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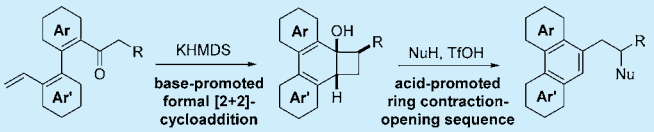
Synthesis of Functionalized Polycyclic Aromatic Compounds via a Formal [2 + 2]-Cycloaddition

Yuuki Nagamoto, Yousuke Yamaoka, Shun Fujimura, Yoshiji Takemoto, and Kiyosei Takasu*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information

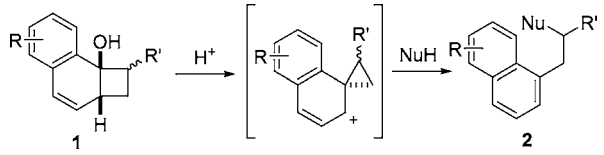
ABSTRACT: A base-promoted formal [2 + 2]-cycloaddition of 2-acyl-2′-vinyl-1,1′-biaryls was developed to provide polycyclic cyclobutanols as a step toward the synthesis of substituted polycyclic aromatic hydrocarbons and their heterocyclic analogues.



The extended π-systems of polycyclic aromatic hydrocarbons (PAHs) convey unique optical and morphological properties[1] that have opened new avenues in material science. PAHs are applicable to electronic devices, such as light emitting diodes (OLEDs)[2] and organic field-effect transistors (OFETs).[3] The optical properties of a PAH depend strongly on the basic architectural structure, including the number of aromatic rings, the manner in which the aromatic rings are fused, and the substituents on the rings. The incorporation of heteroatoms into the π-system of a PAH can tune its properties and expand its utility in materials and devices. Polyaromatic motifs are also of interest in the field of medicinal chemistry. Some PAHs interact with DNA or proteins to provide important pharmacological activities.[4] A variety of synthetic methods have been developed for the preparation of PAHs;[5] however, the need for simple methods that can access structurally diverse PAHs and related compounds remains high.

We previously reported a ring-contraction reaction among fused cyclobutanols to form spirocyclopropanes, triggered by the elimination of a hydroxy group.[6] We also reported a ring-opening reaction of cyclopropanes to yield olefinic adducts.[7] Inspired by these reactions, we recently designed and synthesized a DNA cleaving agent that acted at low pH. We found that, under acidic conditions, cyclobutanaphthalenol **1** reacted with the appropriate nucleophile, such as a nucleic base to give the naphthalene compound **2** through a domino ring-contraction−ring-opening sequence (Scheme 1).[8] Based on these findings, we envisaged that PAHs could be obtained from multibenzo-fused cyclobutanols through a domino sequence. Herein, we report an efficient and highly stereoselective synthesis of dibenzo fused cyclobutanols through a base-promoted formal [2 + 2]-cycloaddition of biaryl ketones and the transformation of the resulting cyclobutanols into PAHs under acidic conditions.

Scheme 1. Domino Ring-Contraction−Ring-Opening Reaction



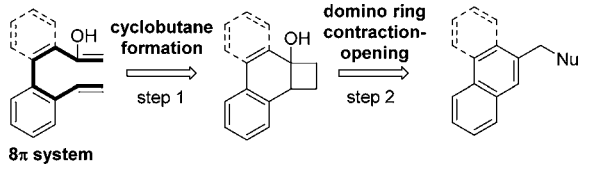
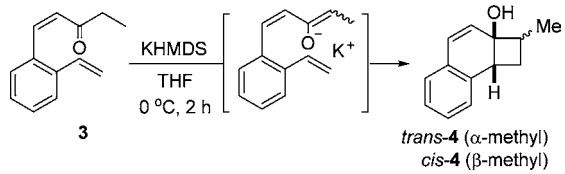


Figure 1. Synthetic plan for PAHs from 2-acyl-2′-vinyl-1,1′-biaryl compounds via formation of fused cyclobutanols.

Scheme 2. Synthesis of Naphthocyclobutanol 4 from the Enone 3



Our initial concept for the preparation of benzo-fused cyclobutanols was inspired by the work of Škorić, Margetić, and co-workers, who demonstrated a domino $8\pi-6\pi$ electrocyclization for the preparation of cyclobutanaphthalenes from benzooctatetraenes.[9] We were intrigued that the installation of a hydroxyl group on the dienyl moiety of the starting materials would generate fused cyclobutanols (Figure 1, step 1), followed by the acid treatment to furnish PAHs (Figure 1, step 2).

