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Synthesis of α-arylacetophenone derivatives by Grignard reactions and transformations of arynes *via* C–C bond cleavage†

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Divergent synthesis of α-arylacetophenones by 1,2-addition and subsequent transformations *via* aryne intermediates is disclosed. The choice of solvent played a critical role in the efficient synthesis of benzocyclobutenols by the Grignard reaction. The generation of arynes from the resulting alcohols *via* the C–C bond cleavage facilitated the synthesis of a diverse array of α-arylacetophenones.

Diverse α-aryl ketones such as zaltoprofen[1a] and chilenine[1b] are of great importance in broad research fields including pharmaceutical sciences and natural product chemistry (Fig. 1A). Despite continuous efforts to develop novel efficient synthesis methods for α-aryl ketones such as palladium-catalyzed α-arylation of ketones (Fig. 1B), it is still challenging to prepare highly functionalized α-aryl ketones from simple starting materials due to the poor functional group tolerance under harsh conditions.[2] Herein, we disclose efficient preparation of α-aryl ketones through the Grignard reactions of benzocyclobutenones and subsequent aryne reactions *via* C–C bond cleavage.

Transformations through aryne intermediates *via* C–C bond cleavage were independently developed by the Li group and our group.[3–5] In 2017, Li and coworkers accomplished the synthesis of α-arylacetic acid esters *via* the generation of aryne intermediates through the C–C cleavage (Fig. 1C).[4] We succeeded in transformations of α-aryl-ketone-type arynes generated *via* the C–C bond cleavage.[5] Benzocyclobutenones used as the aryne precursors were easily synthesized from 1,3-bis(triflyloxy)-2-iodobenzene *via* 3-(triflyloxy)benzyne by our previously developed method (Fig. 1D).[6] Particularly, in 2017, we found that treatment of benzocyclobutenones with organolithiums in the presence of arynophiles such as furan furnished α-aryl ketones by the three-component coupling, in which 1,2-addition of ketones with organolithiums and aryne generation from the resulting alkoxide intermediates took place smoothly.[5a] To avoid the poor functional group tolerance of organolithium reagents, we conceived that diverse alcohols can be synthesized from benzocyclobutenones **2** with organomagnesiums prepared using the turbo Grignard reagent[7,8] (Fig. 1E). Since the turbo Grignard reagent have led to synthesis of divergent products that contain various nucleophile-susceptive moieties such as esters, we expected that synthesizing alcohols from **2** and aryl halides **1** followed by aryne reactions *via* the C–C bond cleavage will enable us to prepare a wide variety of α-aryl ketones under the good transformability of aryne intermediates. Due to the weak C–C bond of benzocyclobutene derivatives[4,5] and strict limitation in choosing solvents for the halogen–magnesium exchange and following 1,2-addition,[7,8] it is challenging to accomplish the facile synthesis of alcohols.

Optimization of the reaction conditions for 1,2-addition to ketone **2a** by an arylmagnesium intermediate prepared from **1a** enabled the synthesis of alcohol **3a** in a practical manner (Table 1). First, we treated **1a** with isopropylmagnesium chloride lithium chloride complex in tetrahydrofuran (THF) at −40 °C followed by the addition of **2a** at −20 °C (entry 1). After aqueous workup of the resulting mixture, we succeeded in the synthesis of alcohol **3a** albeit in low yield, which formed without aryne generation *via* the C–C bond cleavage. Given that ketone **2a** was consumed and a complex mixture of side products was obtained, this result suggested the challenge in synthesizing alcohol **3a** owing to the unstable structure of the alkoxide intermediate. Changing the solvent significantly affected the reaction efficiency. Although the reaction using cyclopentyl methyl ether (CPME) instead of THF resulted in a slight improvement of the yield (entry 2), we accomplished the synthesis of alcohol **3a** in good yield when using diethyl ether as a solvent (entry 3). Moreover, we found that both the I–Mg exchange and subsequent Grignard reaction smoothly took place in toluene without side reactions owing to the labile C–C bonds, allowing us to prepare alcohol **3a** in high yield leaving the ester moiety intact (entry 4). It is worth noting that a gram-scale synthesis of alcohol **3a** was achieved in an excellent yield (entry 5). In contrast, the desired alcohol **3a** was not

