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(Citation)
Tetrahedron Green Chem,4:100052

(Issue Date)
2024-12

(Resource Type)
journal article

(Version)
Version of Record

Tetrahedron Green Chem 4 (2024) 100052

Contents lists available at ScienceDirect

Tetrahedron Green Chem

journal homepage: www.journals.elsevier.com/tetrahedron-green-chem

Sodium dispersion-mediated reductive dimerization of benzylic halides for symmetrical bibenzyls: Column-free applications to natural products

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ARTICLE INFO

Keywords:
Bibenzyls
Natural product
Reductive dimerization
Reductive homocoupling
Decagram-scale synthesis
Sodium dispersion
Sustainability

ABSTRACT

We report a method for the synthesis of symmetrical bibenzyls by the reductive dimerization of benzylic halides using sodium dispersion (SD). SD, a reagent consisting of sodium particles dispersed in mineral oil, has recently attracted attention as a safer but more reactive source of sodium than sodium lump. We have found that the reductive dimerization of benzylic halides proceeds within 1 h at room temperature in tetrahydrofuran (THF) solvent using SD as a reducing agent. This method is highly sustainable for the synthesis of symmetrical bibenzyls since it uses sodium, which is abundant on earth. As the SD-derived mineral oil in the crude product can be readily removed, three natural products were synthesized on a gram scale without the need for column chromatography. The utility of this reaction was also exemplified by a decagram-scale reaction using 2-methyltetrahydrofuran, known as a green alternative solvent to THF.

1. Introduction

Bibenzyls are a group of compounds with a 1,2-diarylethylene skeleton, widely found in natural products [1], organic materials [2], synthetic intermediates [3], and other valuable substances [4]. The structures of bibenzyls are classified as either symmetrical or unsymmetrical ones based on whether their two aryl groups are identical or not. Both types of bibenzyls have been widely found in nature, occasionally showing a diverse array of biological activities [5–8]. Selected examples of symmetrical bibenzyl natural products are shown in Fig. 1 [6–9]. Brittonin A has been reported to exhibit anti-cancer activity [6], orchid-derived 4,4′-dihydroxybibenzyl exhibits estrogen receptor binding affinity [7], and a liverwort-derived bibenzyl with two methylenedioxy groups exhibits calmodulin inhibitory activity [8]. By contrast to these bioactive examples, the possible bioactivities of a number of bibenzyls remain unclear, as exemplified by orchid-derived 4,4′-dimethoxybibenzyl [9]. A wide variety of synthetic methods for bibenzyls [10–28] have been developed due to their potential usefulness as drug discovery resources and so on.

One of the most representative synthetic methods for symmetrical bibenzyls is reductive dimerization of benzylic halides (Fig. 2) [11–27]. This type of reactions was most classically achieved by utilizing stoichiometric or greater amounts of metal reductants (Fig. 2A) [11–19]. The method using sodium lump as the reductant [10a], commonly known as Würtz reaction, is a good option in terms of sustainability since sodium is highly abundant on earth and inexpensive. However, the reaction suffers from high reaction temperature, long reaction time, and the high pyrophoricity or dangerousness of sodium, which could cause fire and explosion. Although the methods using magnesium [11] and zinc (silver) [12] as the reductants take advantage of the non-pyrophoric metal reductants, they suffer from long reaction time and/or low yields of the bibenzyls. While Würtz-type reaction using other metals including indium [13], cobalt [14], and lithium [15] takes advantage of moderate to high yields, these stoichiometrically-used metal reductants are precious and/or expensive. Additionally, the functional group compatibility of these reactions remains unclear since the benzylic halide substrates investigated in these systems were highly limited. Highly reactive Rieke metal (manganese [16], nickel [17], and copper [18])-using reactions result in high yields within short reaction time. However, Rieke metals are need to be prepared from the corresponding metal halides by the stoichiometric use of precious lithium-derived naphthalenide [16–18], or highly pyrophoric potassium metal [19]. Therefore, it has been desired to develop other bibenzyl-forming dimerization reactions free from such drawbacks.

