

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

Yoshiya Sekiguchi, Jia Hao Pang, Jia Sheng Ng, Jiahua Chen, Kohei Watanabe, Ryo Takita,* and Shunsuke Chiba*



Cite This: *JACS Au* 2022, 2, 2758–2764



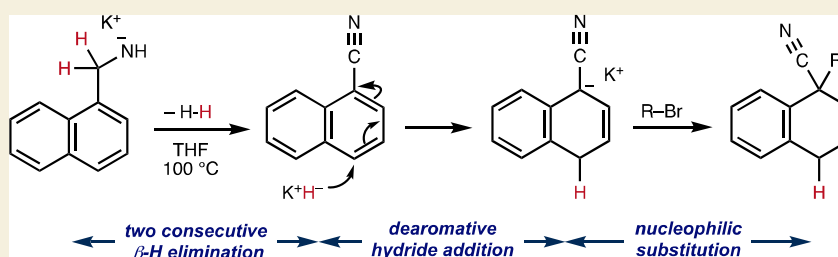
Read Online

ACCESS |

Metrics & More

Article Recommendations

Supporting Information



ABSTRACT: Solvothermal treatment of 1-naphthylmethylenamine 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 PhMe₂SiLi 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 NaBH₄.^{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-naphthylmethylenamine 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.

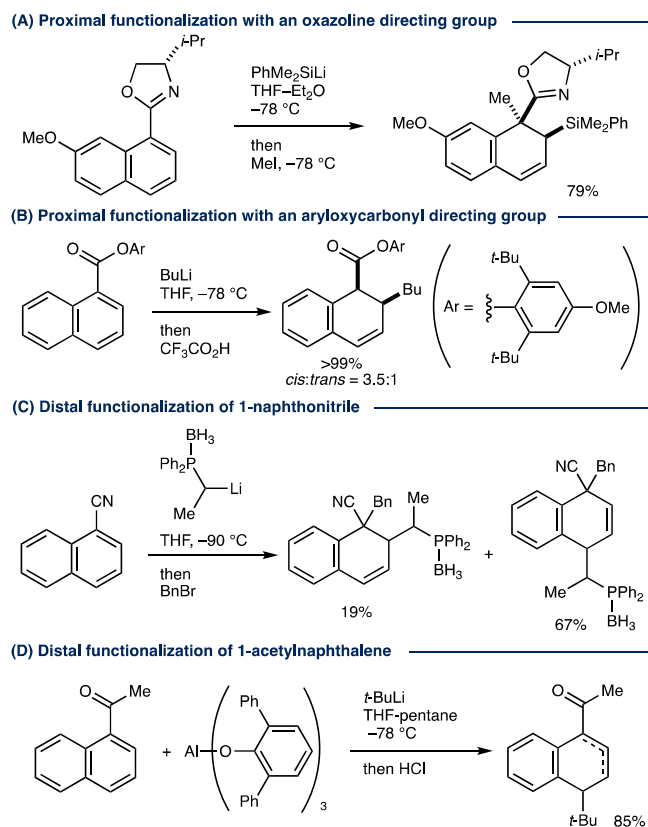
RESULTS AND DISCUSSION

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

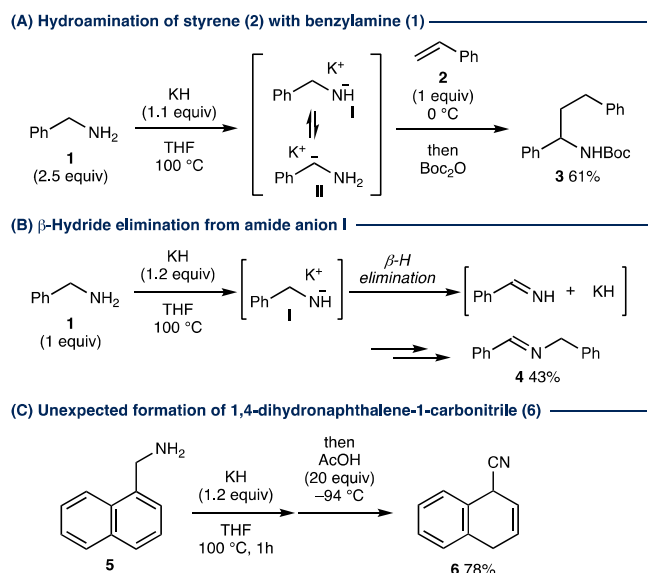
Received: September 6, 2022
Revised: October 27, 2022
Accepted: October 27, 2022
Published: November 30, 2022



