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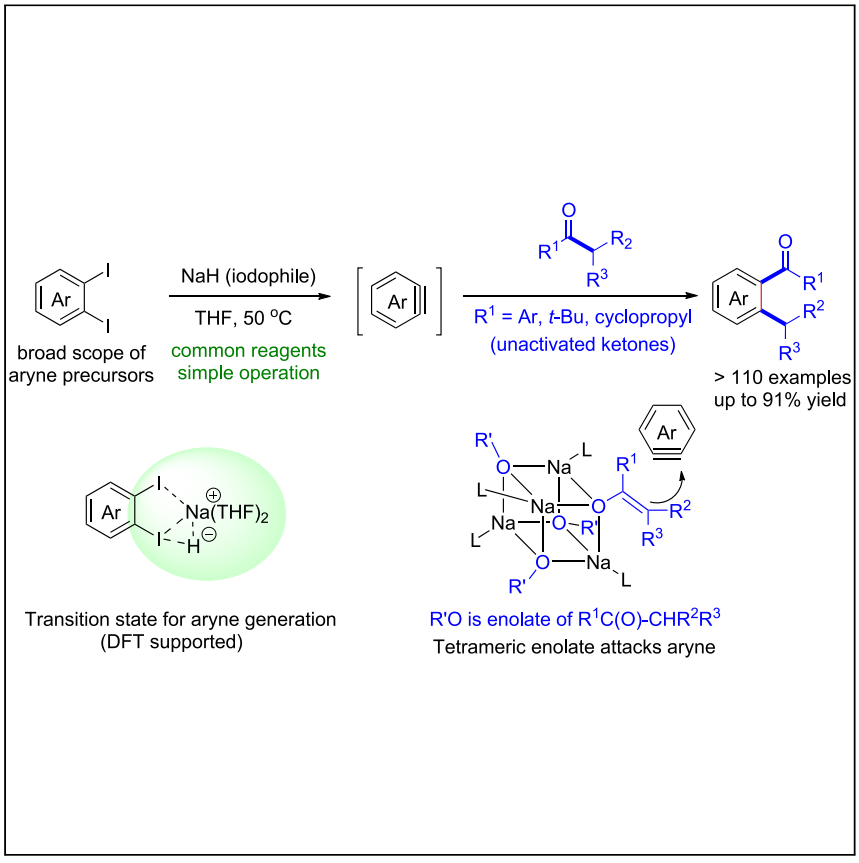

Finding unique ways to generate arynes is instrumental to aryne reactivities, which are vital in new organic transformations. We show that a NaH-mediated programed formation of arynes with *o*-diiodoarenes enables an unprecedented C–C σ-bond-insertion reaction with diverse unactivated ketones, which has been difficult or impossible through existing aryne-engaged processes. DFT calculations reveal that the interaction between NaH and two neighboring iodine atoms facilitates aryne formation. Moreover, a proposed tetrameric enolate produced from the NaH-mediated enolation with a ketone reacts with the resulting aryne to give the C–C σ-bond-insertion product.

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Highlights

o-Diiodoarenes/NaH as an efficient system for aryne generation in a controlled manner

Neighboring-group-assisted metal-halogen exchange process

Sodium hydride as an iodophile reagent

Aryne insertion into C–C σ-bond of unactivated ketones

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Direct insertion into the C–C bond of unactivated ketones with NaH-mediated aryne chemistry

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SUMMARY

Here, we document the reinvention of aryne chemistry with "old" *o*-diiodoarenes as aryne progenitors. We have established a NaH-mediated activation strategy for the generation of highly reactive aryne species in a controlled manner. The resulting arynes can efficiently participate in a C–C σ-bond-insertion reaction with unactivated ketones, which is difficult to achieve by existing methods. Density functional theory (DFT) calculations reveal that the two adjacent iodines in *o*-diiodoarenes play critical roles in the formation of aryne. The nucleophilic attack of hydride to the electrophilic iodine requires that the adjacent iodine act as a directing group to accelerate this process, whereas mono-substituted iodobenzene lacking the neighboring-group participation makes it difficult. The *in-situ*-formed enolates from ketones are proposed to adopt tetrameric aggregates to react with arynes, which accounts for the high regiochemistry for substrates with bulky substituents.

INTRODUCTION

Aryne chemistry has a long-standing interest in organic synthesis.[1–6] The multifaceted reactions of the versatile reactive intermediates with suitable arynophiles offer a strategic approach for rapid functionalization of ubiquitous aromatic structures.[7–12] The reaction efficiency is often dictated by the constitution of the corresponding aryne precursor and the way in which the intermediate is formed. Although various methods have been developed for aryne generation,[1–6,13] practical methods for producing arynes involve the removal of two adjacent atoms or substituents (Scheme 1A) from benzenoid precursors, such as halo(pseudohalo)arenes and *o*-dihaloarenes. In the formation of the active species, strong bases (such as $NaNH_2$), hindered lithium amide (LDA, LiTMP, LDAM, etc.), alkyllithium, or the Grignard reagent are generally used (Scheme 1A).[14,15] The harsh reaction conditions reduce compatibility with functional groups and arynophiles. Moreover, in many cases, low reaction yields are accompanied by complicated side reactions as a result of the difficulty in controlling the formation of the highly reactive aryne and its quick decomposition, even at a reaction temperature as low as −50°C.[16]

Kobayashi's method by using *o*-silylaryl triflates as aryne progenitors has changed the landscape of the aryne chemistry in synthesis (Scheme 1B).[1,17,18] The broad application of the chemistry attributes to the generation of the aryne species in a controllable manner under mild reaction conditions.[1] However, the high cost and tedious synthesis of the *o*-silylaryl triflate precursors restrict the practical application particularly in an industrial setting.[19,20] A new method for the controllable generation of

THE BIGGER PICTURE

Arynes have been recognized as one of the most useful reactive intermediates in organic chemistry because of their unrivaled capacity to deliver structurally diverse molecular architectures. However, the reaction efficiency and utility of arynes are often dependent on the used precursors and reaction conditions. Developing new protocols attests to the synthetic versatility of the intermediates. Here, we describe a simple method for the generation of arynes from *ortho*-diiodoarenes and NaH under mild conditions. Notably, the arynes generated in this manner enable an unprecedented C–C σ-bond-insertion reaction of unactivated ketones with a broad functional-group tolerance. Mechanistic insights into how aryne is generated and reacts with enolates (in tetrameric form) are also provided.

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benzynes/arynes from cost-effective, readily accessible *o*-dihaloarenes would considerably expand the preparative utility of these remarkable intermediates.

o-Diiodobenzene (**1a**) is an attractive benzyne precursor because it is cheap, stable, and commercially available.[21] More importantly, the weak C–I bond (bond-dissociation energy [BDE] = 64 kcal/mol) can be readily cleaved by a base under mild reaction conditions. However, the reported methods for benzyne formation have been challenged by the difficulty in controlling the formation of highly active benzyne species, even in reactions conducted at <−60°C,[17] by delivering complex product mixtures with low reaction yields.[22] Other methods for benzyne generation from *o*-diiodobenzene (**1a**) have been actively pursued.[23–26]

The Chiba group has developed a series of impressive sodium hydride (NaH)-mediated organic transformations,[27] such as hydrodehalogenation of aryl halides[28] and amide-directed C–H sodiation.[29] In our studies of exploring new reactivities of NaH for organic synthesis,[30–32] we serendipitously found that NaH in tetrahydrofuran (THF) or dimethylacetamide (DMA) could generate benzyne efficiently from *o*-diiodobenzene, which was trapped by furan to afford a Diels-Alder adduct in 52% yield (Scheme 5C). These experiments showed for the first time that the phenyl anion could be generated by the removal of iodide ion with NaH.[33] We questioned whether the operationally simple NaH-mediated aryne formation method could be explored for new organic transformations, which are not easily achieved by existing approaches, including Kobayashi's method.