To test the above hypothesis, our experimental efforts began with the reaction of (*Z*)-enone **3**. In the presence of KHMDS, the expected reaction was promoted in THF at 0 °C over 2 h to yield the cyclobutanol **4** in 74% yield as a 55:45 (*trans*/*cis*) mixture of diastereomers (Scheme 2). The stereochemistry of both diastereomers was determined by NOESY. It is worth noting that the reaction of **3** proceeded at 0 °C, whereas the $8\pi-6\pi$ electrocyclization of the nonoxygenated analogues

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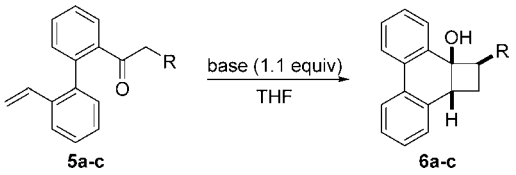
Table 1. Optimization of the Reaction Conditions[a]



5a-c 6a-c

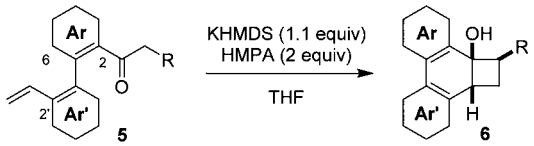
entry	substrate	base	additive	6, yield [%] (dr)[b]
1	**5a** (R = H)	KHMDS	–	**6a**, 72
2	**5a**	NaHMDS	–	**6a**, 5
3	**5a**	LiHMDS	–	**6a**, 0
4	**5a**	KHMDS	HMPA[c]	**6a**, 87
5	**5a**	LiHMDS	HMPA[d]	**6a**, 10
6[e]	**5b** (R = CH_3)	KHMDS	–	**6b**, 93 (49:1)
7[f]	**5c** (R = $CH_2C_6H_5$)	KHMDS	–	**6c**, 90 (>50:1)

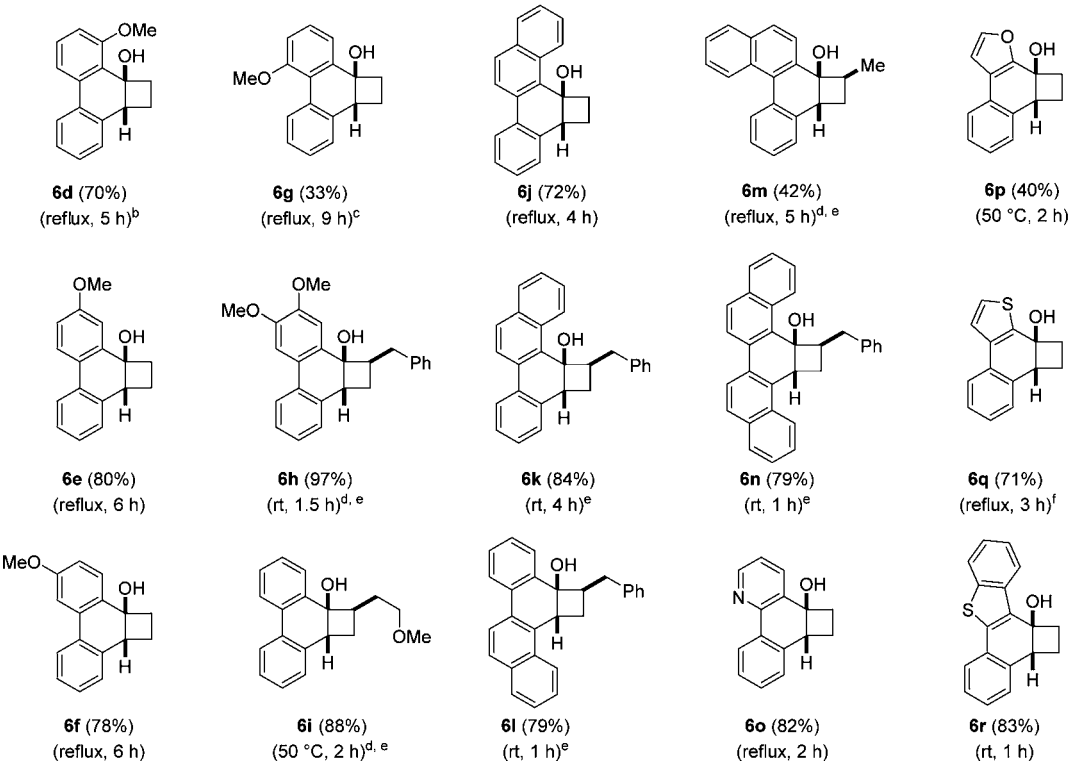
[a]Unless otherwise noted, the reaction was carried out with **5** (1 equiv), base (1.1 equiv), and THF (0.1 M) at the reflux temperature in THF for 4 h. [b]Isolated yields. The diastereomeric ratio was determined by ^{1}H NMR. The R group of the minor diastereomer is located at the α-position. [c]2 equiv. [d]5 equiv. [e]At rt. [f]At 50 °C.