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



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

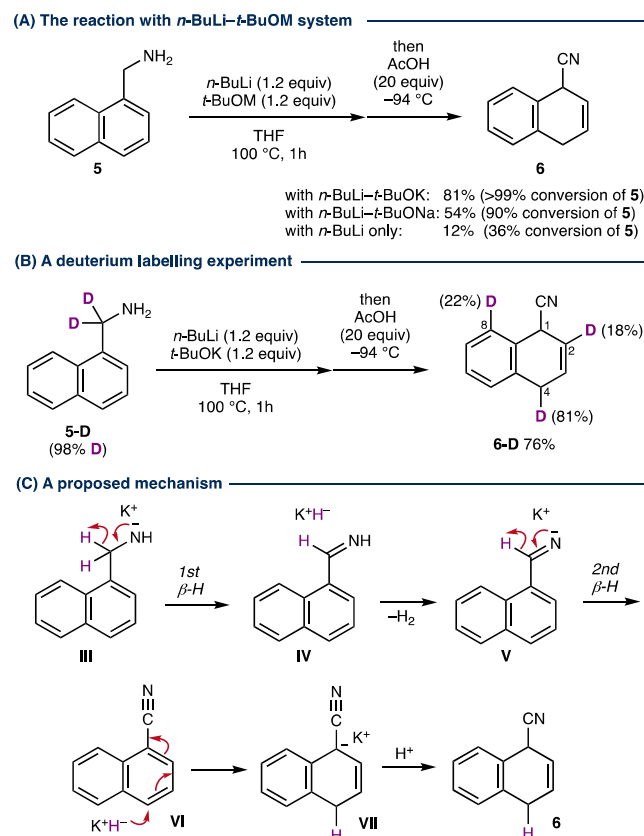


potassium amide I (Scheme 2B).^{18–22} During the course of this study, we were surprised to observe that the treatment of 1-naphthylmethylamine (5) with KH (1.2 equiv) affords 1,4-dihydronaphthalene-1-carbonitrile (6) after careful protonation with acetic acid (AcOH) at -94 °C (Scheme 2C) (see the Supporting 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

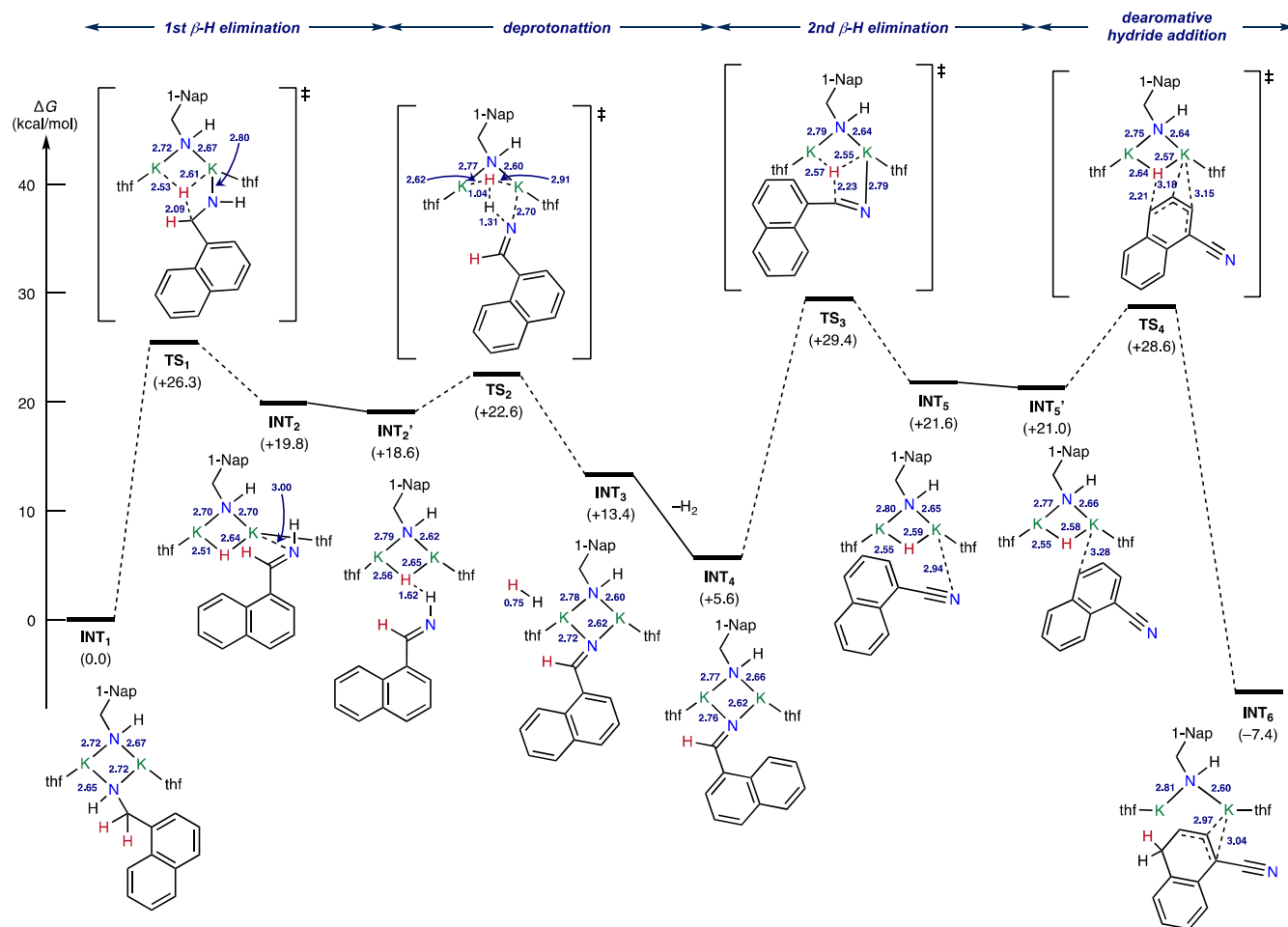
aminomethyl moiety to the cyano group, and thus further detailed investigations were conducted to elucidate the reaction mechanism and to explore its synthetic potential.