Aryne insertion into the C–C σ-bond is an efficient method for the preparation of ubiquitous vicinal difunctionalized arenes.[1,3] Since the pioneering work of Guyot and Molho,[34] Shair et al.,[35] Tambar and Stoltz,[36] and Yoshida et al.,[37] a wide range of active methylene compounds have been identified for this rearrangement.[38–42] However, these processes are restricted to the highly activated ketones bearing either electron-withdrawing groups (EWGs) or aryl groups at the α-position (Scheme 1C). By contrast, simple alkyl ketones possessing intrinsic low activity can react only with the arynes generated from halo(pseudohalo)arenes by using strong bases but affording benzocyclobutenols or anthracenes as the products (Scheme 1C).[11,43–46] Although aryne insertion into a special cyclopentanone was reported by Danheiser and Helgason[47] and cyclohexyne insertion into various cyclic ketones was disclosed by Carreira and co-workers,[48,49] aryne insertion into acyclic ketones remains elusive.

Herein, we wish to disclose the results of the investigation leading to uncovering a new strategy for aryne generation from *o*-diiodoarenes activated by commercially available 60% NaH dispersion in mineral oil. The developed method, which proceeds under operationally simple reaction conditions and can be easily scaled up, does not require any metal additives or stringently anhydrous conditions. Furthermore, the new reactivity of the resulted arynes has been transformed into a viable process for direct aryne C–C σ-bond insertion into unactivated alkyl-aryl ketones. The method serves as a general approach to the rearranged complex *o*-alkyl-aryl ketone products, which are difficult to access by traditional methods, in up to 91% yield (Scheme 1D). Of equal importance, the mechanism of how aryne is generated and then reacts with ketones has been uncovered through DFT calculations.

RESULTS AND DISCUSSION

Exploration and optimization

Our study began with the optimization of the reaction conditions for the generation of benzyne from *o*-diiodobenzene **1a** and the subsequent insertion reaction with

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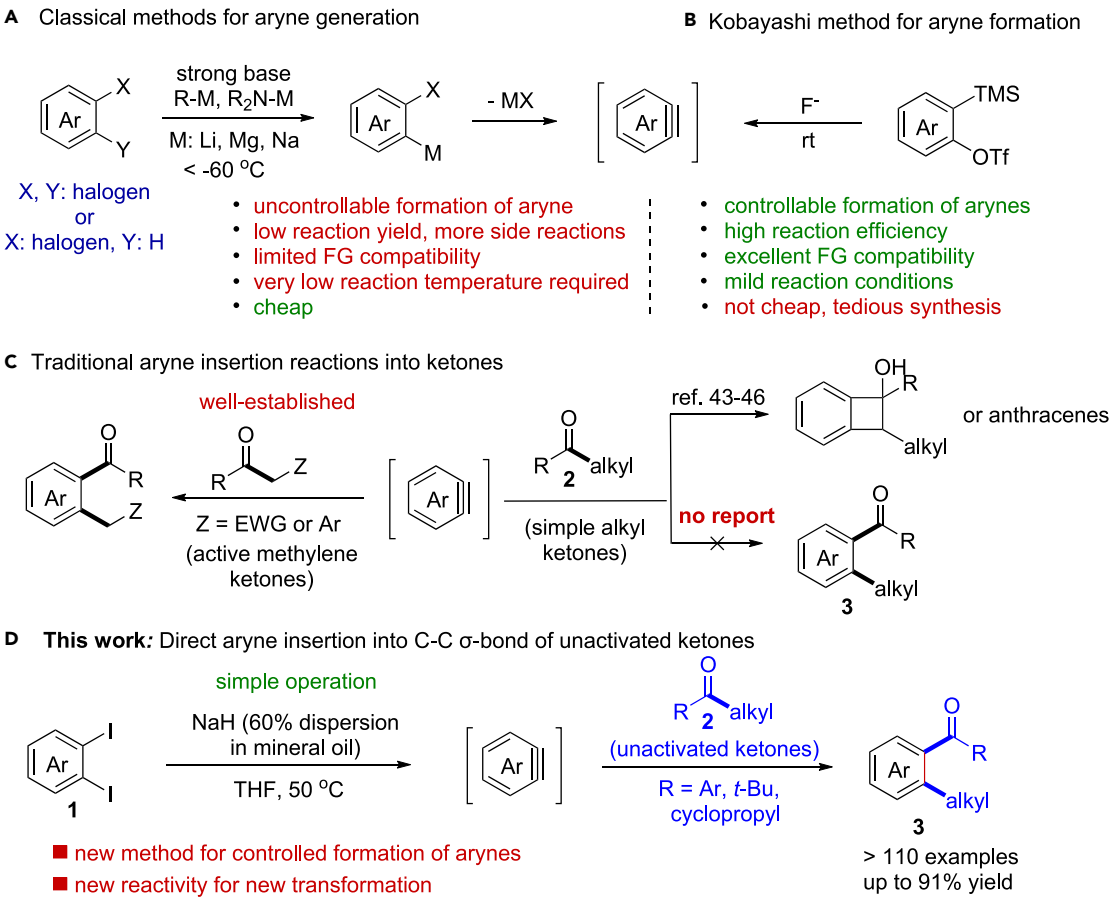

Scheme 1. Aryne precursors and the way to generate arynes, as well as aryne insertion reactions into ketones

(A) Classical methods for aryne generation.

(B) Kobayashi method for aryne formation.

(C) Traditional aryne insertion reactions into ketones.

(D) Our work for direct aryne insertion into C–C σ-bond of unactivated ketones.

p-tolyl ethyl ketone **2a** (Tables 1 and S1). Extensive exploration and optimization studies revealed that the treatment of **2a** in THF (0.05 M) with 2 equiv of *o*-diiodobenzene **1a** and 3 equiv of NaH at 50°C for 4 h afforded *o*-alkyl-aryl ketone **3a** in a 92% ^{1}H NMR yield (entry 1 and Table S1). Decreasing the loading of both **1a** (1.5 equiv) and NaH (2.5 equiv) eroded the reaction yield (80%, entry 2). To illustrate the role of NaH in the process, we probed a variety of frequently used strong bases (entries 3–8). It seems that the nature of counter cations of these hydrides plays a key role in the formation of benzyne (entries 3 and 4) presumably because they can influence solubility of hydride, whereas LDA, BuLi, and *i*-PrMgCl delivered the desired product in no more than 25% yield (entries 5–8). Obviously, these homogeneous phase methods are inferior to the generation of benzyne. The results are consistent with observations in the literature.[15,16] The solvents have a pronounced effect on the process as well. The reaction proceeded smoothly in THF (entry 1) and DMA (88% yield, entry 9), whereas it failed in dimethoxyethane (DME) (entry 10). We believe that the limited solubility of solid base NaH (60% dispersion in mineral oil) in THF, DMA, and DME enabled hydride to be gradually brought into the organic phase for the programed deiodization of *o*-diiodobenzene **1a** to control the generation of the phenyl anion and subsequent benzyne. The failure in DME might be due to

