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Article

Base-Induced Dehydrogenative and Dearomative Transformation of 1-Naphthylmethylamines to 1,4-Dihydronaphthalene-1-carbonitriles

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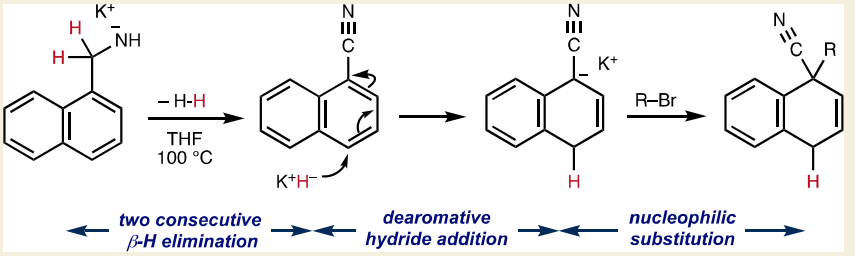

ABSTRACT: Solvothermal treatment of 1-naphthylmethylamine with potassium hydride (KH) or *n*-butyllithium (*n*-BuLi)–potassium *t*-butoxide (*t*-BuOK) in THF induces unusual two consecutive *β*-hydride eliminations to form 1-naphthonitrile and KH. The freshly generated KH is hydridic enough to undergo dearomative hydride addition to the resultant 1-naphthonitrile regioselectively at the C4 position to afford *α*-cyano benzylic carbanion, which could be functionalized by a series of electrophiles, liberating the corresponding 1,4-dihydronaphthalene-1-carbonitriles having a quaternary carbon center.

KEYWORDS: *dearomatization, β-hydride elimination, potassium hydride, potassium amides, DFT calculations*

INTRODUCTION

Dihydro- and tetrahydronaphthalenes are omnipresent in biologically active natural products, such as aryltetralin lignan lactones.[1,2] Downstream dearomative functionalizations of flat aromatic naphthalene cores potentially allows for rapid construction of such sp^3-rich aliphatic ring scaffolds.[3,4] In this context, dearomative nucleophilic addition of organometallic reagents to electron-deficient naphthalenes has been developed (Scheme 1), and the electron-withdrawing chelating groups such as oxazolines (Scheme 1A),[5−7] imines,[8] and carbonyl groups (Scheme 1B)[9,10] directed their addition at the proximal position. On the other hand, there have been reported several examples on the nucleophilic addition at the distal position driven by the steric effect. For example, in the functionalization of 1-naphthonitrile with organolithium reagents, sterically bulkier nucleophiles tend to add more preferentially at the C4 position (Scheme 1C).[11] The reaction of 1-acetylnaphthalene with sterically bulky *t*-BuLi or $PhMe_2SiLi$ in the presence of aluminum *tris*(2,6-diphenylphenoxide) occurred exclusively at the C4 position (Scheme 1D).[12−14] However, nucleophilic addition of a hydride to dearomatize a naphthalene nucleus has rarely been realized with only a few exceptions of the reduction of poly-nitronaphthalenes with $NaBH_4$.[15,16] Herein, we report unprecedented dearomative hydride addition to 1-naphthonitrile by hydridic KH, which is realized when 1-naphthonitrile and KH are generated *in situ via* unusual consecutive two *β*-H eliminations of 1-naphthylmethylamine by its solvothermal treatment with the KH or *n*-BuLi–*t*-BuOK system. The discovery and mechanistic investigation as well as synthetic applications were described.

RESULTS AND DISCUSSION

Our group has recently reported hydroalkylation of styrenes with benzylamines mediated by potassium hydride (KH).[17] Solvothermal treatment of benzylamine (**1**) with KH at 100 °C in THF forms deprotonated anionic species (**I** and **II**), which react with styrene (**2**) as a C-nucleophile to form 1,3-diarylpropylamine **3** (Scheme 2A). It should be noted that large excess use of benzylamine (**1**) to KH is essential to keep the anionic species (**I** and **II**) derived from deprotonation of benzylamine (**1**). When benzylamine (**1**) was treated with slight excess amounts of KH (1.2 equiv), we observed the formation of aldimine **4**, which should be generated *via* *β*-H elimination of