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https://doi.org/10.1016/j.tgchem.2024.100052
Received 10 July 2024; Received in revised form 13 August 2024; Accepted 19 August 2024

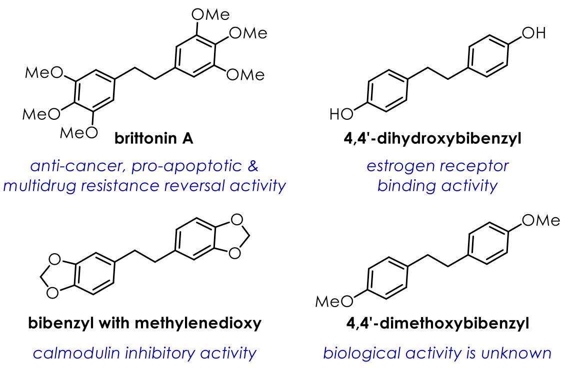


Fig. 1. Natural symmetrical bibenzyls.

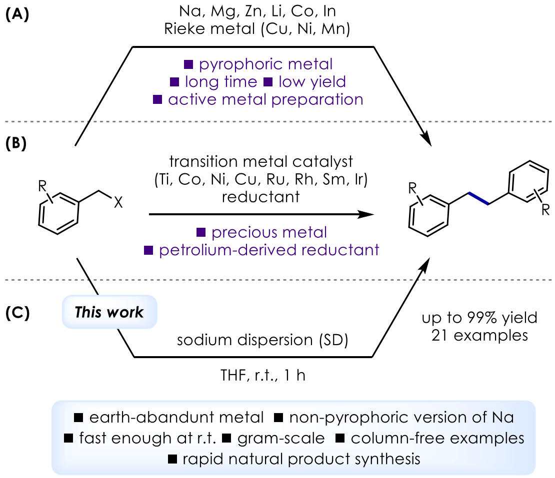


Fig. 2. Reductive dimerization reactions of benzylic halides: (A) stoichiometric, (B) catalytic, and (C) present works.

In recent years, reductive dimerization reactions of benzylic halides have also been accomplished in a large number of transition metal-catalyzed systems as more practical alternatives [20–26]. These methods often afford symmetrical bibenzyls in high yields without elevated temperature and long reaction time [21]. Due to the mild feature of the reported conditions, the accessible bibenzyls could possess a broad range of functionalities such as ester, formyl, and nitro groups [22]. However, these methods mostly require precious metal-derived catalysts [22a,22b,23] and/or reductants [24], and occasionally utilize petroleum-derived reductants [22a,22c,25]. As sustainable alternative methods, several copper-catalyzed approaches were exceptionally mediated by inexpensive iron as the reductant [27]. In addition these reactions proceed in water, one of the best solvents in terms of sustainability. Although they do not employ any precious reductant and solvent, the systems require heating to proceed, mostly resulting in moderate yields. In order to address these issues, we decided to develop a complementary benzylic halide-dimerization system with sustainability. By contrast to such recent mainstream, we paid attention to Würtz reaction [10a], which is one of the most classical methods in this research field. This method was achieved only by sodium (lump), which is inexpensive with no depletion risk due to its abundance on earth. However, its applications are extremely limited at the present time probably because of its low reaction rate and significant fire/explosion risk. We envisioned that the reductive dimerization of benzylic halides could be efficiently mediated by sodium dispersion (SD) [28] instead of the classically-used sodium lump. SD is a fine-particle form of metallic sodium, dispersed in mineral oil, and featured by safe and markedly highly reactive characters, due to the coating and increased surface area of sodium [28].