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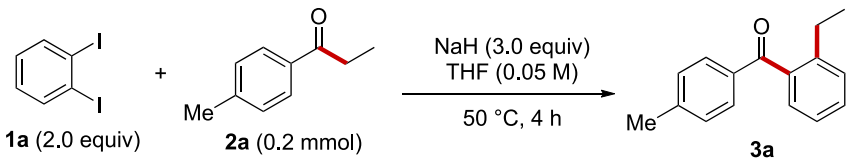
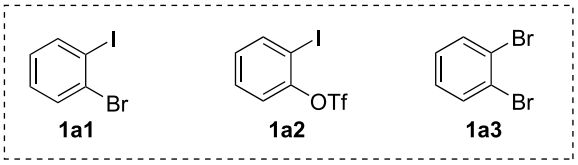
Table 1. Optimization of the reaction conditions





Entry	Deviation from standard conditions	3a (%)[a]
1	none	92 (83[b])
2	1.5 equiv of **1a** and 2.5 equiv of NaH	80
3	KH instead of NaH	22
4	LiH or CaH_2 instead of NaH	no reaction
5	LDA, 0°C → RT instead of NaH, 50°C	25
6	BuLi, 0°C → RT instead of NaH, 50°C	13
7	*i*-PrMgCl, 0°C → RT instead of NaH, 50°C	0
8	LDA or BuLi or *i*-PrMgCl, −78°C → RT	0
9	DMA instead of THF	88
10	DME instead of THF	0
11	60°C, 12 h instead of 50°C, 4 h	85
12	RT, 24 h instead of 50°C, 4 h	68
13	**1a1**, RT, 24 h instead of **1a**, 50°C, 4 h	55
14	**1a2**, RT, 24 h instead of **1a**, 50°C, 4 h	17
15	**1a3**, RT, 24 h instead of **1a**, 50°C, 4 h	no reaction
16	THF (0.1 M)	87
17	THF (0.02 M)	97

Standard reaction conditions: ketone **2a** (0.2 mmol) and *o*-diiodobenzene **1a** (0.4 mmol, 2 equiv) were added to a suspension of NaH (60% in oil, 24 mg, 0.6 mmol, 3 equiv) in dry THF (4 mL) under N_2, and then the reaction mixture was stirred at 50°C for 4 h. Also see Table S1.

[a]As ^{1}H NMR yield.

[b]Isolated yield based on the use of 0.5 mmol **2a**.

the difficulty in the efficient formation of the reactive enolate from its ketone precursor. In addition, the reaction conducted at room temperature (RT) or 60°C was favorable (entries 11 and 12). Three representative *o*-dihalobenzenes, **1a1–1a3**, were then investigated (entries 13–15). 1-Bromo-2-iodobenzene (**1a1**) proved to be a competent benzyne precursor as well in that it produced **3a** in 55% yield (68% from **1a** at RT; entry 12 vs. entry 13). Similarly, *o*-iodophenyl triflate **1a2** also gave the desired product but in low, 17% yield (entry 14). Interestingly, *o*-dibromobenzene was thoroughly inert to NaH, and no reaction occurred (entry 15). Therefore, breaking the relatively weak C–I bond is indispensable in the formation of phenyl anion with NaH to generate benzyne. Finally, we recognized that the concentration of the solution had a considerable influence on the reaction such that the dilute solution gave a higher yield (entries 16 and17). As a compromise, we used 0.05 M to examine the substrate scope.

Substrate scope

Under the optimized conditions, we first probed the generality of the benzyne insertion into diverse aryl alkyl ketones (Scheme 2). We examined a series of

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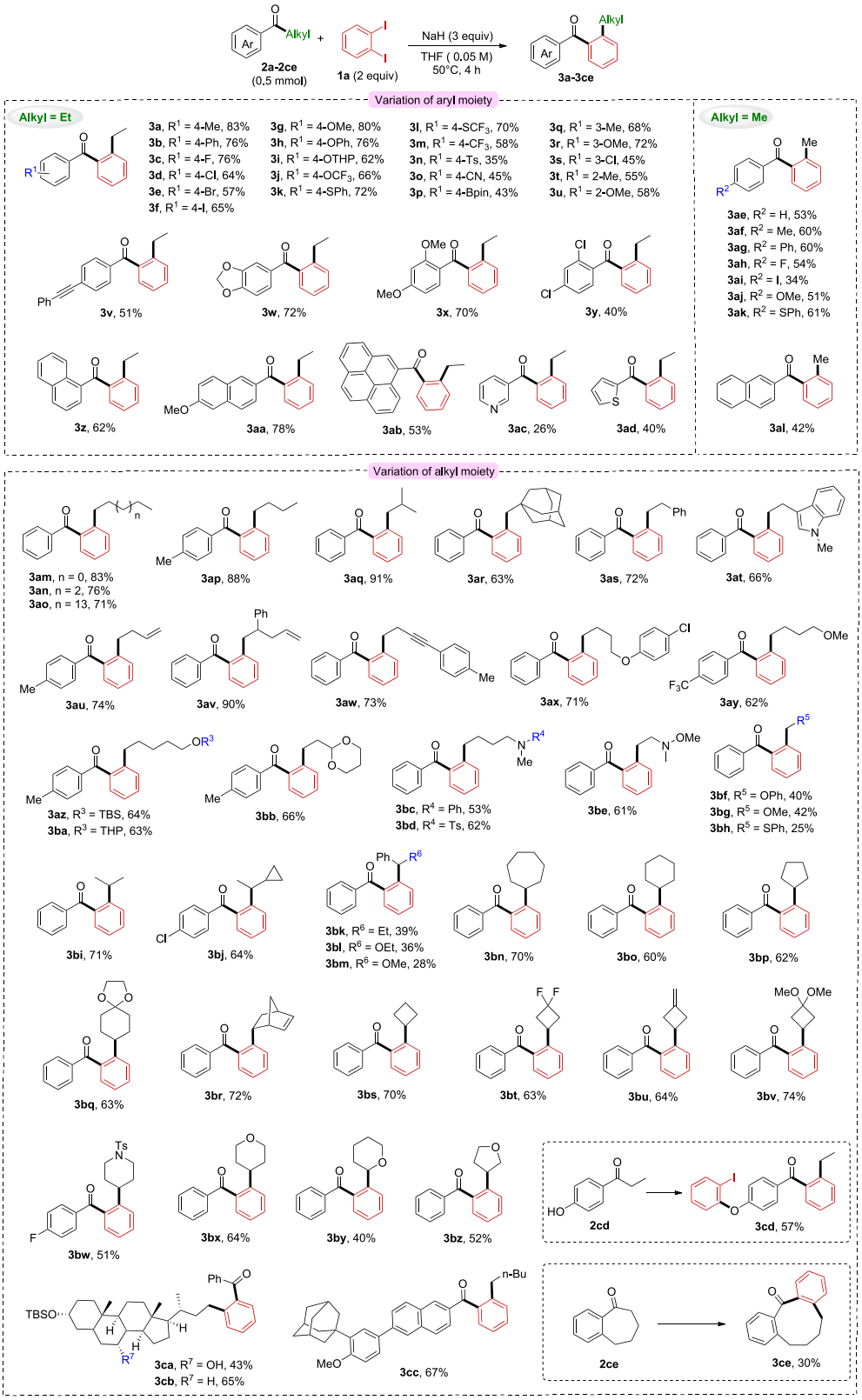

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Scheme 2. Scope of aryl alkyl ketones

See the experimental procedures for reaction conditions, unless otherwise specified. Yields are isolated yields. For products **3ar** and **3bn–3bz**, NaH (3.0 mmol, 6 equiv) and **1a** (2.5 mmol, 5 equiv) were used. For product **3cd**, NaH (2.0 mmol, 4 equiv) and **1a** (1.5 mmol, 3 equiv) were used.

