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Connecting a carbonyl and a π-conjugated group through a *p*-phenylene linker by (5+1) benzene ring formation†

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A benzene ring was formed to connect a carbonyl group of various methyl ketones with a π-conjugated group through a *p*-phenylene linker. Methyl ketones and streptocyanines were used as the C1 and C5 sources, respectively, in the (5+1) annulation, which could form donor–π–acceptor molecules.

Connecting two different molecules with a linker is a fundamental design principle of functional organic molecules such as organic devices,[1] supramolecular materials,[2] bioactive compounds,[3] and ligands for metal–organic frameworks.[4] The *p*-phenylene group is one of the most widely used linkers for the following reasons: (1) the rigid structure of the benzene ring defines the relative position of two substituents on the benzene ring,[5] and (2) the *p*-phenylene group can connect two substituents with π-conjugation, which affects the electronic state of the molecule.[6] Compared with *o*- or *m*-phenylene groups, (3) the *p*-phenylene group can extend π-conjugation more effectively because of steric or electronic reasons, and (4) the planar structure and π-electrons of the benzene ring induce π–π stacking, which can affect the secondary structure of the molecules.[7]

Utilizing these characteristics, various *p*-phenylene-containing molecules were designed and synthesized as functional organic molecules. Particularly, carbonyl-*p*-phenylene-π molecules (Fig. 1a) are used for a wide range of applications such as receptor antagonists,[8] aggregation-induced emission luminogens,[9] and photoinitiators for free radical polymerization.[10] In addition, when a π-conjugated substituent acts as a donor, such a carbonyl-*p*-phenylene-π molecule could be regarded as a donor–acceptor molecule, which is an important core structure of thermally activated delayed fluorescent emitters[11] and photocatalysts mediating proton-coupled electron transfer.[12]

One approach to synthesizing carbonyl-*p*-phenylene-π molecules is the introduction of a π-conjugated substituent to a benzene ring bearing a carbonyl group *via* cross-coupling reactions[13] (Fig. 1b). Another method is the connection of a carbonyl group to a benzene ring to form a ketone (Fig. 1c). The most popular classical approach with respect to the latter method is the Friedel–Crafts reaction of acid chlorides and electron-rich aromatic compounds.[14] The reaction of the Weinreb amide or its analogues with organometallic reagents is an alternative method for ketone formation.[15] Transition-metal-catalyzed ketone formation is also popular.[16] These approaches are valuable, but the scope of the Friedel–Crafts reaction is limited and some aromatic substrates show undesired regioselectivity.

The introduction of a π-conjugated group needs to use both aryl halides and arylmetal reagents that require multistep preparation in most cases. A more convenient regiospecific

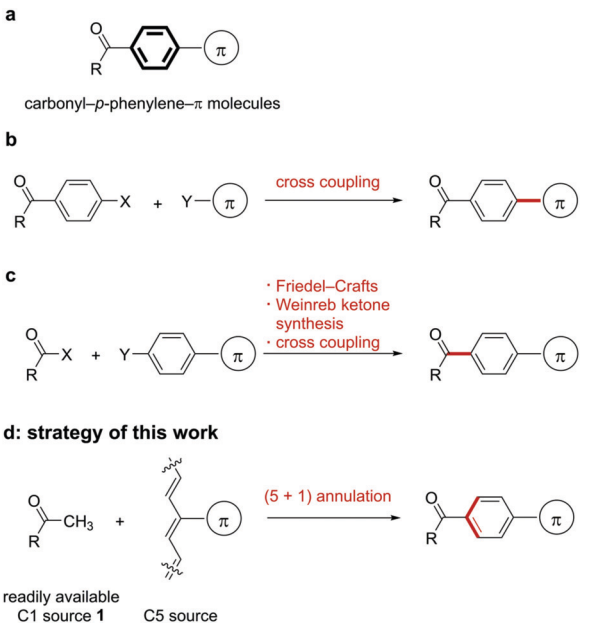

Fig. 1 Strategies for synthesis of carbonyl-*p*-phenylene-π molecules.

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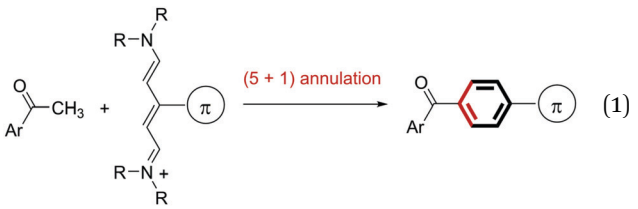
method for synthesizing carbonyl-*p*-phenylene-π molecules is still highly desired.