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-naphthionitrile VI and KH. The freshly generated KH attacks the C4 position of 1-naphthionitrile 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-naphthionitrile (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

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


^aEnergy 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-naphthionitrile (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).

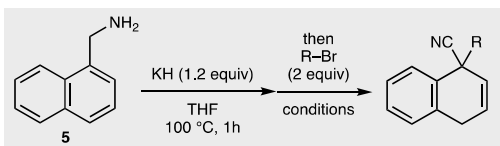
To gain the detailed insights into the reaction pathway of the present dearomative transformation, we carried out density functional theory (DFT) calculations at the M06-2X/6-311++G**/SMD(THF)//M06-2X/6-31+G* level of theory. The diffusion ordered ¹H NMR spectroscopy (¹H DOSY) of potassium amide anion III in *d*₈-THF solution suggested that it might exist as a dimer [KNHCH₂C₁₀H₇·(*d*₈-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 [(KNHCH₂C₁₀H₇·THF)₂] INT₁ 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 TS₁ (ΔG[‡] = +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 (H₂) in an exothermic manner to afford INT₃. After releasing H₂ from INT₃, the resulting imide complex INT₄ undergoes the second β -H elimination *via* TS₃ (ΔG[‡] = +29.4 kcal/mol). Two potassium cations cooperatively accept the hydride anion to facilitate the construction of the cyano group in INT₅. After the conformational change to INT₅', this hydride can attack the C4 position of the resultant 1-naphthionitrile. The transition state TS₄ for the dearomative hydride addition is located at a slightly lower energy than TS₃ (ΔG[‡] = +28.6 kcal/mol), and this step should proceed smoothly and irreversibly under the reaction conditions to afford the α -

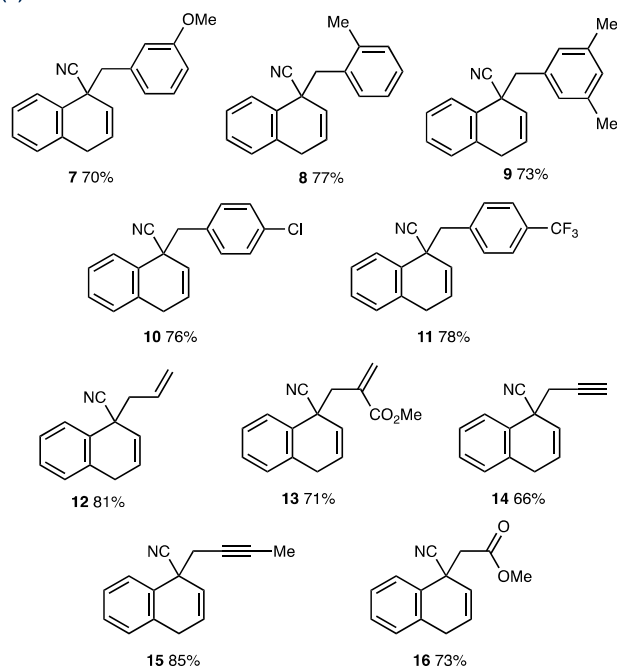
cyano carbanion INT_6 . This irreversible hydride addition renders the present process selective circumventing the potential formation of aldimine (Scheme 2B). Together with the experimental observations on the first β -H elimination (Scheme 2B) and the deuterium labeling experiment (Scheme 3B), the 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