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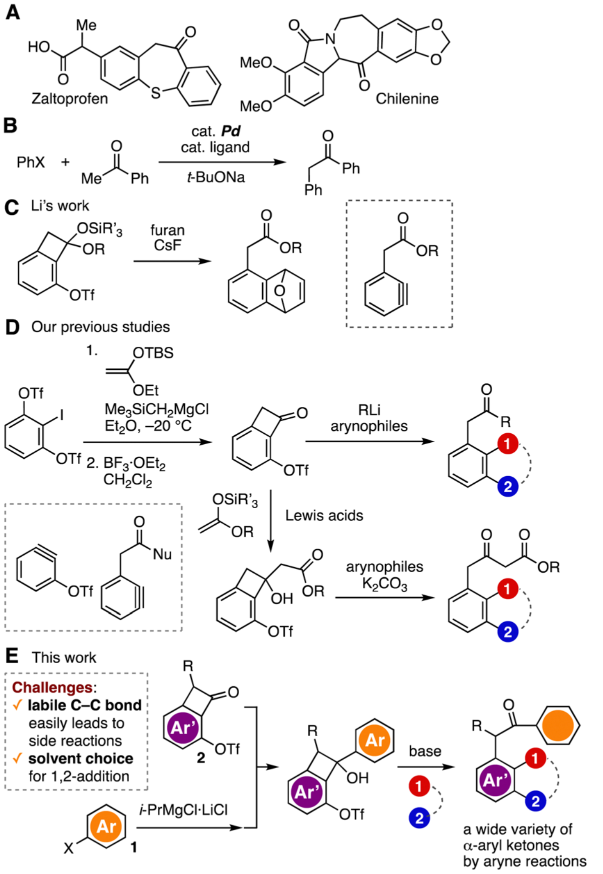
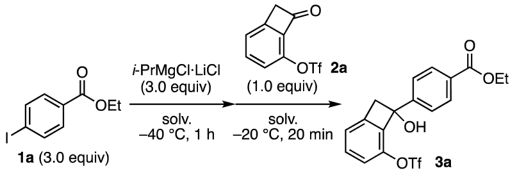


Fig. 1 (A) Significant α-aryl ketones. (B) Palladium-catalyzed synthesis of α-aryl ketones. (C) Li's work. (D) Our previous studies. (E) This work.

Table 1 Optimization of the reaction conditions



Entry	Solv.	Yield[a]/%
1	THF	22
2	CPME	39
3	Et_2O	66
4	Toluene	87[b]
5	Toluene	98[b,c]
6	MeCN	0

[a] Yields based on ^{1}H NMR analysis. [b] Isolated yields. [c] The reaction was performed in 5 mmol scale.