Benzene ring formation would be an alternative approach to synthesize benzene-containing molecules. Various approaches for [2+2+2] and [4+2] benzene ring formation have been developed in the past up to the present.[17] However, it is difficult to synthesize carbonyl-*p*-phenylene-π molecules using the [2+2+2] and [4+2] annulation because of their inherent 1,4-disubstitution pattern. In contrast, (5+1) benzene ring formation[18,19] could be expected to give 1,4-disubstituted benzene derivatives regioselectively.

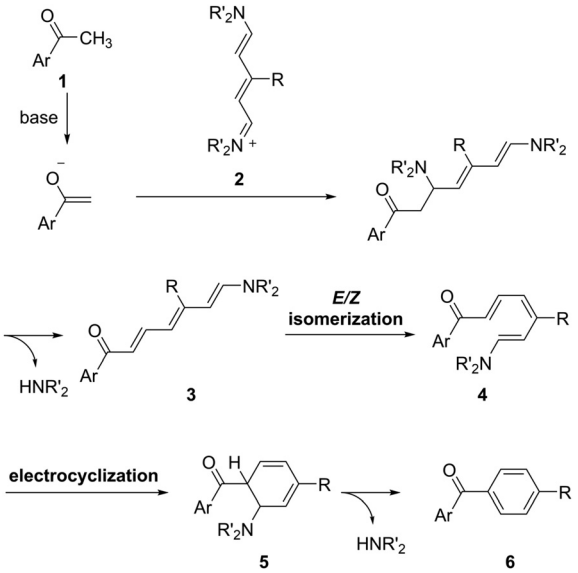
Based on this background, we envisioned that (5+1) benzene ring formation using a methyl ketone **1** as the C1 source and a C5 source bearing a π-conjugated substituent would be an attractive approach to obtaining carbonyl-*p*-phenylene-π molecules because starting methyl ketone **1** is readily available (Fig. 1d). This approach would give the *p*-phenylene-linked products regiospecifically. In relation to the approach, conversion of an acetyl group into an unsubstituted benzoyl group using a conjugated methine compound (streptocyanine) as a C5 source was reported by Jutz.[20] However, the mere formation of an unsubstituted phenyl group, which restricted applicability of this reaction, has not been applied to connecting two fragments through the benzene ring formed. We report here a new method for connecting a carbonyl and a π-conjugated group through a *p*-phenylene linker by benzene ring formation using a methyl ketone as the C1 source and a streptocyanine bearing a π-conjugated substituent as the C5 source (eqn (1)).



(1)

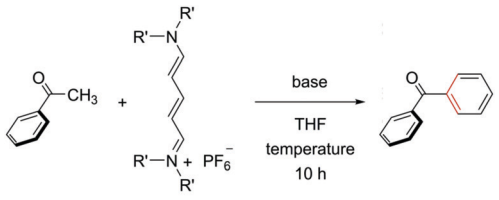
A working hypothesis is that the (5+1) annulation proceeds following a pathway such as that shown in Scheme 1. The enolate generated from methyl ketone **1** and a base attacks an iminium group in streptocyanines **2**, and following the elimination of an amine gives triene intermediate **3**. Triene **3** could be converted thermally to *E*/*Z* isomer **4** because of the push–pull electronic structure.[21] Then, 6π electrocyclization[22] of **4** gives cyclohexadiene **5**, and following the second elimination of the amine produces the desired carbonyl-*p*-phenylene-π molecule **6**. It follows that the base, nitrogen substituents, and reaction temperature could be critical for the successful (5+1) annulation.

We first optimized the reaction conditions for the (5+1) annulation using streptocyanines bearing no internal substituent (Table 1).[20] Acetophenone (**1a**), streptocyanine **2**, and KO^{t}Bu were mixed and stirred in THF at 80 °C for 10 h in a pressure tube to give benzophenone (**6a**) in a 30% yield (entry 1). Higher reaction temperatures increased the yield of the product (entries 2 and 3). The nitrogen substituent in streptocyanine **2** was found to affect the yield, and the piperidinyl substituent turned out to be the best (entries 3–5). The use of NaO^{t}Bu instead of KO^{t}Bu as a base gave the product in an almost quantitative yield (entry 6). The (5+1) benzene ring formation was achieved in one pot without isolating intermediates **3**.



Scheme 1 Proposed reaction mechanism of (5+1) benzene ring formation.