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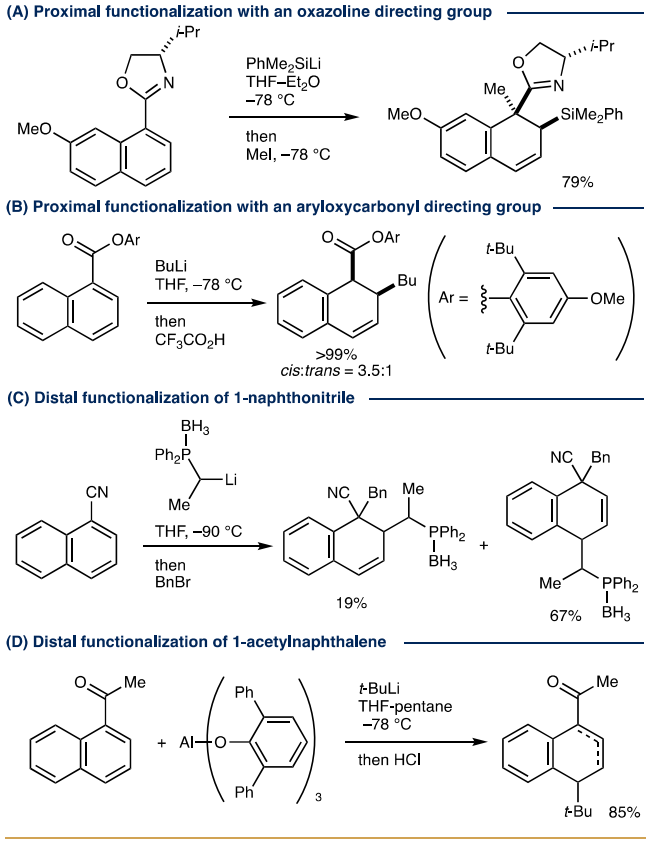
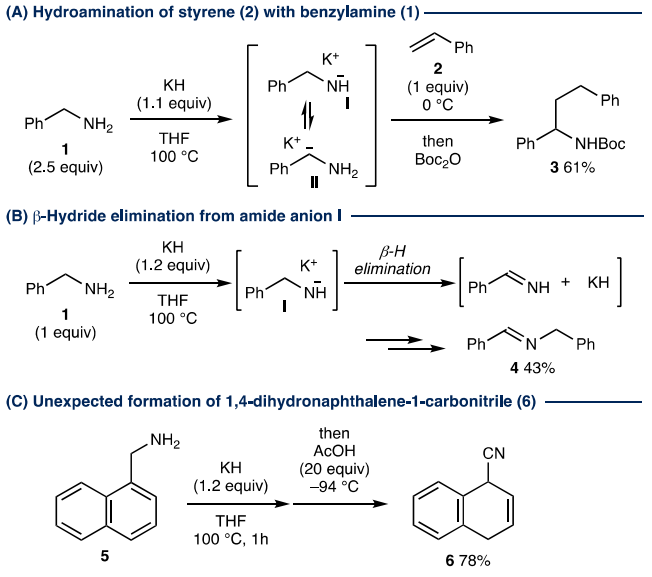
Scheme 1. Prior Arts on the Nucleophilic Dearomative Functionalization of Naphthalenes



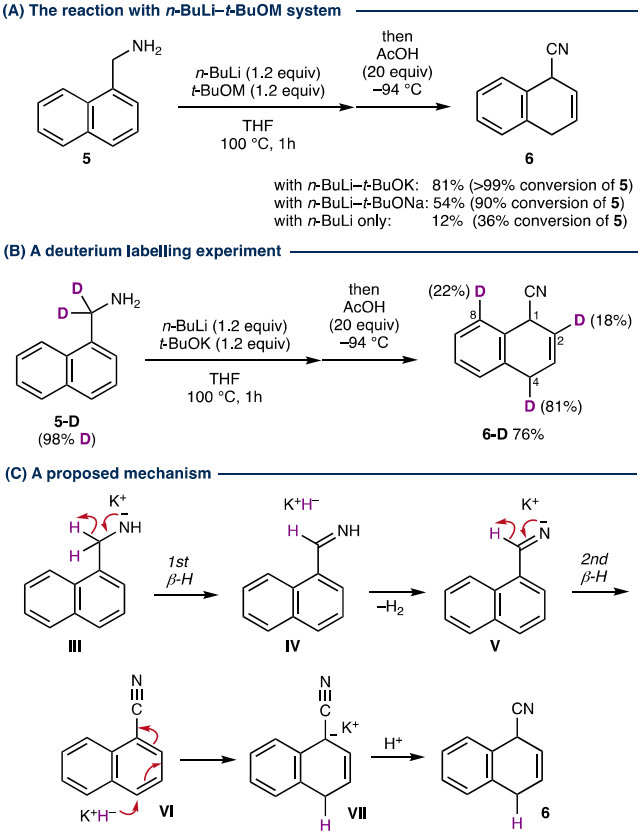
Scheme 2. Reactivity of Potassium Benzylamide and Potassium 1-Naphthylmethylamide