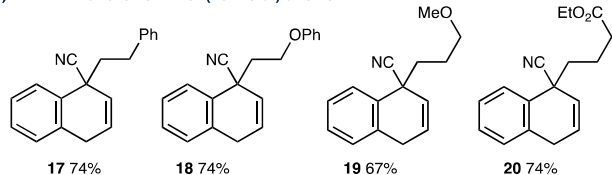
Scheme 5. Construction of the C1 Quaternary Carbon Center with Alkyl Halides



(A) with R-Br at -94°C



(B) with R-Br and $\text{CuCN}\cdot\text{LiCl}$ (10 mol%) at 0°C

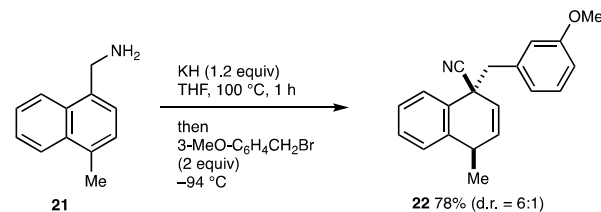


of benzyl bromides could react efficiently at -94°C to afford 7–11 in good yields (Scheme 5A). Similarly, allyl bromides (for 12 and 13) and propargyl bromides (for 14 and 15) as well as methyl bromoacetate (for 16) could be employed. We found that engagement of non-activated alkyl bromides necessitates the aid of $\text{CuCN}\cdot 2\text{LiCl}$ as a catalyst (Scheme 5B).^{42,43} In the presence of $\text{CuCN}\cdot 2\text{LiCl}$ (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).

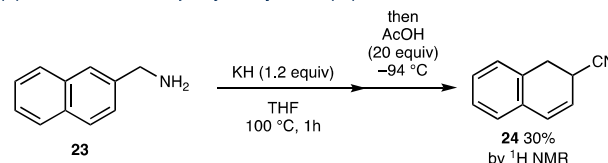
We also found that the present dearomative C4-selective hydride addition was not influenced by the presence of a methyl group at the C4 position of 21 (Scheme 6A). In this case, the

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

(A) Diastereoselective dearomative hydride addition



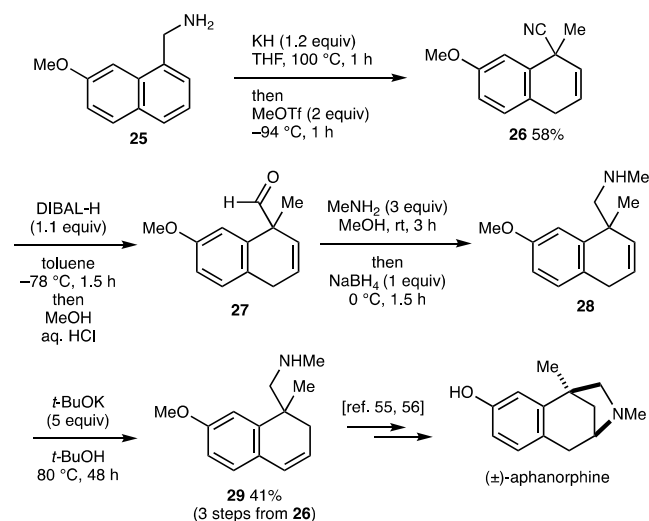
(B) The reaction of 2-naphthylmethanamine (23)



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-naphthylmethanamine (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

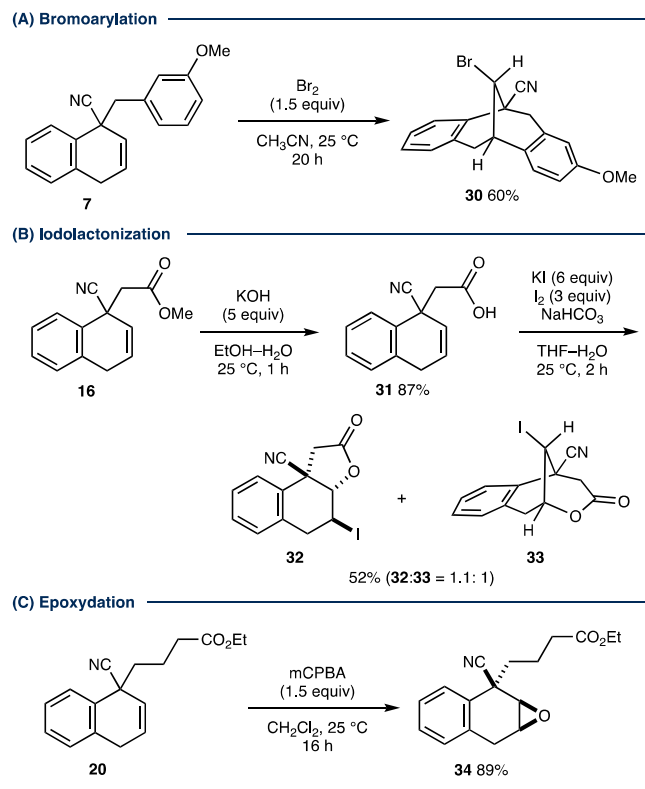
Scheme 7. Formal Synthesis of Aphanorphine