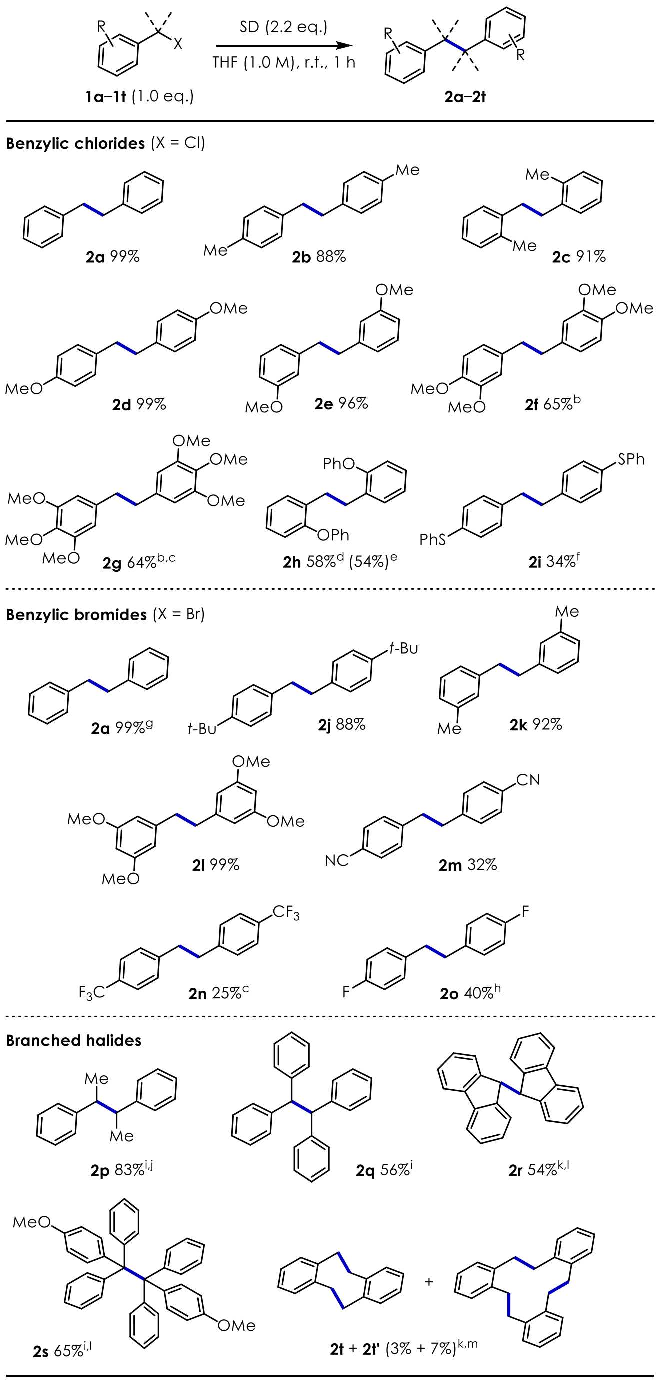
Herein, we report that various benzylic halides are rapidly dimerized by SD in tetrahydrofuran (THF) as the solvent at room temperature (r.t.) to give symmetrical bibenzyls in good yields (Fig. 2C). The substrate scope and limitation of this method were confirmed by twenty-four benzylic halide substrates. The method was applied to column-free gram-scale total synthesis of three natural bibenzyls. The reaction also efficiently proceeded when using 2-methyltetrahydrofuran (2-MeTHF), a sustainable solvent [29] which is derived from biomass, instead of THF in a decagram scale experiment.

2. Results and discussion

We initially investigated the SD-mediated reductive dimerization of benzyl chloride **1a** as the model substrate (Scheme 1). As the solvent, we tested THF, which has been frequently used in many other reported SD-using reactions [28], for the aimed dimerization reaction. To our delight, the reaction of **1a** completed within 1 h when using 1.5 eq. of SD (for the details of SD used in this research, see the Materials section in Supplementary Material) at r. t., yielding the corresponding bibenzyl **2a** quantitatively (see Table S1 in Supplementary Material). The reaction also proceeded without problems with the amount of SD increased to 2.2 eq. to afford **2a** in quantitative yield. It was supposed that this condition with the larger amount of SD would be superior in terms of reproducibility in glove box-free systems. Based on this understanding, we next focused on investigating the substrate scope of the found bibenzyl-forming reaction condition with 2.2 eq. of SD (for Na lump-using reactions, see Table S2 in Supplementary Material).

We first investigated reductive dimerization reactions using various benzylic chlorides (**1a–1i**). The reaction of substrate **1b** with a methyl group at the C4 position, gave bibenzyl **2b** in high yield (88 %). The reaction of benzylic chloride **1c** with a methyl group substituted at the C2 position proceeded smoothly without suffering from the increased steric hindrance around the reacting benzylic carbon to provide bibenzyl **2c** in 91 % yield. The reaction of benzylic chloride **1d** with an electron-donating methoxy group at the C4 position also gave bibenzyl **2d** quantitatively (99 %). Also when using 3-methoxy group having benzylic chloride **1e,** bibenzyl **2e** was obtained in high yield (96 %). In the case of benzylic chloride **1f** with multiple methoxy groups on the benzene ring, the reaction resulted in the decreased yield (65 %) of bibenzyl **2f** due to some unidentified side reactions. Trimethoxy-substituted benzylic chloride **1g** afforded bibenzyl **2g** also in a decreased yield (64 %), due to the side reactions where 4- and 4′-methoxy groups were replaced with hydrogens [30] to give a side product in 20 % yield (see Supplementary Material for details). When 2-phenoxy-substituted benzylic chloride **1h** was used, bibenzyl **2h** was afforded in 58 % yield. It was speculated that this decreased yield was caused by SD-mediated reductive removal of the phenoxy group based on the formation of 2-phenoxybibenzyl **2h'**. In the case of 4-phenylthio-substituted benzylic chloride **1i**, non-substituted bibenzyl **2a** (8 % yield) was also generated along with **2i** (34 % yield) due to the elimination of the phenylthio groups. While the reaction of 3-(chloromethyl)pyridine hydrochloride with a heterocyclic unit was also tested, it did not yield the corresponding bibenzyl due to side reactions.