potassium amide **I** (Scheme 2B).[18−22] During the course of this study, we were surprised to observe that the treatment of 1-naphthylmethylamine (**5**) with KH (1.2 equiv) affords 1,4-dihydronaphthalene-1-carbonitrile (**6**) after careful protonation with acetic acid (AcOH) at −94 °C (Scheme 2C) (see the Supporting Information for the optimization of the reaction conditions). We became interested in this dearomative 1,4-reduction of the naphthalene ring along with oxidation of the aminomethyl moiety to the cyano group, and thus further detailed investigations were conducted to elucidate the reaction mechanism and to explore its synthetic potential.

The use with *n*-BuLi and *t*-BuOK[23,24] in place of KH resulted in the formation of **6** in comparable yield, while that with *t*-BuONa or only *n*-BuLi rendered the process inefficient with incomplete conversion (Scheme 3A). These results suggested

Scheme 3. Investigation of the Reaction Mechanism



that the process is initiated from the potassium amide anion formed *via* deprotonation from the primary amine moiety, and the potassium counter cation plays a crucial role. To cast light on the dearomative process, we next examined the reaction of deuterated substrate **5-D** having two deuterium atoms at the benzylic position with *n*-BuLi and *t*-BuOK (Scheme 3B). It was found that a deuterium atom was installed at the C4 position of **6-D** in 81% incorporation rate. Interestingly, minor deuterium incorporation was also observed at the C2 and C8 positions in 18 and 22%, respectively. Based on these results, the proposed mechanism for this dearomative transformation is depicted in Scheme 3C. The process is initiated by *β*-H elimination of potassium amide anion **III** to generate a pair of aldimine **IV** and KH. Rapid deprotonation then affords iminyl anion **V**, which presumably undergoes the second *β*-H elimination to form a pair of 1-naphthonitrile **VI** and KH. The freshly generated KH attacks the C4 position of 1-naphthonitrile **VI**, generating the dearomatized *α*-cyano carbanion intermediate **VII**, which could be protonated to liberate 1,4-dihydronaphthalene-1-carbonitrile (**6**). It should be noted that the reaction of 1-naphthonitrile (**VI**) with commercially available bulk KH, which is insoluble in THF, was much less efficient, resulting in the formation of **6** in a much lower yield (see the Supporting Information). On the other hand, we assume that KH freshly generated *in situ via* *β*-H