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 (CH₃CN) 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-naphthylmethylamine (**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 μ L, 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 CH₂Cl₂ (three times), and the combined organic phase was washed with brine, dried over Na₂SO₄, 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-naphthylmethylamine (**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 μ L, 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 CH₂Cl₂ (three times), and the combined organic phase was washed with brine, dried over Na₂SO₄, 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-naphthylmethylamine (**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 μ L, 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 μ L, 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 CH₂Cl₂ (three times), and the combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (silica gel, hexane/Et₂O = 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)

Crystal data and structure refinement for 35 (CIF)

AUTHOR INFORMATION

Corresponding Authors

Ryo Takita – Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan; School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka 422-8526, Japan; orcid.org/0000-0003-4104-9890; Email: takita@u-shizuoka-ken.ac.jp

Shunsuke Chiba – School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore; orcid.org/0000-0003-2039-023X; Email: shunsuke@ntu.edu.sg

Authors

Yoshiya Sekiguchi – School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore

Jia Hao Pang – School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore

Jia Sheng Ng – School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore

Jiahua Chen – School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore

Kohei Watanabe – Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan; orcid.org/0000-0002-3146-5439

Complete contact information is available at:
<https://pubs.acs.org/10.1021/jacsau.2c00487>

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.

ACKNOWLEDGMENTS

This work was supported by funding from Nanyang Technological University (NTU) (for S.C.) and the Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2019-T2-1-089 for S.C.) as well as the Naito Foundation (for R.T.). Computational calculations were performed using the resources of the Research Center for Computational Science at Okazaki, Japan (Project nos. 21-IMS-094 and 22-IMS-094). We acknowledge Dr. Yongxin Li (School of Chemistry, Chemical Engineering and Biotechnology, NTU) for assistance in the X-ray crystallographic analysis. We thank Dr. Derek Yiren Ong (JEOL Asia Pte. Ltd.) for his assistance in carrying out ¹H DOSY NMR studies.