required a higher reaction temperature and a longer reaction time (reflux in toluene, 20 h).[9]

Biaryls **5** bearing acyl and alkenyl substituents at the 2 and 2′ positions, respectively, led to polyaromatic cyclobutanols according to a similar method; however, the 8π–6π electrocyclization of dibenzooctatetraene had been unexplored. We were afraid that 8π electrocyclization of **5**, leading to a doubly dearomatized intermediate, would require a high activation energy. We explored the optimal conditions for the base-promoted reaction of the 2-acyl-2′-vinyl-1,1′-biphenyls **5a**–**5c**, which were easily prepared from the 1-acyl-2-bromobenzenes by the Suzuki–Miyaura coupling[10] with 2-styrylboronic acid (Table 1). Upon treatment of **5a** with 1.1 equiv of KHMDS in THF, the expected reaction proceeded at the reflux temperature to give cyclobutaphenanthrene **6a** in 72% yield (entry 1). The reaction was found to be sensitive to the countercation of the base. Almost no reaction occurred in the presence of LiHMDS or NaHMDS (Table 1, entries 2 and 3). The addition of HMPA improved the yield of **6a** to 87% (Table 1, entry 4). Notably, the reaction proceeded in the presence of HMPA, even in the presence of LiHMDS, albeit in a low yield (Table 1, entry 5). The results indicated that the formation of a naked enolate anion was important for the cyclobutanol formation. The reaction of the ketones **5b** and **5c** bearing ethylketo and phenethylketo moieties furnished the corresponding cyclobutanols **6b** and **6c**, respectively, in excellent yield with high stereoselectivity (Table 1, entries 6 and 7). The reaction

Table 2. Substrate Scope for the Synthesis of Polycyclic Cyclobutanols[a]





[a]Unless otherwise noted, the reaction was carried out with **5** (1 equiv), KHMDS (1.1 equiv), HMPA (2.0 equiv), in THF (0.1 M). Yields shown are of the isolated products. [b]In toluene. [c]In DME. [d]In the absence of HMPA. [e]No diastereomeric isomer was detected by ^{1}H NMR. [f]KH (1.5 equiv) was used instead of KHMDS.