propiophenone derivatives (**2a–2y**) bearing various substituents on the benzene ring. We observed that a great number of functional groups were compatible with the reaction conditions, and the electronic and steric perturbations of these substituents were all tolerated, as evidenced by the formation of products **3a–3y** in moderate to good yields. Significantly, all halogens were stable enough to survive the presence of NaH (**3c–3f**, **3s**, and **3y**), thus constituting an important advantage over traditional methods. Interestingly, although *o*-diiodobenzene was reactive to NaH, the single iodine on the benzene ring was intact under the reaction conditions (**3f**). Notably, the substrates involving different types of ether or thioether subunits proceeded smoothly to give the desired rearrangement products in good yields (**3g–3l**, **3r**, **3u**, **3w**, and **3x**). Furthermore, several substrates bearing biologically important fluorine-containing groups, such as –F, $–OCF_3$, $–SCF_3$, and $–CF_3$, could efficiently participate in the process with high efficiency (**3c**, **3j**, **3l**, and **3m**). Moreover, the successful generation of **3o**, **3p**, and **3v** (which contained versatile –CN, –Bpin, and alkynyl groups) allowed for further functionalization of the products. In further exploration, we found that the phenyl moiety of ketone **2a–2y** could be replaced by other aromatic structures, such as naphthalene (**2z** and **2aa**), pyrene (**2ab**), pyridine (**2ac**), and thiophene (**2ad**), delivering the corresponding insertion products **3z–3ad** successfully. Importantly, our strategy also created a concise route for the direct introduction of a methyl group on aromatic rings. The structures are not easily accessed.[50,51] The simple treatment of commercially available aryl methyl ketones **2ae–2al** with *o*-diiodobenzene and NaH afforded *o*-methylaryl ketones **3ae–3al** in good yields.

In addition to methyl and ethyl aryl ketones, other variants are also amenable. A variety of primary (**3am–3bh** and **3ca–3ce**), secondary (**3bi–3bm**), and (hetero)cycloalkyl groups (**3bn–3bz**) can be applied by the protocol for the synthesis of structurally diverse adjacent alkyl-aryl ketones. The length of the linear alkyl from C4 to C17 has a limited effect on the reaction yield (83% for **3am** vs. 71% for **3ao**). Moreover, notably, the alkyl moiety of ketone carrying various functional groups can be tolerated. These functionalities include indole (**3at**), alkene (**3au** and **3av**), alkyne (**3aw**), ether (**3ax** and **3ay**), O-(*tert*-butyldimethylsilyl)hydroxylamine (OTBS) and tetrahydropyranyl (THP) (**3az** and **3ba**), acetal (**3bb**), and amines (**3bc–3be**). Furthermore, ketone substrates bearing oxygen and sulfur featured at the α-position of alkyl moiety can deliver benzyl (thio)ethers (**3bf–3bh**, **3bl**, and **3bm**), useful building blocks, and biologically interesting functional groups. The generality of our protocol is further demonstrated by the synthesis of various (hetero)cycloalkyl products **3bn–3bz**. In these cases, a spectrum of cycloalkanes with ring sizes ranging from four to seven were successfully connected to a benzene ring via the efficient rearrangement process to furnish products **3bn–3bv**. Moreover, piperidine (**3bw**), tetrahydropyran (**3bx** and **3by**), and tetrahydrofuran (**3bz**) were also viable heterocycles for these transformations. Of particular significance is the observation that our method could be used for late-stage skeletal editing of structurally complex molecules, such as **3ca** (from chenodeoxycholic acid), **3cb** (from lithocholic acid), and **3cc** (from adapalene), in impressive yields (43%–67%). It is worth noting that the free phenolic hydroxyl group of ketone **2cd** was identified to be a new reactive site in that it afforded product **3cd**, which possesses an interesting *o*-iodophenyl ether subunit. This discovery could open up a new research direction and exhibits the great potential of the

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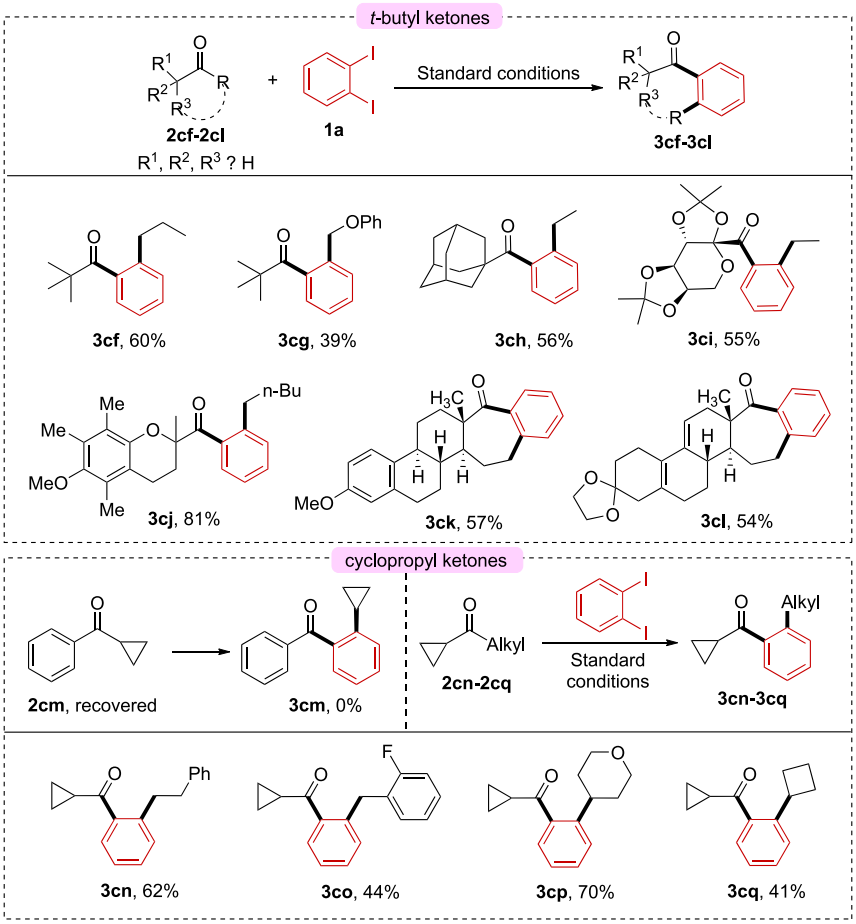

Scheme 3. Scope of dialkyl ketones

See the experimental procedures for reaction conditions, unless otherwise specified. Yields are isolated yields. For products **3ci, 3cp**, and **3cq**, NaH (3.0 mmol, 6 equiv) and **1a** (2.5 mmol, 5 equiv) were used.

o-diiodobenzene/NaH system. Finally, under the standard reaction conditions, a ring-expansion tool was placed with benzocycloheptanone **2ce** to give a synthetically challenging medium 9-membered ring in 30% yield.

