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Three-Component Coupling of Triflyloxy-Substituted Benzocyclobutenones, Organolithium Reagents, and Arynophiles Promoted by Generation of Aryne via Carbon−Carbon Bond Cleavage

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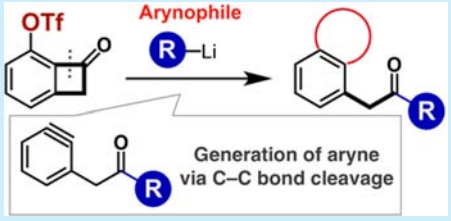
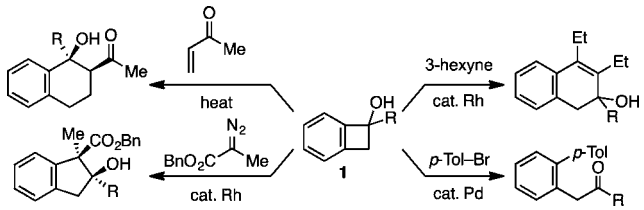
Supporting Information

ABSTRACT: Treatment of benzocyclobutenones bearing a triflyloxy group adjacent to the four-membered ring with organolithium reagents in the presence of arynophiles efficiently affords three-component coupled α-arylketones. Mechanistic studies indicate that the reaction is promoted by generation of the aryne via carbon−carbon bond cleavage of a benzocyclobutenoxide intermediate, which led us to find a fluoride-mediated aryne generation method from triflyloxy-substituted benzocyclobutenone silyl acetal precursors.



Benzocyclobutenols **1** are versatile synthetic intermediates from which a wide range of aromatic compounds have been prepared via two possible types of carbon−carbon (C−C) bond cleavages (Scheme 1).[1−4] We assumed that benzocyclobutenol **4**

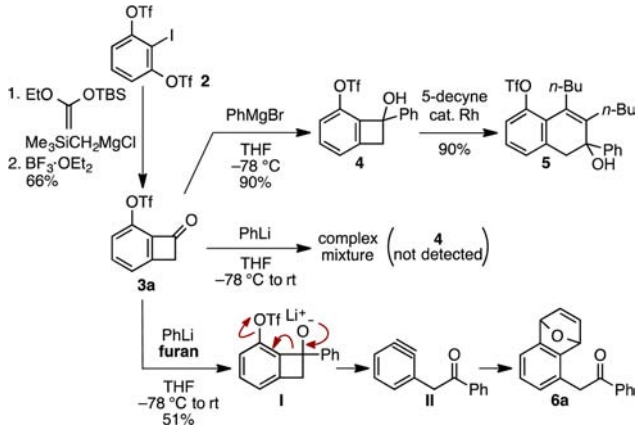
Scheme 1. Transformations of Benzocyclobutenols 1



bearing a triflyloxy group adjacent to the four-membered ring would serve as a useful starting material for these ring-opening transformations, followed by cross-coupling reactions (Scheme 2). Based on this idea, we attempted to synthesize benzocyclobutenol **4** from benzocyclobutenone **3a**, which was easily prepared from 1,3-bis(triflyloxy)-2-iodobenzene (**2**) via [2 + 2]-cycloaddition of 3-(triflyloxy)benzyne[5] with a ketene silyl acetal and subsequent treatment with $BF_3{\cdot}OEt_2$. Treatment of **3a** with phenylmagnesium bromide at −78 °C afforded the desired **4** in high yield. A further attempt of rhodium-catalyzed cycloaddition of **4** with 5-decyne under reported conditions[3b] successfully afforded dihydronaphthalene derivative **5**, leaving the triflyloxy group intact.

During screening for the conditions to prepare benzocyclobutenol **4**, we obtained an intriguing result; treatment of benzocyclobutenone **3a** with phenyllithium at −78 °C and then warming the reaction mixture to room temperature yielded a complex mixture despite the fact that several benzocyclobutenols have been synthesized before from the corresponding

Scheme 2. Attempts to Prepare Benzocyclobutenol 4 Bearing a Triflyloxy Group[a]



[a]See the Supporting Information for details.

benzocyclobutenones using organolithium reagents under similar conditions.[3b,g,4d] We hypothesized that the strong electron-withdrawing nature of the triflyloxy group triggers the C−C bond cleavage[6,7] via the alkoxide intermediate **I** to generate aryne species **II**, resulting in the complex mixture. To verify the hypothesis, we performed the reaction of benzocyclobutenone **3a** with phenyllithium in the presence of furan, used as an arynophile, at −78 °C. After warming the reaction mixture to room temperature, α-arylketone **6a**, which is an expected product of the reaction between 3-(benzoylmethyl)benzyne (**II**) and furan, was obtained in moderate yield. This result

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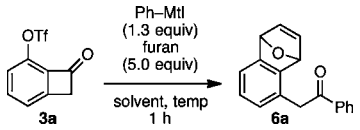
indicated that a three-component coupling reaction between benzocyclobutenone **3a**, phenyllithium, and furan proceeded via generation of aryne **II** without affecting the acidic α-methylene and electrophilic carbonyl groups.