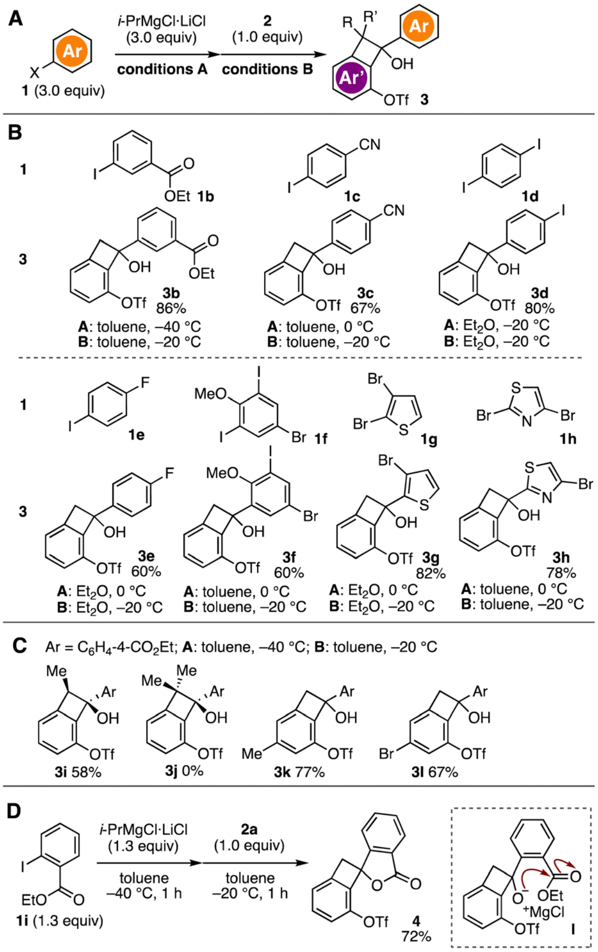


Fig. 2 Synthesis of benzocyclobutenol derivatives. (A) General scheme. (B) Synthesis using various aryl halides **1**. (C) Synthesis using various ketones **2**. See the ESI,† for the structures of **2b–2e**. (D) Synthesis of lactone **4**.

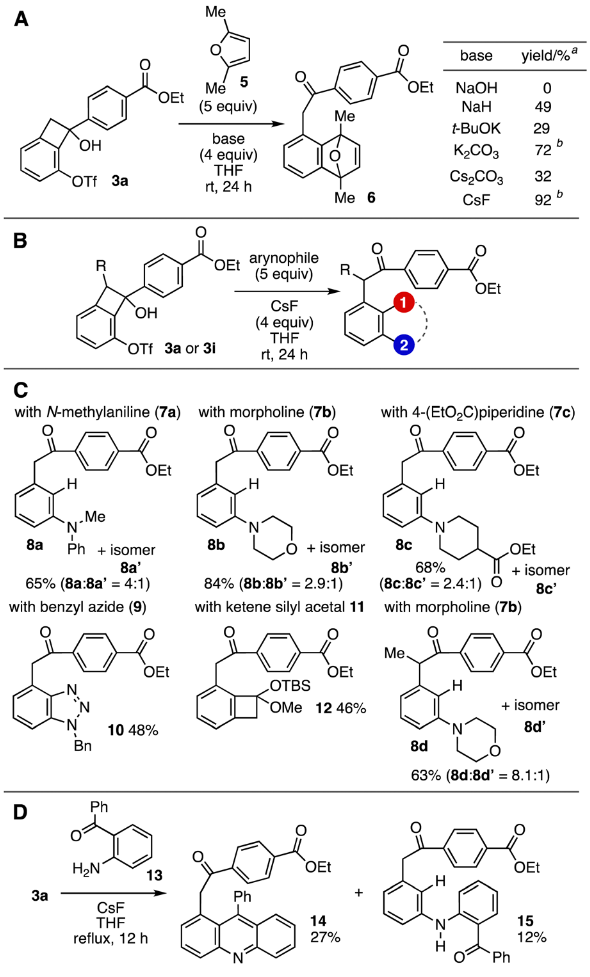
obtained by the reaction in acetonitrile since the I–Mg exchange did not proceed owing to the deprotonation from the solvent (entry 6).

We accomplished the synthesis of a wide range of benzocyclobutenols **3a–3h** from ketone **2a** and various aryl halides **1** (Fig. 2A and B). For example, the I–Mg exchange of ethyl 3-iodobenzoate (**1b**) with the turbo Grignard reagent followed by the 1,2-addition to ketone **2a** proceeded smoothly to afford alcohol **3b** in high yield. Also, we realized the synthesis of alcohol **3c** bearing cyano group through the preparation of the 4-cyanophenylmagnesium intermediate at 0 °C and following the Grignard reaction. Of note, the preparation of a broad variety of benzocyclobutenols **3d–3f** having iodo, fluoro, and bromo groups was achieved using the corresponding aryl halides **1d–1f**. Selective magnesiation of dibromides **1g** and **1h** and subsequent 1,2-addition to ketone **2a** resulted in the efficient synthesis of alcohols **3g** and **3h**, respectively, by the heteroarylations without damaging remaining bromo groups. These good functional group tolerances are obvious advantages over our previous study using organolithium reagents.[5a]