In addition to probing aryl alkyl ketones, we also probed alkyl alkyl ketones. To avoid the reaction complexation by the formation of two regioisomers, we explored the rearrangement process with *t*-alkyl alkyl ketones, in which only one α-position containing H can undergo deprotonation for the formation of enolate (Scheme 3, top). As shown, these substrates performed equally well. Benzyne could efficiently be inserted into their C–C bond to give products **3cf–3cl** in good yields. Moreover, more complex ketone substrates derived from biologically active structures, such as β-D-fructopyranose (**2ci**), trolox (**2cj**), estrone (**2ck**), and estradiene dione-3-keta (**2cl**), could undergo the reaction to afford compounds **3ci–3cl**. Especially impressive was the ring expansion of cyclopentanone in steroid skeleton, which gave rise to cycloheptanone products **3ck** and **3cl**. Again, this demonstrates the preparation power of the method for late-stage skeletal editing. In the study of cyclopropyl-derived ketones (Scheme 3, bottom), we noticed that **2cm** was inert to the process and completely recovered under the reaction conditions. This implies that the

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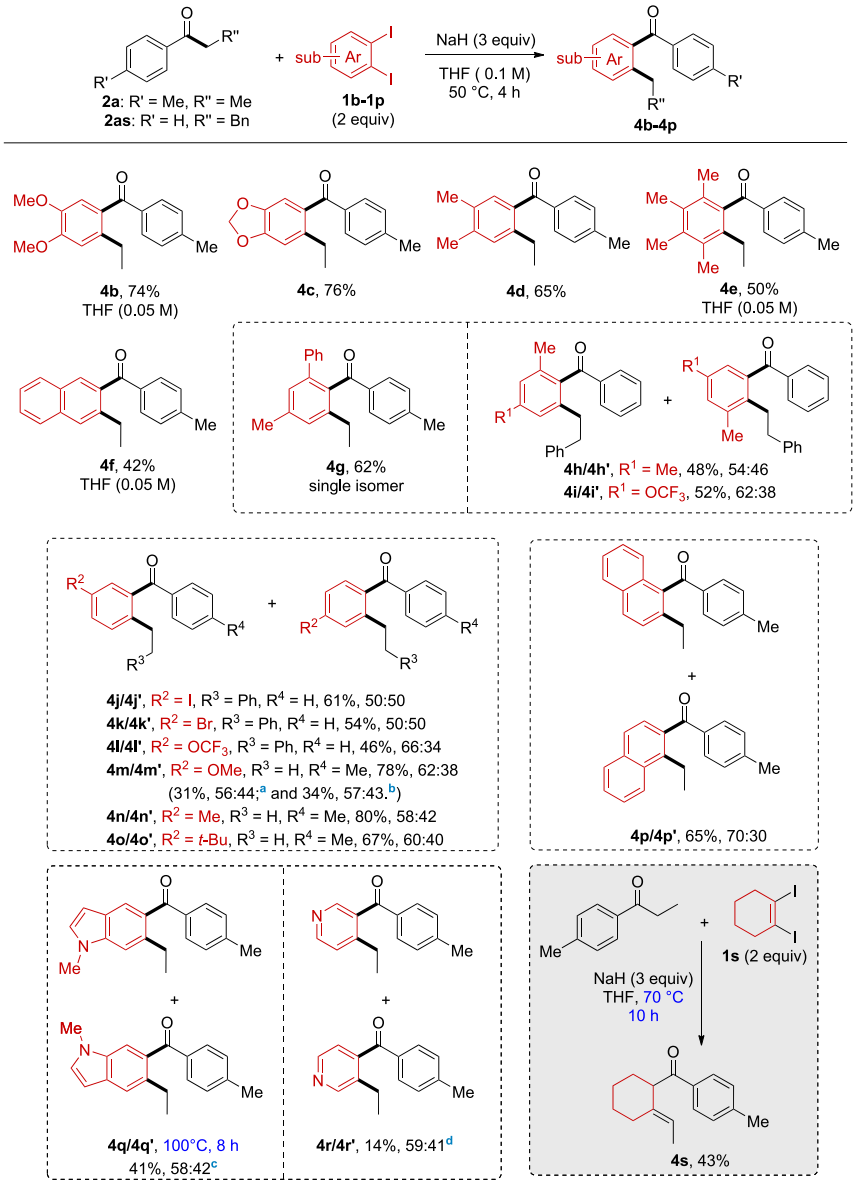

Scheme 4. Scope of aryne precursors

See the experimental procedures for reaction conditions, unless otherwise specified. Yields are isolated yields. Rigioisomer ratios were determined by ^{1}H NMR.

[a]2-bromo-1-iodo-4-methoxybenzene **1m**′ was used as the aryne precursor.

[b]1-bromo-2-iodo-4-methoxybenzene **1m**″ was used as the aryne precursor.

[c]5-bromo-6-iodo-1-methyl-1*H*-indole 1**q** was used as the aryne precursor.

[d]3-bromo-4-iodopyridine **1r** was used as the aryne precursor.

3-membered ring is difficult for enolization. Therefore, we designed new cyclopropyl alkyl ketones for the reaction. To our delight, these substances proceeded regio-exclusively to deliver structures **3cn–3cq** in moderate to good yields. The studies further expand the scope of the process.

To further illustrate the generality of the new method, we evaluated diverse *o*-diiodoarenes as aryne precursors (Scheme 4). We note that these *o*-diiodo compounds could be easily prepared from cheap materials (see the supplemental experimental

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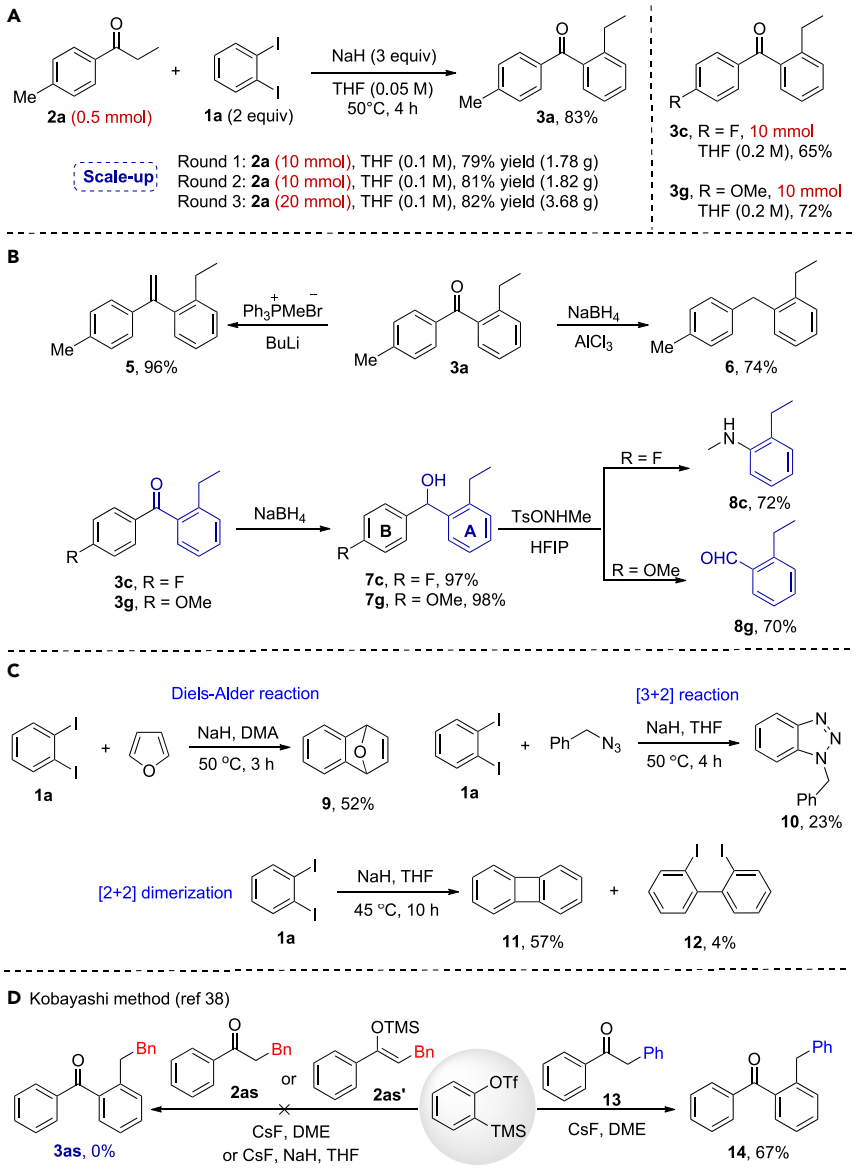
procedures). First, symmetrical precursors **1b–1f** were well tolerated under the optimal reaction conditions to smoothly generate arynes, which then reacted with ketone **2a** to afford regioisomers **4b–4f** in 42%–76% yields. For unsymmetrical *o*-diiodobenzene derivatives, we found that the regioselectivity of the products depended on the type and position of the substituents. For example, the insertion reaction of 3-phenyl-5-methylbenzyne proceeded well to give **4g** in 62% yield and with high regioselectivity. When 3-methyl precursors **1h** and **1i** were used, a mixture of two isomers (**4h**/**4h′** and **4i**/**4i′**) was obtained in a 54:46 and 62:38 ratio, respectively. A similar trend was observed for *meta*-substituted benzynes efficiently generated from **1j–1o**. The desired products **4j–4o** were formed in moderate to good yields and with the regioisomer ratio from 50:50 to 66:34. Again, like the aforementioned **3f** and **3ai**, in the case of **4j**, the single C–I bond in the substrate was not affected under the reaction conditions. In the case of **4m**/**4m′**, when one iodine was replaced by bromine in the aryne precursor, lower yields were obtained but with similar regioselectivity. Subsequently, the conversions of naphthalene-, indol-, and pyridine-based precursors **1p–1r** were also accomplished, leading to two isomers (**4p**/**4p′**–**4r**/**4r′**) in 14%–65% yields. Finally, the more challenging 1,2-diiodocyclohex-1-ene **1s** could also generate strained cyclic alkyne under the promotion of NaH at 70°C and provided an interesting product (**4s**) that might undergo a 4π electrocyclic ring-opening process[49,52,53] (see the supplemental information for the proposed mechanism).