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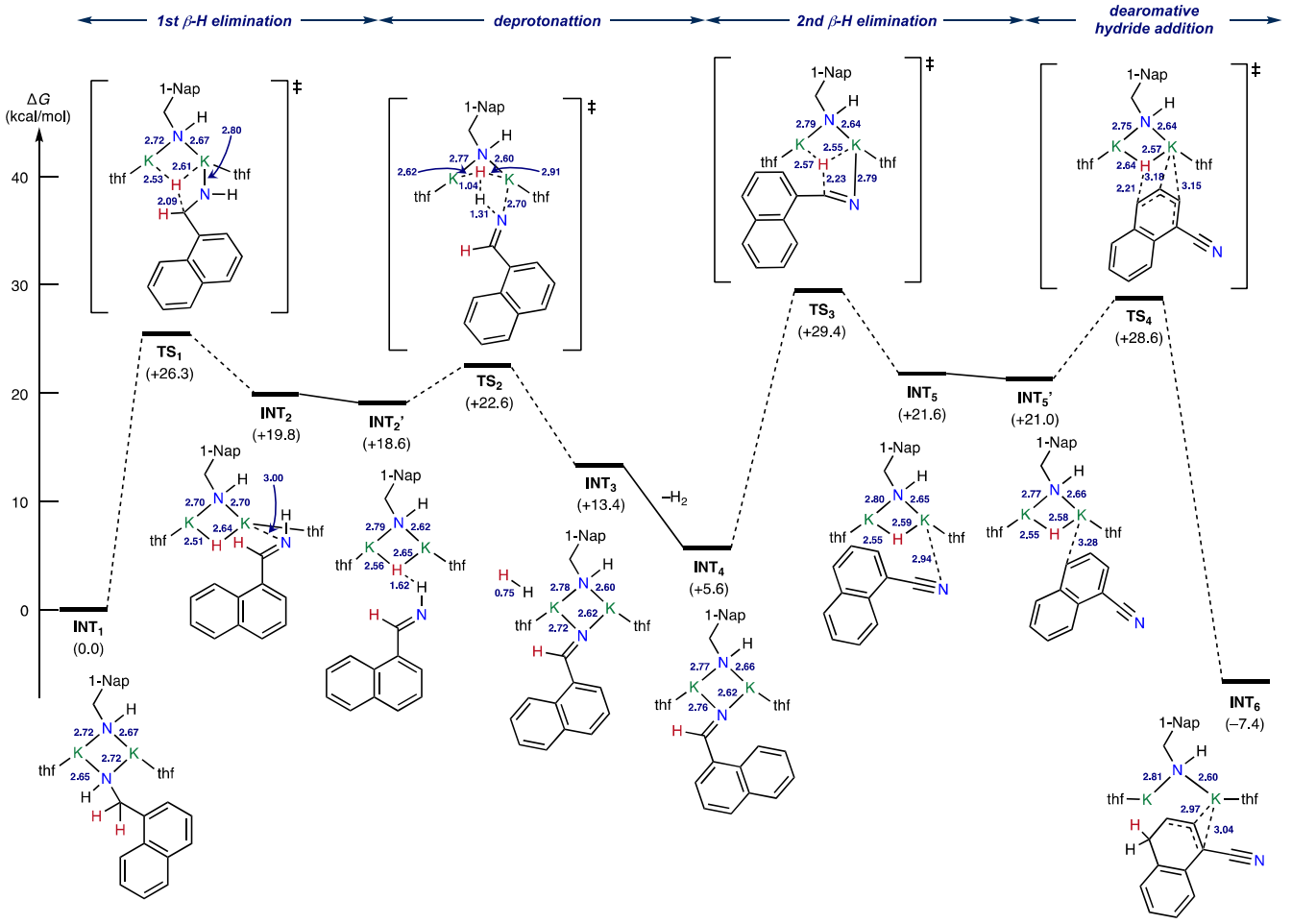
JACS Au 2022, 2, 2758−2764

Scheme 4. DFT Calculations on the Two Consecutive β-H Eliminations and Sequential Dearomative Hydride Addition Starting from Potassium 1-Naphthylmethylamide[a]



[a]Energy changes and bond lengths at the M06-2X/6-311++G**/SMD(THF)//M06-2X/6-31+G* level of theory are shown in kcal/mol and Å, respectively. 1-Nap = 1-naphthyl; thf = tetrahydrofuran.

elimination might be nanomeric in size and thus can possess enhanced hydridic reactivity to enable such an unprecedented hydride reduction of 1-naphthonitrile (**VI**).[25−29] The resultant hydridic KH should also be capable of directed hydride addition to the C2 and C8 positions of potassium amide **III** to form dearomatized anionic intermediates, which can undergo rearomatization *via* elimination of hydride.[30,31] This can explain partial deuterium incorporation at the C2 and C8 in **6-D** observed in Scheme 3B (see the Supporting Information for detail).