REFERENCES

- (1) Sellars, J. D.; Steel, P. G. Advances in the Synthesis of Aryltetralin Lignan Lactones. *Eur. J. Org. Chem.* **2007**, *2007*, 3815–3828.
- (2) Ward, R. S. Lignans, Neolignans and Related Compounds. *Nat. Prod. Rep.* **1997**, *14*, 43–74.
- (3) Huck, C. J.; Sarlah, D. Shaping Molecular Landscapes: Recent Advances, Opportunities, and Challenges in Dearomatization. *Chem* **2020**, *6*, 1589–1603.
- (4) López Ortiz, F.; Iglesias, M. J.; Fernández, I.; Andújar Sánchez, C. M.; Ruiz Gómez, G. Nucleophilic Dearomatizing (DNAr) Reactions of Aromatic C,H-Systems. A Mature Paradigm in Organic Synthesis. *Chem. Rev.* **2007**, *107*, 1580–1691.
- (5) Hulme, A. N.; Henry, S. S.; Meyers, A. I. Asymmetric Synthesis of the Key Intermediates Leading to (–)-Aphanorphine and (–)-Eptazocine. *J. Org. Chem.* **1995**, *60*, 1265–1270.
- (6) Robichaud, A. J.; Meyers, A. I. Asymmetric Additions to Chiral Naphthylloxazolines. An Entry into Tetracyclic Terpene Ring Systems Related to Aphidicolin, Scopadulcic Scid, and Kauranes. *J. Org. Chem.* **1991**, *56*, 2607–2609.
- (7) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. Asymmetric Tandem Addition to Chiral 1- and 2-Substituted Naphthalenes. Application to the Synthesis of (+)-Phyltetralin. *J. Am. Chem. Soc.* **1988**, *110*, 4611–4624.
- (8) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K.-i. Electronic and Steric Control in Regioselective Addition Reactions of Organolithium Reagents with Enaldehydes. *J. Org. Chem.* **2001**, *66*, 7051–7054.
- (9) Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. Stereospecific 1,4-Addition of Organolithium Reagents to Unprotected 1- and 2-Naphthalenecarboxylic Acids. A Facile Route to 1,1,2- and -1,2,2-Trisubstituted 1,2-Dihydronaphthalenes. *J. Org. Chem.* **1996**, *61*, 5206–5207.
- (10) Tomioka, K.; Shindo, M.; Koga, K. Conjugate Addition Reaction of Organolithiums to Naphthalenecarboxylates. *Tetrahedron Lett.* **1990**, *31*, 1739–1740.
- (11) Adújar Sánchez, C. M.; Iglesias, M. J.; López Ortiz, F. Dearomatization of 1- and 2-Cyanonaphthalene through Nucleophilic Conjugate Addition. *Tetrahedron Lett.* **2002**, *43*, 2565–2568.
- (12) Maruoka, K.; Ito, M.; Yamamoto, H. Unprecedented Nucleophilic Addition of Organolithiums to Aromatic Aldehydes and Ketones by Complexation with Aluminum Tris(2,6-diphenylphenoxide). *J. Am. Chem. Soc.* **1995**, *117*, 9091–9092.
- (13) Saito, S.; Sone, T.; Shimada, K.; Yamamoto, H. Conjugate Addition of Lithium Enolates to Aromatic Carbonyl Compounds Complexed with Aluminum Tris(2,6-diphenylphenoxide) (ATPH). *Synlett* **1999**, *1999*, 81–83.
- (14) Saito, S.; Shimada, K.; Yamamoto, H.; de Marigorta, E. M.; Fleming, I. A New Synthetic Route to Allylsilanes: the Reaction of Silyllithium Reagents with Aromatic Carbonyl Compounds and Aluminum Tris(2,6-diphenylphenoxide) (ATPH). *Chem. Commun.* **1997**, 1299–1300.
- (15) Severin, T.; Schmitz, R. Umsetzung von Nitroaromaten mit Natriumborhydrid. *Chem. Ber.* **1962**, *95*, 1417–1419.
- (16) Severin, T.; Schmitz, R.; Temme, H.-L. Umsetzung von Nitroaromaten mit Natriumborhydrid, III. *Chem. Ber.* **1963**, *96*, 2499–2503.
- (17) Pang, J. H.; Wang, B.; Watanabe, K.; Takita, R.; Chiba, S. Hydroalkylation of Styrenes with Benzylamines by Potassium Hydride. *Helv. Chim. Acta* **2021**, *104*, No. e2100120.
- (18) Flynn, M. T.; Stott, R.; Blair, V. L.; Andrews, P. C. Loss of Chirality through Facile Lewis Base Mediated Aza-enolate Formation in Na and K (S)-N-(α -Methylbenzyl)methylamides. *Organometallics* **2016**, *35*, 2707–2714.
- (19) Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. Identifying the Roles of Amino Acids, Alcohols and 1,2-Diamines as Mediators in Coupling of Haloarenes to Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 17818–17826.
- (20) Andrews, P. C.; Koutsaplis, M.; Robertson, E. G. Thermodynamically Favored Anion Rearrangements in Li and Na Complexes of