Having evaluated more than 110 substrates for the synthetic power, we took these conveniently produced products for further synthetic elaboration to demonstrate the practicality and create new structures (Scheme 5). First, we conducted a gram-scale synthesis by using ketone **2a** and *o*-diiodobenzene **1a** under slightly modified reaction conditions (a higher concentration at 0.1 M) to reduce the consumption of solvent (Scheme 5A). Comparable yields to 0.5 mmol scale were obtained at 10 (twice) and 20 mmol levels, showing the reliable reproducibility of our protocol. Moreover, when the concentration was further increased to 0.2 M, similar synthetic efficiency for **3c** and **3g** at 10 mmol level was achieved.

Benzophenones are versatile building blocks in synthesis. As shown in Scheme 5B, the ketone group of **3a** was conveniently transformed into alkene **5** and alkane **6**. Compounds **3c** and **3g** were efficiently reduced to alcohols **7c** and **7g**. Significantly, the resulting diphenylmethanol **7c** and **7g** could be split into respective aniline **8c** and aldehyde **8g** by simple treatment with TsONHMe in hexafluoroisopropanol (HFIP) at RT.[54] The regioselectivity of the products could be easily tuned and controlled by modulation of the electronic properties of ring **B** in alcohol **7**. The EWG (–F) led to the formation of *o*-alkyl aniline (**8c**) as a major product, whereas the electron-donating group (–OMe) formed *o*-alkylbenzaldehyde (**8g**) favorably.

The development of "ideal" aryne generation methods has long been sought by organic chemists because arynes are generated *in situ*.[1–6] The constitution of an aryne precursor and its generation conditions play key roles in aryne-engaged transformation. Because of their ready accessibility and affordability, *o*-dihaloarenes as precursors make a significant contribution to aryne chemistry in the early stage. In the 1950s and 1960s, they were intensively studied with strong bases, such as PhLi, $NaNH_2$, and LDA for aryne generation.[15,16] However, these strategies fall short of compatibility with functional groups and arynophiles that are vulnerable under these harsh conditions. Therefore, they were replaced by other methods, particularly Kobayashi's protocol. In this study, we uncovered a new NaH-mediated aryne-formation strategy using *o*-diiodoarenes as progenitors. The method enables the generation of aryne in a controlled manner. The formed aryne from *o*-diiodoebenzene (**1a**)



Scheme 5. Gram-scale synthesis, reproducibility, synthetic application, cyclization reactions, and comparison with Kobayashi's method

(A) Gram-scale synthesis of products **3a**, **3c**, and **3g**.

(B) Synthetic applications for the products.

(C) Cyclization reactions achieved by our method.

(D) The comparison of our method with Kobayashi's method.[38]

could undergo Diels-Alder and [3 + 2]-cycloaddition reactions with furan and azide and undergo dimerization when no other reactants were present to give biphenylene **11** and a little 2,2′-diiodo-1,1′-biphenyl **12** (Scheme 5C; see the supplemental information for the generation mechanism of **12**). These reactions also provide solid evidence supporting the aryne involvement in these reactions. Furthermore, Kobayashi's protocol failed to deliver the product, as shown in Zeng and co-workers' study of the reaction of *o*-silylaryl triflate with α-phenylethyl ketone **2as** (Scheme 5D).[38] Only active ketones, such as α-benzyl ketone **13**, delivered product **14**. However, our protocol obtained a 72% yield of insertion product **3as** with **2as** (Scheme 2).

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Interestingly, we also found that neither TMS enol ether **2as'** nor the addition of NaH to activate **2as** could give desired product **3as** (Scheme 5D). We believe the unrivaled capacity of NaH mediated the generation of the aryne, and at the same time, the activation of the less reactive ketone made the process possible.

Mechanistic investigations

To gain mechanistic insights into the NaH-mediated aryne formation reaction, we carried out DFT calculations at the SMD(THF)/B3LYP/6-31+G(d) (LANL2DZ for I) level (see the supplemental information for details) with *o*-dioidobenzene substrate **1a**. A complexation (e.g., **Int1**) between **1a** and solvated NaH via the electrophilic I[55,56] and hydridic H interactions is initially formed endergonically by 4.2 kcal/mol (Scheme 6A; Figures S1 and S2). The resulting **Int1** is then transformed into the key phenyl sodium intermediate, **Int2**, through transition state **TS1**, in which the dissociation of the C–I bond is facilitated by the synergistic activation of NaH and the second iodo. Such a network with Na^+ coordinated to both the hydride and the adjacent I helps the reaction, and only an activation free energy of 8.1 kcal/mol is required. The formation of a phenyl anion from mono-iodobenzene is difficult because it requires an estimated activation energy of 32.9 kcal/mol (see the supplemental information and Figures S4 and S5). The neighboring-group-assisted deiodination activation mode was also demonstrated in NaH-mediated Fries rearrangement of 2-iodophenyl benzoate (**15**) via **17** to generate aryl anion **18** in the formation of compound **16** (Scheme 7A; computational evidence for this is given in the supplemental information and Figure S6). The anionic Fries rearrangement[57] reaction here then provided important evidence to support the presumed aryl anion intermediate **Int2**. The activation mode was further validated by the reaction of **19**, which can also go through a similar process to afford rearrangement product **3bi** (Scheme 7B). The extrusion of the second iodide in **Int2** yields the key benzyne species, which is exergonic by 3.5 kcal/mol and easy with an estimated activation energy of 4.7 kcal/mol (no transition state can be located, as demonstrated by a flexible scan of the C–I bond in **Int2**; see the supplemental information and Figure S3). Overall, NaH-mediated benzyne formation is a favorable process with a calculated activation free energy of 8.1 kcal/mol. This is consistent with the experimental observation that the formation of arynes is carried out under RT reaction conditions. This also agrees with the experimental observation that the weak C–I bond facilitates the elimination of the NaI for aryne formation (Table 1, entries 1 vs. 13–15).