As has been demonstrated through extensive studies on synthetic aryne chemistry,[8−12] including our recent achievements, arynes bearing a transformable functional group, such as 3-(triflyloxy)arynes,[5,7,10] 3-(propargyloxy)arynes,[11a] and arynes bearing an azido group,[11c] are suitable synthetic intermediates of a wide range of diverse aromatic compounds. We anticipated that the three-component coupling reaction involving the generation of aryne would increase options for diversity-oriented syntheses of aromatic compounds,[13] particularly α-arylketones, which are known as good synthetic building blocks.[14] Herein, we report on the optimization and mechanistic studies of the three-component coupling reaction between benzocyclobutenones, organolithium reagents, and arynophiles triggered by generation of arynes via C−C bond cleavage.

We initially screened for the conditions that allowed the efficient formation of **6a** via the generation of aryne **II** from **3a** and cycloaddition with furan (Table 1). Among the conditions

Table 1. Optimization of the Reaction Conditions



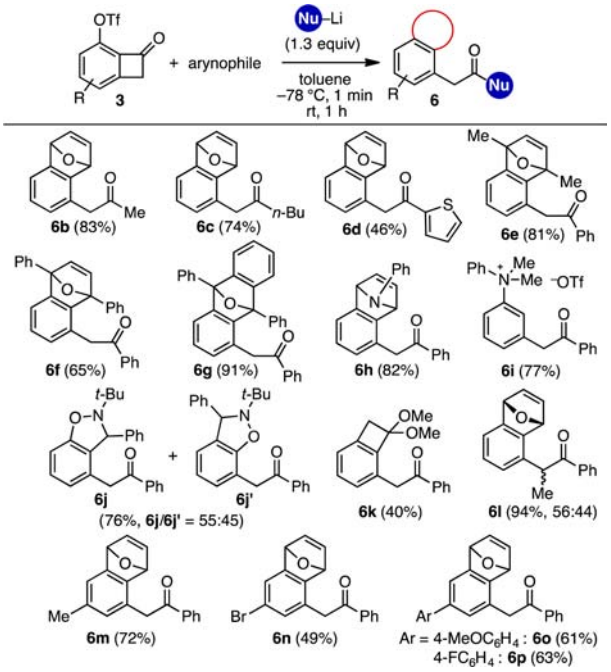
entry	Ph–MtI	solvent	temp (°C)	yield (%)[a]
1	PhLi	CPME	−78 to rt[b]	61
2	PhLi	*n*-hexane	−78 to rt[b]	19[c]
3	PhLi	toluene	−78 to rt[b]	84[d]
4	PhLi	toluene	−78	1[e]
5	PhLi	toluene	−30	62
6	PhLi	toluene	0	61
7[f]	PhLi	toluene	−78 to rt[b]	80[d]
8	PhMgBr	toluene	−78 to rt[b]	0[e]

[a]Yields based on ^{1}H NMR analysis, unless otherwise noted. [b]The reaction was performed at −78 °C for 1 min and at rt for 1 h. [c]Complex mixture of products was obtained. [d]Isolated yield. [e]Alcohol **4** was obtained as a major product. [f]**3a** (6.0 mmol, 1.6 g) was used. CPME = cyclopentyl methyl ether.

tested, the use of toluene as a solvent largely improved the yield of **6a** (Table 1, entries 1−3); treatment of a mixture of **3a** and furan in toluene with phenyllithium for 1 min at −78 °C and then 1 h at room temperature afforded **6a** in high yield (Table 1, entry 3). When the reaction was performed at −78, −30, or 0 °C, **6a** was obtained in low to moderate yields (Table 1, entries 4−6). The optimized conditions were applicable to the gram-scale synthesis of **6a** without a significant decrease of the yield (Table 1, entry 7). The reaction using phenylmagnesium bromide instead of phenyllithium afforded benzocyclobutenol **4** in 83% yield, whereas **6a** was not obtained at all (Table 1, entry 8).