Table 1 Optimization of the reaction conditions[a]



1a 2 6a

Entry	R′, R′	Base	Temp. (°C)	Yield[b] (%)
1	Me, Me	KO^{t}Bu	80	30
2	Me, Me	KO^{t}Bu	100	53
3	Me, Me	KO^{t}Bu	120	84
4	–$(CH_2)_2O(CH_2)_2$–	KO^{t}Bu	120	29
5	–$(CH_2)_5$–	KO^{t}Bu	120	89
6	–$(CH_2)_5$–	NaO^{t}Bu	120	99 (94)[c]

[a] Acetophenone (**1a**) (0.2 mmol), streptocyanine **2** (1.5 equiv.), and base (1.5 equiv.) were stirred at the indicated temperature in THF (4 mL) for 10 h. [b] Yield of the products was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

Next, we prepared streptocyanines bearing a π-conjugated substituent at the 3-position, **2**, for the (5+1) annulation synthesizing carbonyl-*p*-phenylene-π molecules. The procedure for synthesizing streptocyanines **2** is illustrated in Fig. 2.[23] *N*-Arylation of 4-substituted pyridine **7** with 2,5-dinitrochlorobenzene gave the corresponding *N*-arylpyridinium salt **8** (Fig. 2, A). The resulting *N*-arylpyridinium **8** was treated with piperidine, and following salt exchange gave the desired streptocyanine **2** (Fig. 2, B). Streptocyanines bearing a π-conjugated substituent such as a phenyl group, a biphenyl group, a naphthyl group, a benzothiophenyl group, and a pyrenyl group were prepared (**2b–2f**). Streptocyanines bearing a diphenylamino group, a carbazolyl group, and a *tert*-butyl group were also synthesized in the

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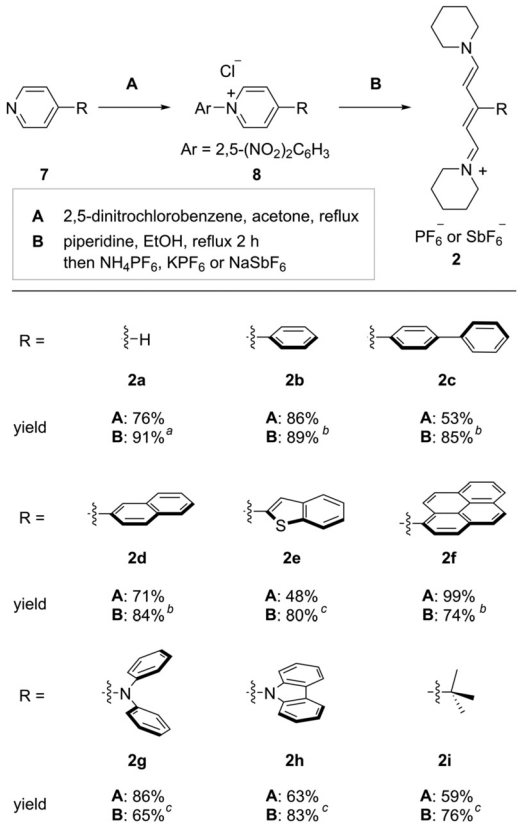

Fig. 2 Synthesis of streptocyanines bearing a substituent. [a] NH_4PF_6 was used. [b] KPF_6 was used. [c] $NaSbF_6$ was used.

same manner (**2g–2i**). It should be noted that streptocyanines **2a–2i** could be purified by filtration and washing and did not require purification by column chromatography.

The synthesized streptocyanines **2** were used for (5+1) annulation under the optimized reaction conditions described in Table 1. Some of the scope of the reaction is shown in Fig. 3. The functional group compatibility of the present transformation is remarkable. Acetophenones bearing an electron-donating group and an electron-withdrawing group gave the corresponding products (**6b–6h**) in excellent to moderate yields. Particularly, iodo- or bromo-substituted products (**6e**, **6f**) are valuable because further transformation of the products is easy using a transition-metal catalyst. Additionally, benzylacetone, which is an aliphatic ketone, could also be used for (5+1) annulation to give the corresponding product **6i**.

This annulation reaction was applied to the synthesis of carbonyl-*p*-phenylene-π molecules. Reactions of acetophenone (**1a**) with streptocyanines bearing a phenyl substituent **2b** gave corresponding product **6j** in excellent yield. The reaction also worked well on a gram scale. Sterically hindered *o*-methylacetophenone was also a good substrate for (5+1) annulation (**6k**). Heteroaryl methyl ketones such as 2-acetyl thiophene and 1-methyl-3-acetylindole gave the corresponding heteroaryl–carbonyl-*p*-phenylene-π molecules (**6l**, **6m**).