To gain the detailed insights into the reaction pathway of the present dearomative transformation, we carried out density functional theory (DFT) calculations at the M06-2X/6-311++G**/SMD(THF)//M06-2X/6-31+G* level of theory. The diffusion ordered ^{1}H NMR spectroscopy (^{1}H DOSY) of potassium amide anion **III** in d_8-THF solution suggested that it might exist as a dimer $[KNHCH_2C_{10}H_7{\cdot}(d_8\text{-THF})_3]_2$ (MW = 863 g/mol, error +1%) at ambient temperature (see the Supporting Information for details), while the structure of the aggregates that trigger the first β-H elimination at the actual reaction temperature (100 °C) is unclear. It is known that the aggregation status of alkali metal amides could heavily depend on temperature, and some complexes could exist under equilibrium between oligomers and smaller aggregates including monomers.[32−35] Although the solvation level on the potassium cations (K^+) might also be uncertain at the actual reaction temperature, the coordinatively unsaturated status on K^+ should be required when the β-H elimination takes place. Based on these considerations and the previous reports on the structures of potassium amides,[36−38] a coordinatively unsaturated potassium amide dimer $[(KNHCH_2C_{10}H_7{\cdot}THF)_2]$ **INT$_1$** was adopted as the model for this study (Scheme 4).[39] The first β-H elimination is facilitated by the flexibility of the dimeric complex, where the liberated hydride is captured *via* the open-form transition state **TS$_1$** ($\Delta G^{\ddagger}$ = +26.3 kcal/mol). The resultant potassium hydride species can easily deprotonate the proton of the N−H imine moiety, leading to the formation of the imide complex and dihydrogen (H_2) in an exothermic manner to afford **INT$_3$**. After releasing H_2 from **INT$_3$**, the resulting imide complex **INT$_4$** undergoes the second β-H elimination *via* **TS$_3$** ($\Delta G^{\ddagger}$ = +29.4 kcal/mol). Two potassium cations cooperatively accept the hydride anion to facilitate the construction of the cyano group in **INT$_5$**. After the conformational change to **INT$_5$'**, this hydride can attack the C4 position of the resultant 1-naphthonitrile. The transition state **TS$_4$** for the dearomative hydride addition is located at a slightly lower energy than **TS$_3$** ($\Delta G^{\ddagger}$ = +28.6 kcal/mol), and this step should proceed smoothly and irreversibly under the reaction conditions to afford the α-

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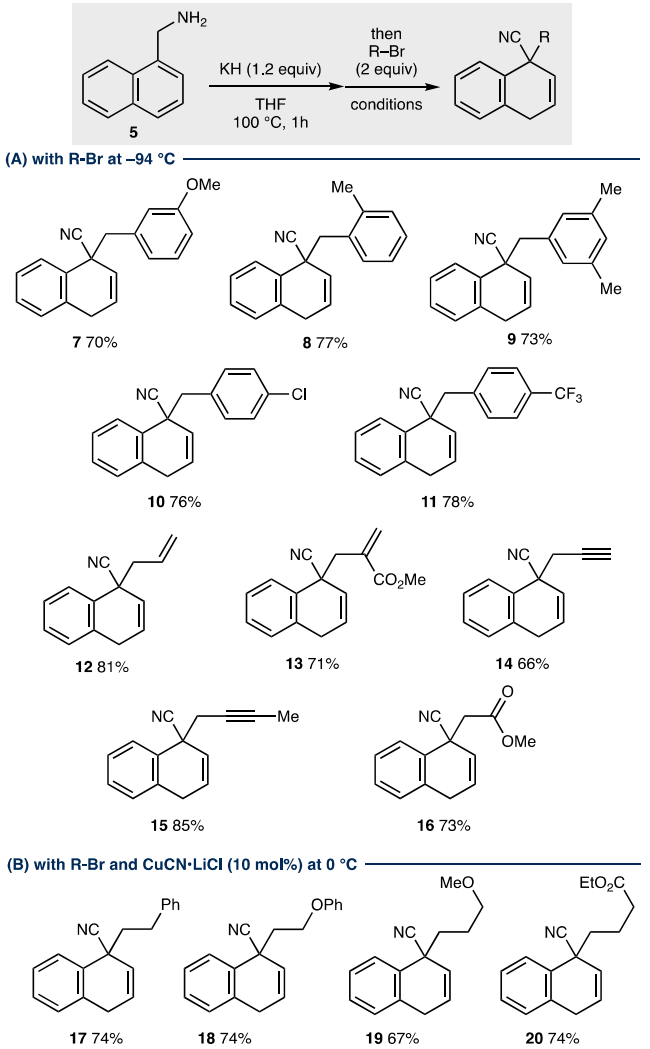
JACS Au 2022, 2, 2758−2764

cyano carbanion **INT$_6$**. This irreversible hydride addition renders the present process selective circumventing the potential formation of aldimine (Scheme 2B). Together with the experimental observations on the first β-H elimination (Scheme 2B) and the deuterium labeling experiment (Scheme 3B), the present theoretical study corroborates that the multistep process containing two consecutive β-H eliminations and sequential dearomative hydride addition is feasible starting from a dimeric potassium amide complex **INT$_1$**.