- (S)-N- α -(Methylbenzyl)allylamine. *Organometallics* **2009**, *28*, 1697–1704.
- (21) Andrews, P. C.; Armstrong, D. R.; Baker, D. R.; Mulvey, R. E.; Clegg, W.; Horsburgh, L.; O'Neil, P. A.; Reed, D. Synthetic, Structural, Mechanistic, and Theoretical MO Studies of the Alkali-Metal Chemistry of Dibenzylamine and Its Transformation to 1,3-Diphenyl-2-azaallyl Derivatives. *Organometallics* **1995**, *14*, 427–439.
- (22) Andrews, P. C.; Armstrong, D. R.; Mulvey, R. E.; Reed, D. Evidence for Extreme Activation of Carbon-hydrogen Bonds in [(PhCH₂)₂NNa]_n: Resultant Carbon-hydrogen Bond Cleavage to Give {[PhC(H)NC(H)Ph]Na-PMDETA}_n. *J. Am. Chem. Soc.* **1988**, *110*, 5235–5236.
- (23) Ong, D. Y.; Pang, J. H.; Chiba, S. Sodium and Potassium Complexes in Organic Synthesis. In *Comprehensive Organometallic Chemistry IV*; Parkin, G., Meyer, K., O'Hare, D., Eds.; Elsevier: Oxford, 2022; Vol. 11, pp 57–77.
- (24) Schlosser, M. Superbases for Organic Synthesis. *Pure Appl. Chem.* **1988**, *60*, 1627–1634.
- (25) Ong, D. Y.; Fan, D.; Dixon, D. J.; Chiba, S. Transition-Metal-Free Reductive Functionalization of Tertiary Carboxamides and Lactams for α -Branched Amine Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 11903–11907.
- (26) Chan, G. H.; Ong, D. Y.; Yen, Z.; Chiba, S. Reduction of N,N-Dimethylcarboxamides to Aldehydes by Sodium Hydride–Iodide Composite. *Helv. Chim. Acta* **2018**, *101*, No. e1800049.
- (27) Huang, Y.; Chan, G. H.; Chiba, S. Amide-Directed C–H Sodiotion by a Sodium Hydride/Iodide Composite. *Angew. Chem., Int. Ed.* **2017**, *56*, 6544–6547.
- (28) Ong, D. Y.; Tejo, C.; Xu, K.; Hirao, H.; Chiba, S. Hydrodehalogenation of Haloarenes by a Sodium Hydride-Iodide Composite. *Angew. Chem., Int. Ed.* **2017**, *56*, 1840–1844.
- (29) Too, P. C.; Chan, G. H.; Tnay, Y. L.; Hirao, H.; Chiba, S. Hydride Reduction by a Sodium Hydride–Iodide Composite. *Angew. Chem., Int. Ed.* **2016**, *55*, 3719–3723.
- (30) Martin, J.; Eyslein, J.; Grams, S.; Harder, S. Hydrogen Isotope Exchange with Superbulky Alkaline Earth Metal Amide Catalysts. *ACS Catal.* **2020**, *10*, 7792–7799.
- (31) Rösch, B.; Gentner, T. X.; Elsen, H.; Fischer, C. A.; Langer, J.; Wiesinger, M.; Harder, S. Nucleophilic Aromatic Substitution at Benzene with Powerful Strontium Hydride and Alkyl Complexes. *Angew. Chem., Int. Ed.* **2019**, *58*, 5396–5401.
- (32) Woltornist, R. A.; Collum, D. B. Sodium Hexamethyldisilazide: Using ¹⁵N–²⁹Si Scalar Coupling to Determine Aggregation and Solvation States. *J. Am. Chem. Soc.* **2020**, *142*, 6852–6855.
- (33) Mulks, F. F.; Bole, L. J.; Davin, L.; Hernán-Gómez, A.; Kennedy, A.; García-Alvarez, J.; Hevia, E. Ambient Moisture Accelerates Hydroamination Reactions of Vinylarenes with Alkali-Metal Amides under Air. *Angew. Chem., Int. Ed.* **2020**, *59*, 19021–19026.
- (34) Neufeld, R.; John, M.; Stalke, D. The Donor-Base-Free Aggregation of Lithium Diisopropyl Amide in Hydrocarbons Revealed by a DOSY Method. *Angew. Chem., Int. Ed.* **2015**, *54*, 6994–6998.
- (35) Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; Ramsay, D. L.; Robertson, S. D. Concealed Cyclotrimeric Polymorph of Lithium 2,2,6,6-Tetramethylpiperidide Unconcealed: X-Ray Crystallographic and NMR Spectroscopic Studies. *Chem.—Eur. J.* **2013**, *19*, 14069–14075.
- (36) Kennedy, A. R.; Klett, J.; O'Hara, C. T.; Mulvey, R. E.; Robertson, G. M. Structural Elucidation of tmeda-Solvated Alkali Metal Diphenylamide Complexes. *Eur. J. Inorg. Chem.* **2009**, *2009*, 5029–5035.
- (37) Gärtner, M.; Görls, H.; Westerhausen, M. Poly[[μ -dioxane- κ^2 O':O'-dioxane- κ O- μ -diphenylamido- κ^2 N:N-potassium] Dioxane Solvate]. *Acta Crystallogr.* **2007**, *E63*, m2287–m2288.