The above results are in contrast to those of the procedure of generating benzynes by using strong bases, such as $NaNH_2$, RLi, and RMgX, and a recent example reported by Asako et al.[58] shows that the aryne generation is often carried out at low reaction temperature (<−60°C). The relatively weaker basicity of NaH can efficiently promote I-Na exchange with a weak C_{sp2}–I bond (BDE = 64 kcal/mol). No reaction occurred with *o*-dibromobenzene substrate, which has the stronger C–Br bond (BDE for C_{sp2}–Br = 79 kcal/mol; Table 1, entry 15). In addition, the metal cation Na^+ is also important for aryne formation. Studies have shown that for a given halogen, the ease of elimination of metal halides is in the order Na > Li > MgBr.[59] Homogeneous activation by strong bases (such as $NaNH_2$, RLi, and RMgX) can rapidly accumulate the species, making the reaction messy. In a similar manner to Kobayashi's protocol,[1–6] the high efficiency of aryne-engaged reaction can be ascribed to the low solubility of NaH in THF, which allows for the gradual reaction with *o*-diiodobenzene to slowly produce *o*-iodo organometallic intermediate. The suitable alkaline environment created by NaH is particularly unique for uncovering new aryne reactions, as demonstrated by the efficient insertion into an unactivated ketone C–C σ-bond with broad functional-group tolerance.

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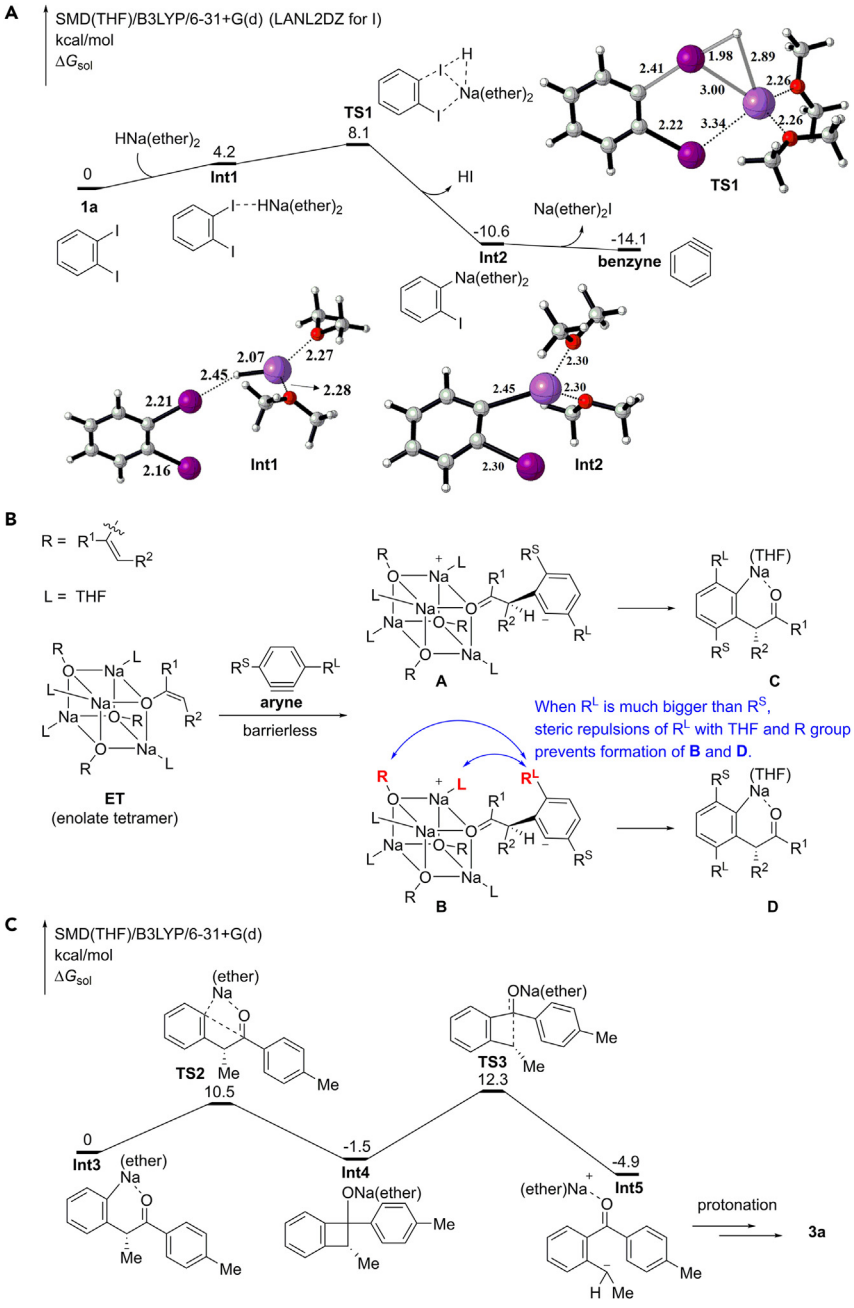

Scheme 6. The computed energy profiles and proposed regiochemistry model

(A) The energy profile for the generation of benzyne.

(B) The proposed reaction of terameric enolate with the aryne and regiochemistry model.

(C) The computed energy profile for the generation of product **3a**.

We then investigated how the reaction of the resulting benzyne with substrate **2a** proceeded to give product **3a** and understood the regioselectivity (Schemes 6B and 6C and Figures S7–S11). The formed enolate intermediate, named here as **ET**, is proposed as a tetrameric aggregate according to Tomasevich and Collum's study.[60] The reaction between **ET** and aryne is a barrierless and irreversible process that forms two possible intermediates, **A** and **B**, which give Na^+-chelated ketone aryl anions **C** and **D**, respectively. Intermediate **Int3** (R^S = R^L = H) is supported by a

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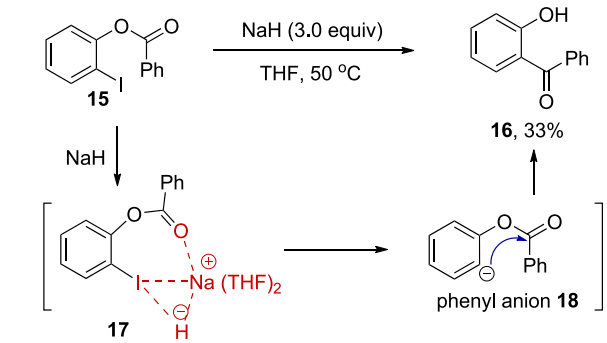
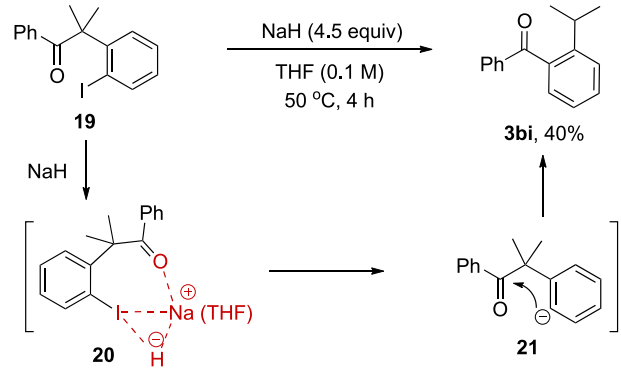
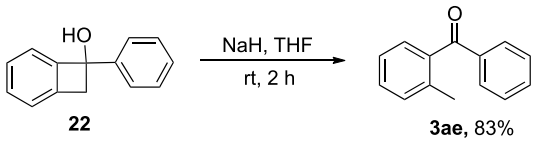
A Fries rearrangement assisted by neighboring carboxylate facilitating deiodination for aryl anion formation