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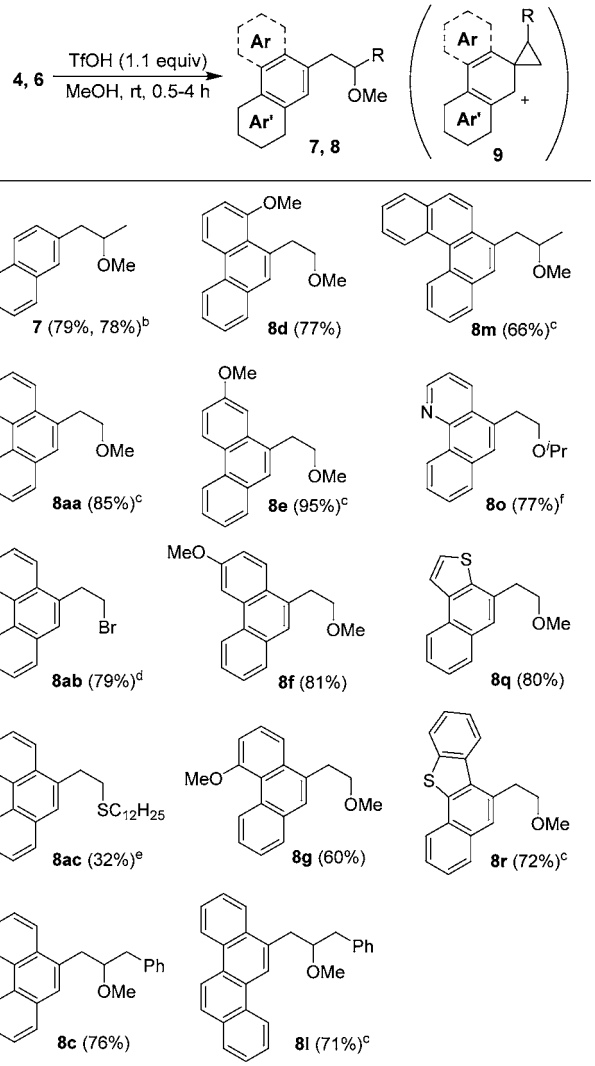
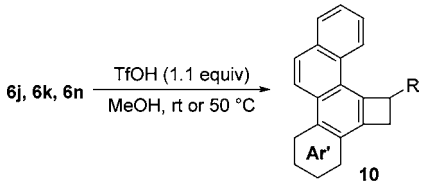
Table 3. Transformation of Cyclobutanols into PAHs[a]



[a]Standard conditions: **4** or **6** (1 equiv), TfOH (1.1 equiv) in MeOH (0.1 M) at rt for 0.5−4 h. [b]Yields from *trans*-**4**, *cis*-**4**, respectively. [c]At 50 °C. [d]Aqueous HBr (1.5 equiv) instead of TfOH; MeCN instead of MeOH. [e]$C_{12}H_{25}SH$ (1.5 equiv) was added; MeCN instead of MeOH. [f]With refluxing in *i*PrOH.

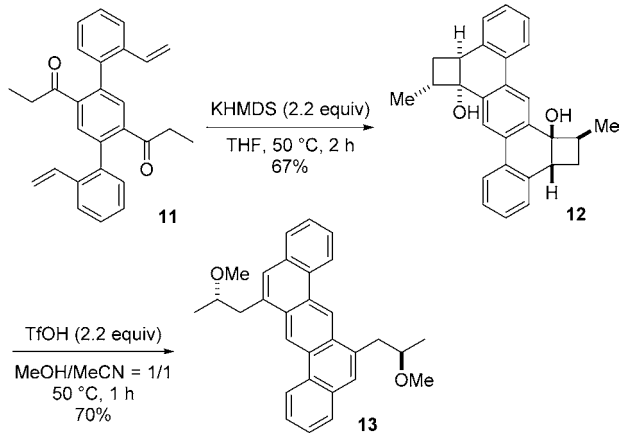
Scheme 3. Unexpected Elimination Reaction



10j; Ar' = benzene, R = H (77% at rt)
10k; Ar' = benzene, R = $CH_2C_6H_5$ (64% at 50 °C)
10n; Ar' = naphthalene, R = $CH_2C_6H_5$ (78% at rt)

proceeded smoothly, even in the absence of HMPA. The stereochemistry of the major isomer of **6b** having three contiguous stereogenic centers on the cyclobutane ring was determined by NOESY. Borschberg and co-workers reported the synthesis of **6c** from the allylalcohol derivative. The structure of **6c** was similar to that of **5c** and was identified as an unexpected product during their study of the intramolecular

Scheme 4. Stereoselective Double Formal [2 + 2]-Cycloaddition of Terphenyl 11, and the Formation of the Pentacyclic Aromatic Compound 13



anionic oxy-ene reaction.[11] They suggested that cyclobutanol formation resulted from a domino nucleophilic addition initiated by 8-*endo*-trig cyclization. It is not yet clear whether the formal [2 + 2]-cycloaddition in our system proceeded via a concerted or a polar pathway.