We next explored the possibility to construct a quaternary carbon center at the C1 position by trapping α-cyano carbanion **VII** with alkyl halides (Scheme 5).[40,41] We observed that a series

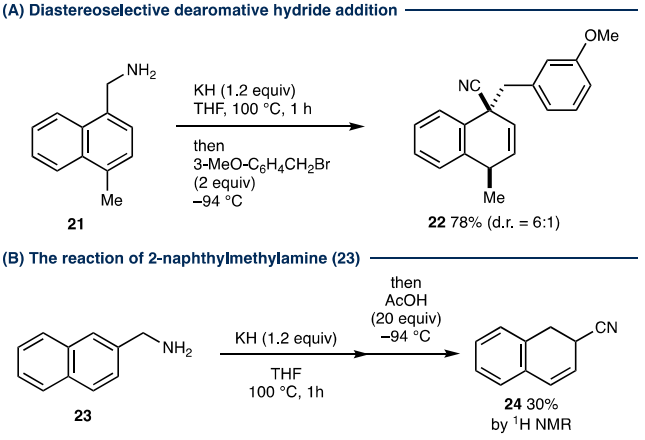
Scheme 5. Construction of the C1 Quaternary Carbon Center with Alkyl Halides



of benzyl bromides could react efficiently at −94 °C to afford **7**−**11** in good yields (Scheme 5A). Similarly, allyl bromides (for **12** and **13**) and propargyl bromides (for **14** and **15**) as well as methyl bromoacetate (for **16**) could be employed. We found that engagement of non-activated alkyl bromides necessitates the aid of CuCN·2LiCl as a catalyst (Scheme 5B).[42,43] In the presence of CuCN·2LiCl (10 mol %) at 0 °C, primary alkyl bromides having various functionalities could be utilized to efficiently construct the corresponding C1 quaternary carbon center (for **17**−**20**).

We also found that the present dearomative C4-selective hydride addition was not influenced by the presence of a methyl group at the C4 position of **21** (Scheme 6A). In this case, the

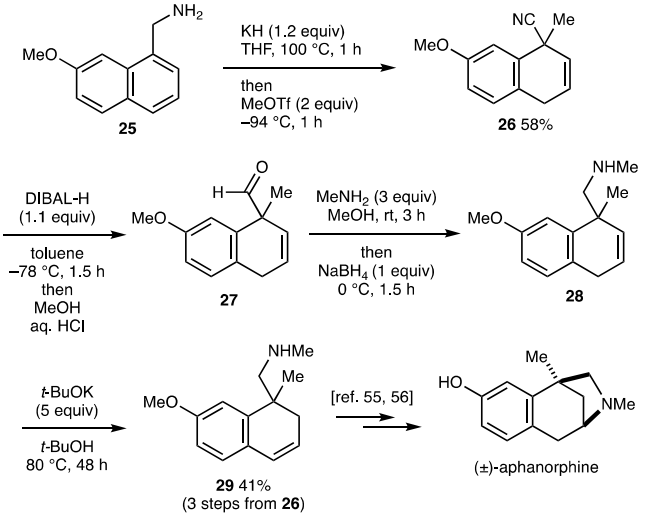
Scheme 6. Reactivity of (4-Methylnaphthalen-1-yl)methanamine (21) and 2-Naphthylmethylamine (23)



downstream functionalization of the α-cyano carbanion with 3-methoxybenzyl bromide occurred in a diastereoselective manner: namely, nucleophilic substitution proceeded at the opposite face with the C4-methyl group to provide **22** in 78% yield with 6:1 diastereomeric ratio. However, the transformation of 2-naphthylmethylamine (**23**) was not very productive, providing 1,2-dihydronaphthalene-2-carbonitrile (**24**) only in 30% yield (Scheme 6B). This is presumably due to the instability of the conjugated alkene of **24** under the strongly basic reaction conditions.