(5+1) benzene ring formation using acetophenone and streptocyanines bearing various π-conjugated substituents was

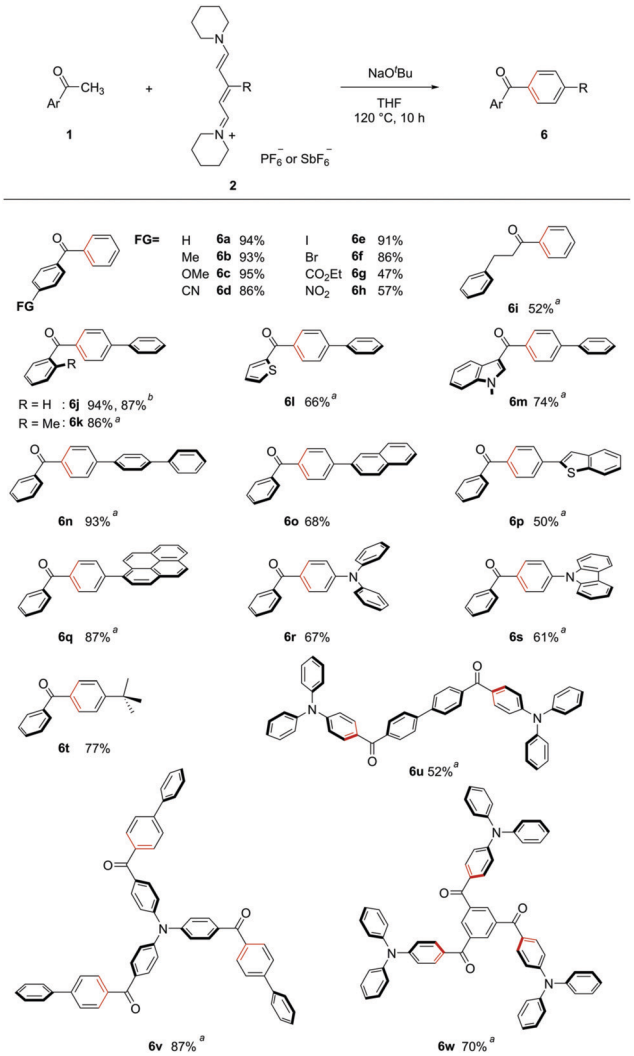

Fig. 3 Scope of (5+1) benzene ring formation. Aryl methyl ketone **1** (0.5 mmol), streptocyanine **2** (1.5–6 equiv.), and NaO^{t}Bu (1.5–18 equiv.) were stirred at 120 °C in THF for 10 h. [a] Reaction run on 0.2 mmol scale. [b] Reaction run on a gram scale (12 mmol scale). See ESI† for details.

carried out. Biphenyl-, naphthyl-, and 2-benzothiophenyl-substituted streptocyanines were found to be good substrates for the annulation (**6n–6p**). Use of pyrenyl-substituted streptocyanine **2f** gave corresponding product **6q**, which was used as a photoinitiator.[10] Using diphenylamino- or carbazolyl-substituted streptocyanines (**2g**, **2h**), the present method could be applied to the synthesis of carbonyl-*p*-phenylene-donor molecules (**6r**, **6s**, respectively). The reaction of acetophenone with *tert*-butyl-substituted streptocyanine **2i** gave *p*-*tert*-butylphenyl phenyl ketone (**6t**).

An advantage of this method is the availability of versatile acetyl compounds as a counterpart to streptocyanines. Even di- or tri-acetyl-substituted compounds are also readily available. By using such compounds as a starting material, we applied this method to the synthesis of symmetric molecules bearing *p*-phenylene groups connecting the triphenylamine moiety as the donor and carbonyl groups as the acceptor. C_{2h} symmetric

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donor–acceptor molecule **6u** was synthesized from 4,4′-diacetylbiphenyl and **2g** *via* double (5+1) benzene ring formation. Using 4,4′,4″-triacetyltriphenylamine and **2b** as starting materials, triple-*p*-phenylene group formation was achieved to give the corresponding C_3 symmetric donor–acceptor molecule **6v**. The reaction of 1,3,5-triacetylbenzene with **2g** also gave the C_3 symmetric donor–acceptor molecule **6w**.

In conclusion, we have developed an efficient method for synthesizing carbonyl-*p*-phenylene-π molecules from readily available methyl ketones and easily synthesized streptocyanines in one pot. This convenient method was applied to the synthesis of symmetric donor–acceptor molecules that have two or three such linkages.

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Conflicts of interest

There are no conflicts to declare.

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