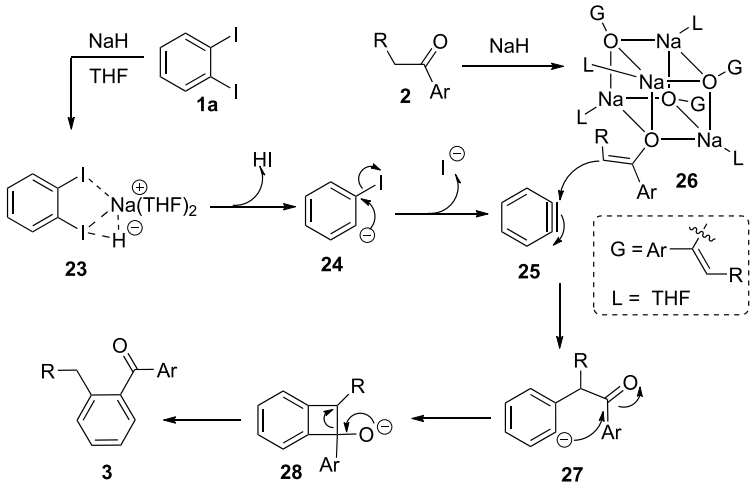
B Neighboring ketone faclitating deiodination for aryl anion engaged rearrangement



C Benzocyclobutenol undergoing a NaH-mediated ring opening



D Proposed reaction mechanism



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Scheme 7. Validation of key reaction intermediates and proposed reaction mechanism

(A) Fries rearrangement assisted by neighboring carboxylate facilitating deiodination for aryl anion formation.

(B) Neighboring ketone faclitating deiodination for aryl anion-engaged rearrangement.

(C) Preformed benzocyclobutenol undergoes a NaH mediated ring opening.

(D) Proposed reaction mechanism.

flexible scan of the newly formed C–C bond (see the supplemental information). The observed regioselectivity can be rationalized by the model. Both tetramer intermediates **A** and **B** can be formed if R^S and R^L groups in arynes have similar sizes. The degradation or ligand exchange of tetramers delivers the two corresponding monomers **C** and **D**, which then furnish two regioisomers, as observed in **4h**/**h′**–**4r**/**r′**. However, when the R^L group is much bigger than the R^S group, steric repulsions make it difficult to generate **B** in this diffusion-controlled step. Therefore, the single isomer **4g** in the reaction of **2a** and **1g** is observed. This is attributed to the steric repulsion between the large phenyl group (R^L) in **1g** and the tetrahydrofuran (L) and enolate (R) in **B**, which leads to the difficult formation of **D** and therefore the formation of a single isomer, **4g**. It should be noted that if a monomeric enolate reacts with aryne, the process is barrierless, and therefore no regiochemistry can be observed (see the supplemental information and Figures S8–S10). This is opposite to the experiments, and therefore this possibility was ruled out.

Intermediate **Int3** then undergoes a Fries-type rearrangement via an intramolecular nucleophilic attack of the carbonyl group to give 4-membered ring intermediate **Int4**. The activation free energies of 10.5 kcal/mol (via **TS2**) and 13.8 kcal/mol (via **TS3**) are required for the formation and opening, respectively, of the 4-membered ring. The ring opening is exergonic by 3.4 kcal/mol to afford **Int5**, which then converts to final ketone product **3a** after protonation in workup. To validate that **Int4** is a key intermediate in the process, we prepared a stable benzocyclobutenol, **22**, which we then treated with NaH. This compound was smoothly transformed to ketone product **3ae** in 83% yield (Scheme 7C).[61] Our computational results support the fact that anionic ring opening for this process is easier for the generation of the final product than for its neutral process (see Figures S11–S15).[62,63]

On the basis of the above studies, we propose a plausible reaction mechanism (Scheme 7D). NaH-mediated nucleophilic attack of hydride to the electrophilic iodine of *o*-diiodobenzene **1a** via transition state **23** gives phenyl anion **24**. Then, anion **24** extrudes the second iodide and delivers key benzyne species **25**. Nucleophilic enolate **26** in a tetrameric form, engendered by NaH-mediated deprotonation of ketone **2**, reacts with the benzyne to give carbanion **27**. Finally, intramolecular nucleophilic addition to the carbonyl triggers a Fries-type rearrangement via benzocyclobutenoxide intermediate **28** to afford the final *o*-alkyl-aryl ketone product **3**.

Conclusion

In conclusion, we have reinvented aryne chemistry by using "old" *o*-diiodoarenes as aryne progenitors. Distinct from classical methods using strong bases (such as $NaNH_2$, RLi, and RMgX), at low temperature (<−60°C) in homogeneous solution, a NaH-mediated two-phase reaction in THF at 50°C enables the generation of the highly active aryne species in a controlled manner. The generated arynes can participate in an efficient C–C σ-bond-insertion reaction with unactivated ketones. The process proceeds highly efficiently with broad functional groups, as evidenced by more than 110 products. Importantly, the protocol can be used for late-stage skeletal editing of structurally complex molecules. The new activation mode for controlling the formation of aryne active species holds significant potential for applications

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to a broad spectrum of novel organic reactions, a proposal that will guide our further efforts in this area. Importantly, understanding how the two adjacent I atoms in the benzyne precursor synergistically generate benzyne is given through DFT calculations, and a new mode of benzyne reaction with tetrameric enolate is proposed to rationalize the observed regioselectivity.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Shi-Lei Zhang (zhangshilei@suda.edu.cn).

Materials availability

Unique and stable reagents generated in this study will be made available on request, but we might require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and code availability

There is no dataset or code associated with the paper. Full experimental procedures are provided in the supplemental information.

Images of the key spectral and analytical data of the compounds generated in this study are included in the supplemental information.

Methods

General procedure for the synthesis of 3

Ketone **2** (0.5 mmol) and *o*-diiodoarene **1** (1.0 mmol, 2.0 equiv) were added to a suspension of NaH (60% dispersion in mineral oil, 60.5 mg, 1.5 mmol) in anhydrous THF (10 mL) at 0°C stirring for 5 min. The mixture was warmed to 50°C for 4 h. The mixture was then quenched with saturated aqueous NH_4Cl solution (6 mL) at 0°C. The mixture was then extracted with EtOAc (8 mL × 4). The combined extracts were dried over Na_2SO_4, concentrated under vacuum. The resulting residue was purified by silica gel chromatography, affording *o*-alkylaryl ketones **3**.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2023.05.032.

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AUTHOR CONTRIBUTIONS

F.L., C.-L.L., P.J., Y.Z., J.G., L.C., Y.Y., X.Z., Y.H., Xiaobei Chen, X.L., and Xiaodong Chen planned, conducted, and analyzed the experiments. S.-L.Z., Z.-X.Y., and W.W. planned, designed, and directed the project, and S.-L.Z., Z.-X.Y., and W.W. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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