Having developed a method for concise construction of 1,4-dihydronaphthalene-1-carbonitriles, we next explored their further derivatization to complex scaffolds. We first attempted a formal synthesis of aphanorphine, a tricyclic alkaloid based on a 3-benzazepine core having a bridged quaternary carbon center (Scheme 7).[44−56] The dearomative hydride addition followed by methylation with methyl trifluoromethanesulfonate (MeOTf) was successfully implemented with amine **25**, affording **26** in 58% yield. We then conducted the following

Scheme 7. Formal Synthesis of Aphanorphine



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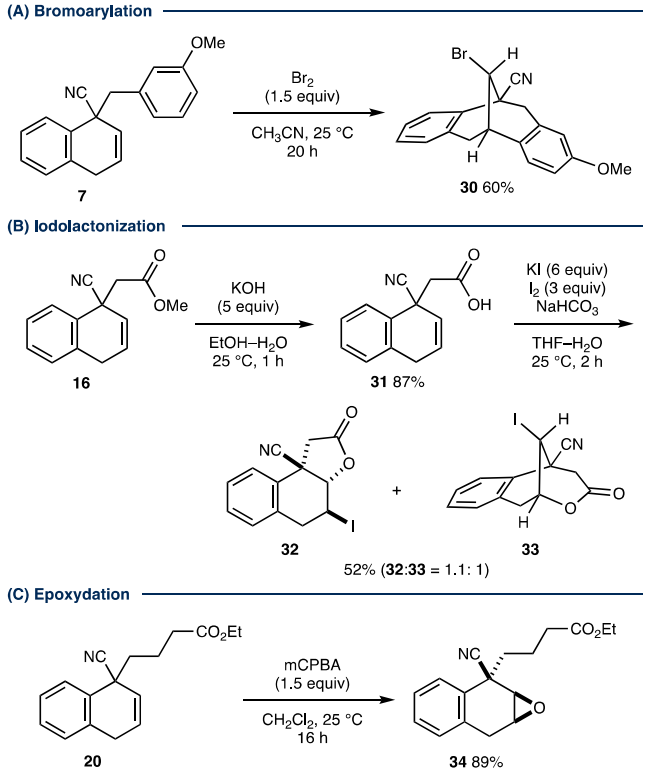
three transformations consecutively: (i) reduction of α-quaternary nitrile **26** to aldehyde **27**, (ii) reductive amination of **27** with methylamine to form *N*-methyl amine **28**, and (iii) translocation of alkene of **28** by the treatment with *t*-BuOK in *t*-BuOH,[57] leading to the synthetic intermediate **29** reported by Meyers[5,55] in 41% yield (from **26** *via* three steps).

With respect to the functionalization of the alkene moiety of 1,4-dihydronaphthalene-1-carbonitriles, the treatment of **7** with bromine in acetonitrile (CH_3CN) induced bromoarylation of the alkene, leading to bicyclo[3.3.1]nonane **30** in 60% yield (Scheme 8A).[58] Iodolactonization of acid **31**, which was

Scheme 8. Derivatization of 1,4-Dihydronaphthalene-1-carbonitriles



prepared from ester **16** *via* its alkaline hydrolysis, afforded a mixture of lactones **32** and **33** (Scheme 8B). We also demonstrated epoxidation of **20**, which proceeded in a diastereoselective manner to form **34** in 89% yield (Scheme 8C).

CONCLUSIONS

In summary, we have established a protocol for the synthesis of 1,4-dihydronaphthalene-1-carbonitriles from 1-naphthylmethyl amines by their solvothermal treatment with KH or *n*-BuLi–*t*-BuOK in THF. The process involves unusual two consecutive β-H eliminations of potassium 1-naphthylmethyl amides and subsequent C(4)-selective dearomative hydride addition of freshly generated KH onto 1-naphthonitrile intermediates. The resulting α-cyano benzylic carbanions could be functionalized by a series of electrophiles, liberating the corresponding 1,4-dihydronaphthalene-1-carbonitriles having a quaternary carbon center. The synthetic utility of the method was demonstrated by the formal synthesis of a tricyclic alkaloid, aphanorphine, as well as the facile diastereoselective construction of a series of polycyclic scaffolds. Further investigation to apply the present dearomative protocol for the synthesis of complex molecules is underway in our laboratory.