Various α-arylketones containing a ring-fused arene structure were successfully obtained under the optimized conditions (Scheme 3). Alkyllithium and heteroaryllithium reagents were also effective for generating the corresponding arynes from benzocyclobutenone **3a** in the presence of furan, providing the desired cycloadducts **6b−d**. Various dienes, including 2,5-dimethylfuran, 2,5-diphenylfuran, 1,3-diphenylisobenzofuran, and *N*-phenylpyrrole uneventfully reacted with in situ generated 3-(benzoylmethyl)benzyne (**II**) to afford three-component

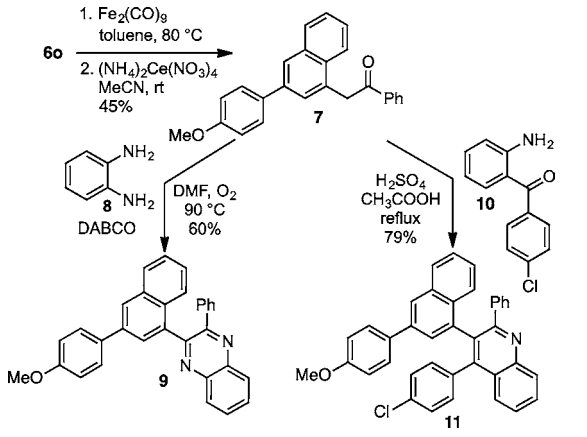
Scheme 3. Three-Component Coupling Products



coupling products **6e−h**. An addition reaction of *N*,*N*-dimethylaniline to aryne **II** provided adduct **6i** selectively. The reactions of aryne **II** with *N*-*tert*-butyl-α-phenylnitrone or ketene dimethyl acetal proceeded to afford cycloadducts **6j**/**6j′** or **6k**.[15] A variety of substituted benzocyclobutenones also participated in this reaction to afford a wide range of cycloadducts **6l−p**. These results demonstrate the wide scope of this three-component coupling approach, which is potentially useful for facile construction of a chemical library comprising a diverse range of α-arylketones.

Facile derivatization of a three-component coupled product to multisubstituted heterocyclic compounds further increased the synthetic utility of this method (Scheme 4). For example,

Scheme 4. Syntheses of Quinoxaline 9 and Quinoline 11



aromatization of cycloadduct **6o** using nonacarbonyldiiron(0) in hot toluene[16] and subsequent oxidative removal of the resulting iron residue by cerium ammonium nitrate (CAN)[5b] afforded 1,3-disubstituted naphthalene **7**, which was heated with *o*-phenylenediamine (**8**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) under an oxygen atmosphere to give 2,3-diaryl-

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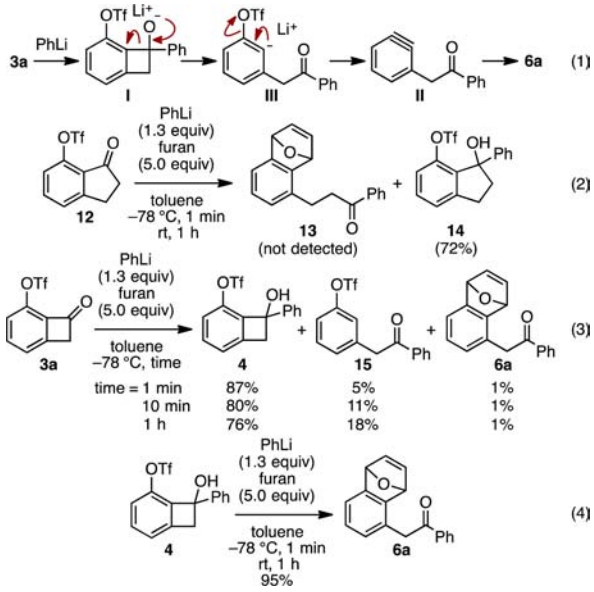
quinoxaline **9**.[14b,f] The reaction between α-naphtylacetophenone **7** and 2-aminobenzophenone derivative **10** also proceeded efficiently to afford 2,3,4-triarylquinoline **11**.[14a]