The reactions with benzylic bromides (**1a**–**Br**, and **1j**–**1o**) instead of benzylic chlorides (**1a**–**1i**) were then examined. When benzyl bromide **1a-Br** was used instead of benzyl chloride **1a**, bibenzyl **2a** was also formed quantitatively. The reactions of C3- and C4-alkyl group-substituted substrates **1j** and **1k** also yielded the corresponding bibenzyls **2j** and **2k** in high yields (88 % and 92 % yields, respectively). The reaction of 3,5-dimethoxybenzyl bromide **1l** quantitatively gave bibenzyl **2l** without any problems of side reactions unlike the cases of **1f** and **1g**. The substrates **1m**, **1n**, and **1o** with electron-withdrawing cyano, trifluoromethyl, and fluoro substituents formed significant amounts of unidentified side products as well as only low yields of the desired bibenzyls **2m**, **2n**, and **2o** (32 %, 25 %, and 40 % yields,

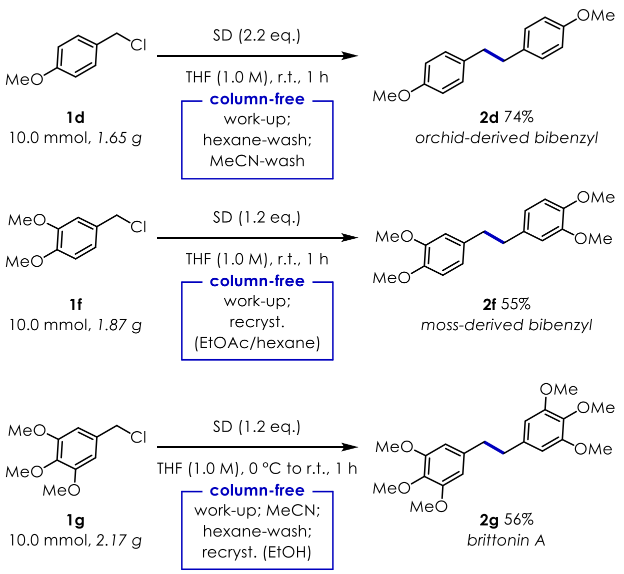


Scheme 1. Reductive dimerization of benzylic halides **1a**–**1t** with SD to from symmetrical bibenzyls **2a**–**2t**.[a] (a) Reactions were performed with benzylic halides **1** (1.0 eq.), SD (2.2 eq.), and THF (1.0 M) at r.t. for 1 h, unless otherwise stated. (b) Reactions were performed with SD (1.2 eq.). (c) Yield was determined by ^{1}H NMR using triphenylmethane as internal standard. (d) 2-Phenoxybibenzyl **2d′** was also obtained in 16 % yield. (e) Reaction was performed with SD (1.2 eq.) to give **2d** (54 %) after recrystallization. (f) Reaction was performed with SD (1.1 eq.) for 20 h. (g) Benzyl bromide (**1a-Br**) was used instead of **1a**. (h) Reaction was performed with SD (1.1 eq.) for 4 h. (i) Benzylic chloride substrate (X = Cl) was used. (j) **2p** was obtained as a diastereomeric mixture (*dl/meso* = 1/1). (k) Benzylic bromide substrate (X = Br) was used. (l) Reactions were performed with SD (1.0 eq.) at 0 °C to r.t. (m) Reaction was performed with SD (4.4 eq.), and THF (0.050 M).

respectively). In the cases of 4-iodo- and 4-benzoyl-substituted benzylic chlorides, no symmetrical bibenzyls were obtained, as the reactions resulted in complex mixtures.