METHODS

Procedure for the Synthesis of 6 *via* Protonation (Scheme 2C)

In an Ar-filled glovebox, a 25 mL sealed Schlenk tube equipped with a glass-covered stir bar was charged with KH (24.1 mg, 0.601 mmol), 1-naphtylmethylamine (**5**) (78.6 mg, 0.500 mmol), and THF (2.5 mL). The flask was closed and removed from the glovebox, and the mixture was stirred at 100 °C (oil bath) for 1 h. To the deep green reaction mixture was then added excess amounts of acetic acid (570 μL, 10 mmol) at −96 °C (hexane/liquid nitrogen bath). After 10 min, the reaction mixture was poured into 10 mL of pre-cooled 1 M HCl aqueous solution (ice bath) and stirred at 0 °C for 10 min. The organic materials were extracted with CH_2Cl_2 (three times), and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (silica gel, hexane/EtOAc = 19:1) to afford **6** (60.5 mg, 0.390 mmol) in 78% yield.

Procedure for the Synthesis of 7 *via* Benzylation (Scheme 5A)

In an Ar-filled glovebox, a 25 mL sealed Schlenk tube equipped with a glass-covered stir bar was charged with KH (24.1 mg, 0.601 mmol), 1-naphtylmethylamine (**5**) (78.6 mg, 0.500 mmol), and THF (2.5 mL). The flask was closed and removed from the glovebox, and the mixture was stirred at 100 °C (oil bath) for 1 h. To the deep green reaction mixture was added 3-methoxybenzyl bromide (201 mg, 1.0 mmol) at −96 °C (hexane/liquid nitrogen bath). After 1 h, the reaction mixture was quenched with excess amounts of acetic acid (570 μL, 10 mmol) at the same temperature and stirred for additional 10 min. The reaction mixture was poured into 10 mL of pre-cooled 1 M HCl aqueous solution (ice bath) and stirred at 0 °C for 10 min. The organic materials were extracted with CH_2Cl_2 (three times), and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by automated flash chromatography (silica gel, hexane/EtOAc = 19:1) to afford **7** (96.4 mg, 0.350 mmol) in 70% yield.

Procedure for the Synthesis of 17 *via* Cu-Catalyzed Alkylation (Scheme 5B)

In an Ar-filled glovebox, a 25 mL sealed Schlenk tube equipped with a glass-covered stir bar was charged with KH (24.1 mg, 0.601 mmol), 1-naphtylmethylamine (**5**) (78.9 mg, 0.502 mmol), and THF (2.5 mL). The flask was closed and removed from the glovebox, and the mixture was stirred at 100 °C (oil bath) for 1 h. To the deep green reaction mixture were then added CuCN·2LiCl (1 M in THF, 50 μL, 0.05 mmol) and 2-phenylethyl bromide (185 mg, 1.0 mmol) at 0 °C (ice bath). After 1 h, the reaction mixture was cooled to −96 °C (hexane/liquid nitrogen bath), quenched with excess amounts of acetic acid (570 μL, 10 mmol), and stirred for 10 min. The reaction mixture was poured into 10 mL of pre-cooled 1 M HCl aqueous solution (ice bath) and stirred at 0 °C for 10 min. The organic materials were extracted with CH_2Cl_2 (three times), and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (silica gel, hexane/Et_2O = 19:1) to afford **17** (96.1 mg, 0.371 mmol) in 74% yield.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00487.

Experimental procedures, characterization data of compounds, and calculation details (PDF)

Crystal data and structure refinement for **32** (CIF)

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Crystal data and structure refinement for **35** (CIF)

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Author Contributions

CRediT: **Yoshiya Sekiguchi** investigation, writing-original draft; **Jia Hao Pang** investigation; **Jia Sheng Ng** investigation; **Jiahua Chen** investigation; **Kohei Watanabe** investigation; **Ryo Takita** conceptualization, funding acquisition, investigation, methodology, resources, writing-original draft, writing-review & editing; **Shunsuke Chiba** conceptualization, funding acquisition, investigation, methodology, resources, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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