With the optimized conditions in hand, a number of biarylketones were tested for their utility in the synthesis of polycyclic cyclobutanols having a variety of scaffolds (Table 2). Moderate to excellent yields were obtained. The diastereomeric selectivity was almost perfect, provided that the R group of **5** was not a hydrogen (**6h**, **6i**, and **6k**−**n**). Substrates bearing naphthyl groups afforded the corresponding penta- or hexacyclic products **6j**−**6n**. Moreover, heterocyclic substrates (pyridine, furan, thiophene, and benzothiophene) could be used in our system to afford the heteroaryl products **6o**−**6r**. Generally, the reaction rate of the substrate bearing an acetyl group was slower than the reaction rate of biaryls having an α-substituted ketone (i.e., **6j** vs **6k**). The introduction of a substituent at the 6-position of the acyl aromatic ring of the substrate dramatically decreased the reactivity (**6g** and **6m** vs Table 1, entry 1). These results suggested that coplanarity of the aromatic rings in the transition state critically influenced the promotion of the desired reaction.

We next investigated the transformation of the cyclobutanols into PAHs under acidic conditions (Figure 1, step 2). Upon treatment of *trans*-**4** with 1.1 equiv of TfOH in MeOH at rt, the domino ring-contraction−ring-opening reaction was completed within 4 h to give the 2-substituted naphthalene **7** in 79% yield (Table 3). The diastereomer *cis*-**4** displayed a similar reactivity and gave the same product **7**. MeOH functioned as both a solvent and a nucleophile in the reaction. The addition of the nucleophile to the possible intermediate **9** selectively occurred at the R-branched carbon on the cyclopropane ring. The cyclobutanols **6** could be transformed into the corresponding PAHs and the heterocycles **8** in moderate to good yield. Use of the appropriate nucleophile in CH_3CN under acidic conditions resulted in the introduction of a bromine atom and a mercapto group (**8ab** and **8ac**). It is noteworthy that our method enabled the selective synthesis of regiochemical isomers bearing a substituent on the polyaromatic ring (**8d**−**g**).

By contrast, the cyclobutanols **6**, which possessed a napthalene ring at the upper rim of the cyclobutane, did not undergo the expected reaction sequence to yield **8**. The

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treatment of **6j**, **6k**, and **6n** with TfOH furnished zigzag (armed-chair) shaped PAHs, such as the chrysenes **10j** and **10k** and picene **10n**, which have been demonstrated to display semiconductor properties[3d] (Scheme 3). The products were formed by an E1-type elimination reaction with the assistance of the acid catalyst. The formation of the spirocyclic intermediate **9** was prohibited by the steric repulsion of the upper-rimmed naphthalene ring. A careful survey of the reaction mixtures used in the reactions of **6d** and **6r** clarified that trace amounts of the elimination products **10d** and **10r**, respectively, were formed.

Our synthetic route to PAHs from biaryls was ultimately applied to the reaction of terphenyl **11** bearing two pairs of reactive sites toward the preparation of a more extended π-system. Gratifyingly, the reaction of **11** with 2.2 equiv of KHMDS furnished heptacyclic bis(cyclobutanol) **12** in 67% yield as a single diastereomer (Scheme 4). Acid-promoted aromatization succeeded in giving the S-shaped PAH **13** as a single diastereomer. The structures of **12** and **13** were determined to be *meso* stereoisomers by X-ray crystallography. Interestingly, during the formation of **12**, the initially generated cyclobutane was expected to dominate the stereochemistry of the successive cyclobutane ring. The stereochemical information in the cyclobutane would be transmitted to the second formal [2 + 2]-cycloaddition through the transient axial chirality of the biaryl intermediate. The relative stereochemistry of **13** depended on that of **12** because both the ring-contraction and ring-opening reactions were stereospecific processes.

In summary, we developed a KHMDS-promoted formal [2 + 2]-cycloaddition reaction of the 2-acyl-2′-vinylbiaryls to provide polycyclic cyclobutanols in a highly stereoselective manner. We also demonstrated a versatile method for the preparation of polycyclic aromatic compounds via this cycloaddition, followed by a TfOH-promoted rearrangement. A variety of substituted PAHs and related heteroaromatics may be synthesized in short steps. The polyaromatic framework and the substituents may be prepared by retrosynthetically designing biaryl compounds that can be readily prepared by the Suzuki−Miyaura coupling reaction. Furthermore, we demonstrated the double cyclobutane formation reaction of terphenyl, which proceeded in a stereoselective manner. Further investigations are anticipated to clarify the reaction mechanisms underlying the formal [2 + 2]-cycloaddition reactions. Applications of these methods toward the synthesis of useful materials are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of new products, X-ray data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kay-t@pharm.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

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