Various benzocyclobutenones **2** successfully participated in the alcohol synthesis with ethyl 4-iodobenzoate (**1a**) (Fig. 2A and C). For instance, after I–Mg exchange of **1a**, treatment of α-methyl-substituted ketone **2b** with the resulting arylmagnesium intermediate provided the alcohol **3i** in a diastereoselective manner. The stereochemistry was confirmed by the nuclear Overhauser effect spectroscopy (NOESY) experiment.[9] Unfortunately, arylation of α,α-dimethyl-substituted ketone **2c** did not take place probably due to the steric hindrance. We accomplished the synthesis of alcohols **3k** and **3l** from ketones **2d** and **2e**, which were prepared from 5-methyl- and 5-bromo-substituted 1,3-bis(triflyloxy)-2-iodobenzene by [2+2] cycloaddition of 3-(triflyloxy)aryne intermediates.[6]

We achieved the synthesis of spirocyclic lactone **4** from ethyl 2-iodobenzoate (**1i**) and ketone **2a** (Fig. 2D). Indeed, treatment of **1i** with the turbo Grignard reagent followed by the addition of ketone **2a** furnished lactone **4** in good yield. The lactone formation would involve the 1,2-addition and following cyclization of the resulting alkoxide intermediate **I**.

A wide range of α-arylacetophenone derivatives were synthesized by the base-promoted aryne generation from alcohol **3a** through the C–C bond cleavage (Fig. 3A). Among various bases screened, potassium carbonate facilitated the aryne generation to afford cycloadduct **6** with 2,5-dimethylfuran (**5**) in good yield. Furthermore, we found cycloadduct **6** was efficiently synthesized with cesium fluoride as an activator.[9] With optimized conditions for aryne generation in hand, we succeeded in the preparation of highly functionalized α-arylacetophenones *via* the aryne intermediate (Fig. 3B and C). For example, *N*-arylation of the aryne generated from alcohol **3a** proceeded smoothly to provide **8a–8c** when using *N*-methylaniline (**7a**), morpholine (**7b**), or 4-(ethoxycarbonyl)piperidine (**7c**), where meta adducts were obtained as major isomers.[10] We succeeded in the synthesis of cycloadduct **10** by the [2+3] cycloaddition of the aryne intermediates with azide **9**, in which the regioisomer was not observed.[11] The preparation of silyl acetal **12** was realized by the aryne-generation-[2+2]-cycloaddition sequence from **3a** and ketene silyl acetal **11** without the regioisomer.[12] To our surprise, side products generated *via* the desilylation from **12** were not observed although cesium fluoride was used as an activator. In addition, the amination of the aryne intermediate generated from methyl-substituted benzocyclobutenol **3i** took place efficiently using morpholine (**7b**) as an arynophile. Moreover, we achieved the synthesis of acridine **14** from alcohol **3a** and 2-benzoylaniline (**13**) in one-step *via* nucleophilic attack of aniline **13** to the aryne intermediate, cyclization of the resulting carbanion, and dehydration (Fig. 3D).[13] In the reaction, *meta*-aminated side product **15** was obtained in low yield, showing protonation of the anionic intermediate also took place.



base	yield/%[a]
NaOH	0
NaH	49
t-BuOK	29
K_2CO_3	72[b]
Cs_2CO_3	32
CsF	92[b]

Fig. 3 (A) Aryne generation from **3a**. (B) General scheme for transformations of **3** *via* aryne intermediates. (C) Synthesis of various α-arylacetophenone derivatives. See the ESI,† for the structures of arynophiles. (D) Synthesis of acridine **14**. [a] Yields based on ^{1}H NMR analysis. [b] Isolated yields.

have developed a modular synthetic route to α-arylacetophenone derivatives from 3-(triflyloxy)aryne precursors, aryl halides, and arynophiles *via* two types of aryne intermediates such as **II** and **III** (Fig. 4). First, treatment of aryne precursor **16** with (trimethylsilyl)-methylmagnesium chloride in the presence of ketene silyl acetal **11** and following formation of the carbonyl group with boron trifluoride diethyl ether complex provided the corresponding benzocyclobutenone *via* aryne **II** in one-pot fashion according to our previous study.[6b] Second, benzocylobutenol synthesis was accomplished using 4-iodobenzonitrile (**1c**) through the I–Mg exchange and subsequent Grignard reaction, wherein the structural integrity of hydroxy, methyl, triflyloxy, and cyano groups remained intact. Third, we succeeded in the synthesis of benzotriazole **17** through the generation of aryne intermediate **III** followed by [2+3] cycloaddition with azide **9**. Thus, the modular synthesis allowed preparing α-arylacetophenone **17** from four components **16**, **11**, **1c**, and **9** in short steps. Due to the great transformability of aryne intermediates, this modular synthetic route will serve in the construction of α-arylacetophenone derivatives by combinatorial chemistry.