We subsequently examined reactions using benzylic halides with secondary and tertiary benzylic carbons **1p**–**1t** as substrates. The reaction of 1-phenethyl chloride **1p** proceeded smoothly, generating the corresponding bibenzyl **2p** as a 1:1 diastereomeric mixture in 83 % yield. On the other hand, when benzhydryl chloride **1q** where its benzylic carbon is branched with an additional phenyl group was treated with SD, the yield of the corresponding bibenzyl **2q** was decreased to 56 %. This is presumably due to the increased steric hindrance at the reacting benzylic carbon, and/or the stabilization/deactivation of benzylic radical and/or anion intermediates by the π-conjugation system extended by the added phenyl groups. The reaction of fluorenyl bromide **1r** gave fluorenane in 52 % yield, presumably resulting from protonation of the fluorenyl anion without any observation of the desired bibenzyl **2r**. This is possibly because of the high aromatic stability or less reactivity of fluorenyl anion, which is formed by the reduction of substrate **1r**. Although substrate **1r** needs to be involved in the SD-mediated dimerization as the reaction partner with in situ generated benzylic radical and/or anion species in order to form bibenzyl **2r**, the competing fluorenyl anion-forming substrate consumption would have been too fast to dimerize with the radical and/or anion intermediates. Conducting the reaction of **1r** at 0 °C to suppress fluorenane formation foutunately gave **2r** in 54 % yield. The use of triarylmethyl chloride **1s** as a substrate also gave a complex mixture without the formation of the corresponding bibenzyl **2s**. Instead, performing the reaction at 0 °C delightfully afforded **2s** in a moderate yield (65 %). In the system utilizing dibromoxylene **1t** with two halogenated benzylic carbons as a substrate, the corresponding cyclophane **2t** was obtained only in 3 % yield due to various competing side reactions, along with trimer **2t’** (7 % yield). We also attempted to synthesize an unsymmetrical bibenzyl by reacting benzyl bromide (**1a-Br**) and 4-methoxybenzyl chloride (**1d**). However, the desired cross-coupling product, 4-methoxybibenzyl, was obtained in low yield (8 %) due to the competition from homo-coupling reactions, which led to the formation of symmetrical bibenzyls, **2a** and **2d** (see Scheme S1 in the Supplementary Material).

Next, we applied our method for the larger-scale and column-free total synthesis of bibenzyl-type natural products, 4,4′-dimethoxybibenzyl (**2d**), 3,3′,4,4′-tetramethoxybibenzyl (**2f**), and brittonin A (**2g**). These natural products have been isolated from an Orchidaceae



Scheme 2. Application to column-free natural product synthesis.

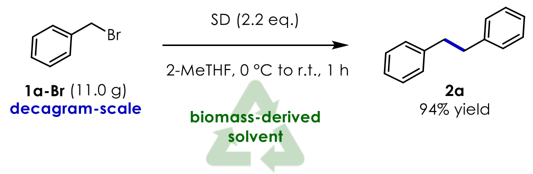
plant, *Dendrobium devoniam* [31], and liverworts, *Frullania inouei* [32], and *Frullania musciola* (Scheme 2) [32,33]. Notably, **2f** and **2g** are known to exhibit anti-cancer activities [6,32], while the biological function of **2d** has not been reported to date. We anticipated that SD-derived mineral oil, which inevitably contaminates each crude product, could be easily removed without column purification owing to its high lipophilicity. It would be facile to scale up the reactions to obtain larger quantities of bibenzyls through column-free purification processes. When a gram-scale reaction was performed with 4-methoxybenzyl chloride **1d** (10.0 mmol, 1.65 g), it was successful to remove the mineral oil from the crude solid product by washing with hexane. Subsequent washing the crude with acetonitrile to remove other side products yielded an orchid-derived bibenzyl **2d** in 74 % yield in pure form (Scheme 2, first row). In the case of 3,4-dimethoxybenzyl chloride **1f** (10.0 mmol, 1.87 g), the removal of side products in addition to mineral oil was accomplished by recrystallizing the crude product in a mixed solvent system of ethyl acetate and hexane to provide a liverwort-derived bibenzyl **2f** (Scheme 2, second row). The mineral oil included in the crude product, which was obtained from the reaction with **1g** (10.0 mmol, 2.17 g) was removed by washing the crude solution in acetonitrile with hexane. After concentrating the solution, the resulting residue was recrystallized from hot ethanol to give brittonin A (**2g**) in 56 % yield (Scheme 2, third row). As above, we have demonstrated that SD-derived mineral oil was easy-to-remove through column-free purification processes to obtain three bibenzyl natural products in practically good yields via (multi)gram-scale reactions.

