et_2O fractions were washed with an aqueous solution of LiOH (10%), LiCl (20%), and water, and then dried with activated molecular sieves (powdered, 4 Å). The sieves were filtered off and washed with dry Et_2O. The combined Et_2O extracts were stirred with LiH (1.0 g) for 24 h under an argon atmosphere at room temperature, filtered to remove any residual LiOH and LiH, and evaporated under reduced pressure to afford brown oil. The oil was dissolved in acetonitrile (100 mL) and the solution was stirred overnight with activated charcoal (200 mg). The charcoal was filtered off through Celite® pad and washed with acetonitrile.

Combined filtrates were evaporated, and the product was dried under reduced pressure (1.0 × 10^{-1} hPa/130ºC, 7 days) to give the title compound as white powder in 68% yield (1958 mg). This compound was previously reported.[21] $^{1}H\{^{11}B\}$ NMR (500 MHz, acetone-d_6): 2.33 (bs, 5H), 3.03 (bs, 1H); HRMS (ESI-TOF) *m*/*z* calcd. for $CH_6B_{11}Br_6$ ($[M]^-$): 616.6605, found: 616.6604.

Synthesis of Lithium 1-carba-closo-dodecaborate, $LiCB_{11}H_{12}$. **[92468-37-6]**

According to the Typical Procedure A, using $NMe_3HCB_{11}H_{12}$ (2.0 g, 9.84 mmol) and $LiOH\cdot H_2O$ (4958 mg, 29.5 mmol), the titled compound was obtained as white powder in 74% yield (1092 mg). This compound was previously reported.[22] $^{1}H\{^{11}B\}$ NMR (500 MHz, acetone-d_6): 1.57 (bs, 5H), 1.66 (bs, 5H), 1.73 (bs, 1H), 2.23 (bs, 1H); HRMS (ESI-TOF) *m*/*z* calcd. for $CH_{12}B_{11}$ ($[M]^-$): 143.2035, found: 143.2038.

General Procedure for Carbonyl-Ene Reaction of Citronellal **(3)**

$LiCB_{11}H_6Br_6$ (13.7 mg, 0.022 mmol) and dichloromethane (5.0 mL) were charged in a dried Schlenk tube in a glove box. To the mixture was added citronellal (17.1 mg, 0.11 mmol). The mixture was stirred at 0ºC for 24 h, and then the reaction was quenched by brine. The generation of the desired compound (**4**: mixture of two isomer) (69%) was confirmed by comparison of ^{1}H NMR spectrum and GC/MS trace of the authentic sample.[12d] Chemical yield was determined by GC analysis using tridecane as an internal standard.

Major isomer of 4: *Isopulegol* [7786-67-6]. ^{1}H NMR data are consistent with those previously reported.[12d]

General Procedure for Bromination of Benzene (6) with NBS (5)

Benzene (3.0 mL), $LiCB_{11}H_6Br_6$ (62.3 mg, 0.1 mmol), and *N*-bromosuccinimide (**5**, 17.2 mg, 0.1 mmol) were charged in a dried Schlenk tube in a glove box. The mixture was stirred at 100ºC for 24 h in the dark, and the reaction was quenched by brine. The generation of the desired compound **7** (84%) was confirmed by comparison of ^1H NMR spectrum and GC/MS trace of the commercially available authentic sample. Chemical yield was determined by GC analysis using tridecane as an internal standard.

Bromobenzene (7): [7786-67-6]. ^1H NMR data are consistent with a commercially available authentic sample.

Major isomer of 8: 1,4-Dibromobenzene [106-37-6]. 1,4-Dibromobenzene (47%) was obtained by using $LiCB_{11}H_6Br_6$, NBS (**5**), and bromobenzene (**7**) at 150ºC. Chemical yield was determined by GC analysis using tridecane as an internal standard. ^1H NMR data are consistent with commercially available authentic sample.

General Procedure for Friedel-Crafts Alkylation

Benzene (1.0 mL) and $LiCB_{11}H_6Br_6$ (12.0 mg, 0.02 mmol) were charged in a dried Schlenk tube in a glove box. To the mixture was added benzyl alcohol (**9**, 10.4 mg, 0.1 mmol). The mixture was stirred at 100ºC for 24 h, then the reaction was quenched by brine. The generation of the desired compound **10** (94%) was confirmed by comparison of ^1H NMR spectrum and GC/MS trace of the authentic sample.[23] Chemical yield was determined by GC analysis using tridecane as an internal standard.

1,1-Diphenylmethane (10): [612-00-0]. ^{1}H NMR data are consistent with commercially available authentic sample.[23]

General Procedure for Indole Cyclization of 2-Phenylethynylaniline **(11)**

Toluene (27 mL), $LiCB_{11}H_6Br_6$ (19.3 mg, 0.031 mmol), and 2-phenylethynylaniline (**11**, 30 mg, 0.155 mmol) were charged in a dried Schlenk tube in a glove box. The mixture was stirred at 120ºC for 24 h, and the reaction was quenched by brine. The generation of the desired compound **12** (50%) was confirmed by comparison of ^{1}H NMR spectrum and GC/MS trace of the authentic sample.[24] Chemical yield was determined by GC analysis using tridecane as an internal standard.

2-Phenyl-1*H*-indole (13): [948-65-2]. ^{1}H NMR data are consistent with those previously reported.[24]

Associated Content

Supporting Information

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

UV-vis absorption spectra, representative ^{7}Li NMR spectra, and copies of ^{1}H NMR spectra of known compounds for purity.

Author Information

Corresponding Authors

*E-mail: ryo.takita@riken.jp

*E-mail: uchi_yama@riken.jp

Notes

The authors declare no competing financial interest.

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