To gain insight into the reaction mechanism of this three-component coupling reaction, we conducted several control experiments (Scheme 5). Based on the results shown in Scheme 5, eqs 2–4, we consider that the reaction proceeds in a stepwise manner; addition of phenyllithium to ketone **3a** providing alkoxide **I**, C–C bond cleavage to give aryl anion intermediate **III**, and then β-elimination of the triflyloxy group to generate aryne **II** (Scheme 5, eq 1). The reaction using benzocyclopentenone **12** instead of benzocyclobutenone **3a** furnished the simple addition product **14** without affording aryne-mediated cycloadduct **13** (Scheme 5, eq 2). This result indicates that the strain of the four-membered ring facilitates the ring opening via C–C bond cleavage of alkoxide **I**.[6] Quenching the reaction performed at −78 °C after 1 min, 10 min, or 1 h with precooled wet THF suggested the initial formation of alkoxide **I**, which completed within 1 min, and its gradual transformation into aryl anion **III**, which was supported by the observation of the time-dependent increase of α-(3-triflyloxyphenyl)acetophenone (**15**) at −78 °C (Scheme 5, eq 3). This step and generation of aryne were facilitated by increasing the reaction temperature to room temperature. Furthermore, when the reaction was performed using benzocyclobutenol **4** instead of benzocyclobutenone **3a**, cycloadduct **6a** was obtained in excellent yield (Scheme 5, eq 4). This result also supports the mechanism involving the ring opening of alkoxide **I**.[17,18]

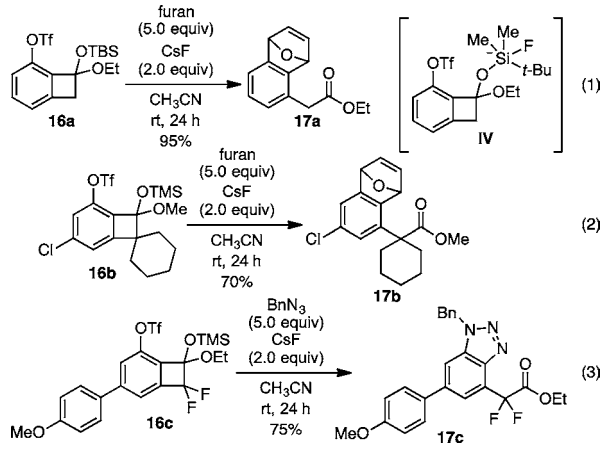
Mechanistic consideration of the three-component coupling reaction inspired us to examine whether arynes could be generated from silyl acetal of triflyloxy-substituted benzocyclobutenones through treatment with a fluoride anion (Scheme 6). As expected, treatment of the acetonitrile solution of silyl acetal **16a** and furan with cesium fluoride at room temperature afforded cycloadduct **17a** in high yield, indicating that an aryne was generated smoothly via silicate intermediate **IV** (Scheme 6, eq 1).[19] Similarly, spiro-cyclic benzocyclobutenone silyl acetal **16b** bearing a chloro group also participated in the reaction to afford highly functionalized naphthalene derivative **17b** efficiently (Scheme 6, eq 2). Notably, fluoride-mediated generation of aryne from difluoro-substituted benzocyclobutenone silyl acetal **16c** in the presence of benzyl azide afforded α-aryl-α,α-difluoroacetic acid ester **17c** selectively, indicating that the electron-withdrawing difluoromethylene group contributed to induce the high regioselectivity in the cycloaddition between an aryne and azide (Scheme 6, eq 3). As we reported previously, because benzocyclobutenone silyl acetals **16** could be easily synthesized by the [2 + 2]-cycloaddition between 3-triflyloxyarynes and ketene silyl acetals, the generation method of arynes via C–C bond cleavage of silyl acetals **16** would provide a new option for preparing a wide range of α-arylacetic acid esters in a modular synthetic manner via assembling 3-triflyloxyarynes, ketene silyl acetals, and arynophiles.

In summary, we found that arynes were efficiently generated via the C–C bond cleavage of triflyloxy-substituted benzocyclobutenoxides. Considering the ready availability of benzocyclobutenones **3** and benzocyclobutenone silyl acetals **16**, the modular synthesis based on the aryne relay chemistry, combining 3-(triflyloxy)aryne precursors, ketene silyl acetals, and a variety of arynophiles with or without organolithium reagents, would enable efficient syntheses of diverse aromatics. Further studies expanding the scope of benzocyclobutene derivatives and arynophiles for addition reactions or difunctionalizaition of aryne intermediates generated by this method are now in progress.

Scheme 5. Mechanistic Studies



Scheme 6. Syntheses of α-Arylacetic Acid Esters



■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization for new compounds including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(17) The C−C bond cleavage might be facilitated by the strong ionic character of lithium alkoxide **I** compared with that of magnesium alkoxide, although the detailed studies to explain the different reactivity between PhLi and PhMgBr are yet to be investigated.

(18) Treatment of ketone **15** with phenyllithium in the presence of furan did not afford cycloadduct **6a**, indicating that generation of aryne **II** via protonated product **15** is unlikely.

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