Then, we performed the reaction on a decagram scale using biomass-derived 2-MeTHF instead of THF, which is preferred in terms of sustainability (Scheme 3). It was turned out that the reaction of benzyl bromide **1a-Br** (11.0 g), and 2.2 eq. of SD in 2-MeTHF was significantly exothermic. Therefore, SD was slowly added to the system with stirring while the flask in an ice-water bath. After adding SD, the reaction flask was removed from the cooling bath and the mixture was stirred at r.t. for 1 h. The resulting crude was purified to yield **2a** in high yield (94 %), similarly to the case of the reaction conducted in THF as the solvent. Finally in order to estimate the sustainability of our method, we calculated three green metrics [34]—reaction mass efficiency, atom economy, and mass intensity—for the present and eight previously reported methods, and compared them. The results demonstrate that our discovered method outperforms the others (see Table S3 in Supplementary Material).

Mechanistically, there are two possible reaction pathways (Fig. 3): the first one is radical-radical coupling leads to the formation of bibenzyl **2** (Fig. 3, path A). In this pathway, benzylic halide **1** is first reduced by SD-derived electron (e^-) by single electron transfer (SET) to generate radical anion species **3**. The subsequent homolytic cleavage of the C–X bond of this radical anion **3** produces sodium halide (NaX) and benzylic radical **4**. Radical-radical coupling between two molecules of this benzylic radical **4** produces bibenzyl **2**. The other pathway involves substitution reaction (Fig. 3, path B). In this process, benzylic radical **4** is reduced by second SET to form benzylic sodium species **5**. This nucleophilic species **5** then undergoes substitution through S_N1 and/or S_N2 reactions with the remaining electrophile **1** to give bibenzyl **2**.

3. Conclusion

We have developed a reductive dimerization reaction for benzylic halides using SD, a safe source of metallic sodium, as the reducing agent. When SD was applied to THF solutions of various benzylic halides at r.t., the reaction proceeded quickly, yielding various bibenzyls in high yields within 1 h. The substrate scope of this reaction was confirmed using twenty-four different benzylic halides, giving symmetric bibenzyls in good yields in many cases. The reaction was found to give symmetric bibenzyls in moderate to high yields, even when the benzyl carbon of the substrate was branched. On the other hand, when the aromatic ring of the substrate was substituted with alkoxy, phenoxy, phenylthio, cyano, trifluoromethyl, or fluoro groups, and dibromoxylene was used as the substrate, the yields of bibenzyls were low to moderate, which was caused by various side reactions. The SD-derived mineral oil included in the crude product was easy-to-remove through column-free purification protocols, allowing the gram-scale and column-free total synthesis of three bibenzyl natural products **2d**, **2f**, and **2g** (Scheme 2). The reaction also proceeded smoothly on a decagram scale when using a biomass-derived sustainable solvent, 2-MeTHF, instead of THF. The existing reductive dimerization methods of benzylic halides mostly require long reaction time, high temperature, pyrophoric explosive materials, and reductants derived from precious metals and petroleum raw materials. Our discovered method, free from such drawbacks, could be a safe sustainable alternative to produce a variety of useful bibenzyls. Detailed mechanistic analysis of this reaction and the development of SD-mediated related transformations are currently underway.



Scheme 3. Decagram-scale reaction with 2-MeTHF instead of THF.

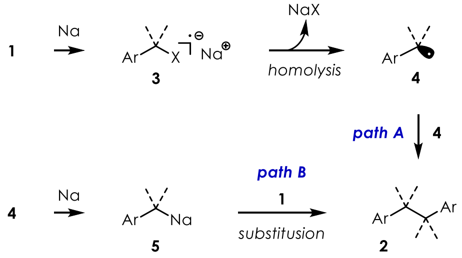


Fig. 3. Proposed reaction mechanism.

CRediT authorship contribution statement

Bubwoong Kang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tatsuro Imamura:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Tetsuya Satoh:** Writing – review & editing, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS KAKENHI, Grant No. JP21K14792 for Bubwoong Kang; JSPS KAKENHI, Grant No. JP20H02745 for Bubwoong Kang, and Tetsuya Satoh).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.tgchem.2024.100052.

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