- (38) Antolini, F.; Hitchcock, P. B.; Khvostov, A. V.; Lappert, M. F. Synthesis and Structures of Alkali Metal Amides Derived from the Ligands [N(SiMe₂Ph)(SiMe₃)][−], [N(tBu)(SiMe₃)][−], [N(Ph)(2-C₅H₄N)][−], and [N(2-C₅H₄N)₂][−]. *Eur. J. Inorg. Chem.* **2003**, *2003*, 3391–3400.
- (39) We also calculated using a potassium amide monomer [KCH₂C₁₀H₇(THF)₂]. See the [Supporting Information](#) for details.
- (40) Fleming, F. F.; Zhang, Z. Cyclic Nitriles: Tactical Advantages in Synthesis. *Tetrahedron* **2005**, *61*, 747–789.
- (41) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. Addition and Substitution Reactions of Nitrile-Stabilized Carbanions. *Org. React.* **1984**, *31*, 1–364.
- (42) Yang, X.; Nath, D.; Morse, J.; Ogle, C.; Yurtoglu, E.; Altundas, R.; Fleming, F. Cyclic Alkenenitriles: Copper-Catalyzed Deconjugative α -Alkylation. *J. Org. Chem.* **2016**, *81*, 4098–4102.
- (43) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. Metalated Nitriles: Organolithium, -magnesium, and -copper Exchange of α -Halonenitriles. *J. Org. Chem.* **2005**, *70*, 2200–2205.
- (44) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. Aphanorphine, A Novel Tricyclic Alkaloid from the Blue-green Alga *Aphanizomenon flos-aquae*. *Tetrahedron Lett.* **1988**, *29*, 4381–4384.
- (45) Zhang, C.; Hu, W.; Lovinger, G. J.; Jin, J.; Chen, J.; Morken, J. P. Enantiomerically Enriched α -Borylzinc Reagents by Nickel-Catalyzed Carbozincation of Vinylboronic Esters. *J. Am. Chem. Soc.* **2021**, *143*, 14189–14195.
- (46) Wang, C.; Guan, Y. Concise Total Synthesis of (+)-Aphanorphine. *Synlett* **2021**, *32*, 913–916.
- (47) Chiou, W.-H.; Chen, P.-C. Synthesis of (\pm)-Aphanorphine Using Rh-Catalyzed Cyclohydrocarbonylation. *J. Org. Chem.* **2017**, *82*, 8213–8219.
- (48) Zhu, D.-Y.; Xu, M.-H.; Tu, Y.-Q.; Zhang, F.-M.; Wang, S.-H. Catalytic Asymmetric Construction of α -Quaternary Cyclopentanones and Its Application to the Syntheses of (−)-1,14-Herbertenediol and (−)-Aphanorphine. *Chem. - Eur. J.* **2015**, *21*, 15502–15505.
- (49) Wang, Z.; Zheng, H.; Yang, J.; Xie, X.; She, X. Gold(I)-Catalyzed Tandem Reaction of γ -Amino-Substituted Propargylic Esters to Pyrrolines and its Application in the Formal Synthesis of (\pm)-Aphanorphine. *Adv. Synth. Catal.* **2015**, *357*, 2082–2088.
- (50) Peterson, L. J.; Wolfe, J. P. Palladium-Catalyzed Alkene Carboamination Reactions of Electron-Poor Nitrogen Nucleophiles. *Adv. Synth. Catal.* **2015**, *357*, 2339–2344.
- (51) Yang, X.; Zhai, H.; Li, Z. Enantiocontrolled Synthesis of (−)-9-epi-Pentazocine and (−)-Aphanorphine. *Org. Lett.* **2008**, *10*, 2457–2460.
- (52) Grainger, R. S.; Welsh, E. J. Formal Synthesis of (−)-Aphanorphine Using Sequential Photomediated Radical Reactions of Dithiocarbamates. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377–5380.
- (53) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. Synthesis of (−)-Aphanorphine Using Aryl Radical Cyclization. *Org. Lett.* **2001**, *3*, 2427–2429.
- (54) Fuchs, J. R.; Funk, R. L. Total Synthesis of (\pm)-Lennoxamine and (\pm)-Aphanorphine by Intramolecular Electrophilic Aromatic Substitution Reactions of 2-Amidoacroleins. *Org. Lett.* **2001**, *3*, 3923–3925.
- (55) Meyers, A. I.; Schmidt, W.; Santiago, B. Asymmetric Syntheses of O-Methylaphanorphine. *Heterocycles* **1995**, *40*, 525–529.
- (56) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. The Enantioselective Total Synthesis of Natural (−)-Aphanorphine. *J. Chem. Soc., Chem. Commun.* **1990**, 290–292.
- (57) Uthoff, F.; Löwe, J.; Harms, C.; Donsbach, K.; Gröger, H. Chemoenzymatic Synthesis of a Chiral Ozanimod Key Intermediate Starting from Naphthalene as Cheap Petrochemical Feedstock. *J. Org. Chem.* **2019**, *84*, 4856–4866.
- (58) Miller, B.; Shi, X. Novel Rearrangement and Cyclization Processes Resulting from Bromination of 1,1-Dibenzyltetralin Derivatives. *J. Org. Chem.* **1992**, *57*, 1677–1681.