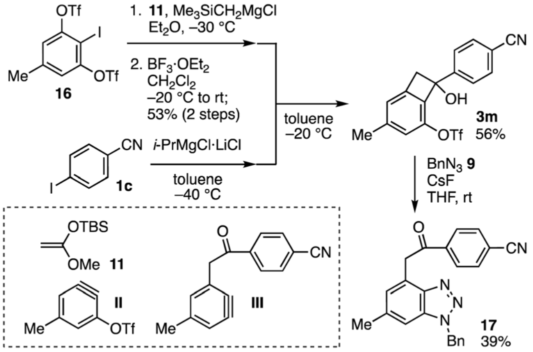


Fig. 4 Modular synthesis of α-arylacetophenone derivative **17**.

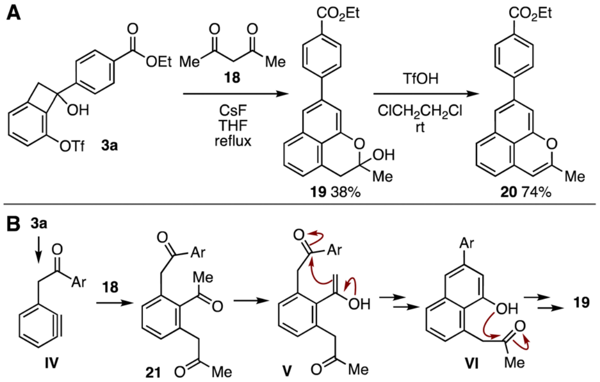


Fig. 5 (A) Synthesis of benzo[*de*]chromene derivatives. (B) Plausible reaction mechanism. Ar = C_6H_4-4-(CO_2Et).

A synthetic advantage for highly functionalized α-arylacetophenone derivatives was demonstrated by benzo[*de*]chromene synthesis from alcohol **3a** in only two steps (Fig. 5A). Indeed, acylalkylation of the aryne intermediate **IV** generated from alcohol **3a** with acetylacetone (**18**) in boiling THF efficiently proceeded to afford hemiacetal **19** in moderate yield without damaging ester moiety along with a complex mixture of side products (Fig. 5A and B).[14] The unique straightforward formation of the benzo[*de*]chromene skeleton would be realized *via* acylalkylated product **21** and following twice cyclizations of intermediates **V** and **VI**. Further dehydration of **19** with triflic acid smoothly occurred to provide benzo[*de*]chromene **20** in good yield. Since benzo[*de*]chromene was synthesized from 3-(triflyloxy)benzyne precursor, ketene silyl acetal **11**, ethyl 4-iodobenzoate (**1a**), and acetyl acetone (**18**) in short steps, a wide variety of benzo[*de*]chromene derivatives would be prepared by changing simple modules, whereby will serve in broad disciplines including natural product chemistry and pharmaceutical sciences.[15]

In summary, we have developed a facile synthetic route to α-arylacetophenone derivatives by the Grignard reaction of ketones **2** and subsequent transformations of aryne intermediates through C–C bond cleavage. While changing solvents significantly affected the efficiency of alcohol synthesis *via* the I–Mg exchange and subsequent 1,2-addition, we succeeded in the facile synthesis of alcohols 3 using toluene as a solvent without side reactions through the cleavage of labile C–C bonds. Good functional group tolerance of the synthesis with a turbo Grignard reagent and divergence of aryne intermediates will contribute to the synthesis of various molecules that contain α-aryl ketone scaffolds. Further studies including diverse α-arylacetophenone synthesis using various arynophiles[16] and detailed mechanistic studies on the unique aryne generation *via* the C–C cleavage are ongoing in our research group.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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