Formation of Isolable Dearomatized [4 + 2] Cycloadducts from Benzenes, Naphthalenes, and *N*-Heterocycles Using 1,2-Dihydro-1,2,4,5-tetrazine-3,6-diones as Arenophiles under Visible Light Irradiation

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ABSTRACT: We report that the dearomative [4 + 2] cycloaddition between 1,2-dihydro-1,2,4,5-tetrazine-3,6-diones (TETRADs) and benzenes, naphthalenes, or N-heteroaromatic compounds under visible light irradiation affords the corresponding isolable cycloadducts. Several synthetic transformations including transition-metal-catalyzed allylic substitution reactions using the isolated cycloadducts at room temperature or above were demonstrated. Computational studies revealed that the retro-cycloaddition of the benzene-TETRAD adduct proceeds via an asynchronous concerted mechanism, while that of the benzene-MTAD adduct (MTAD = 4-methyl-1,2,4-triazoline-3,5-dione) proceeds via a synchronous mechanism.

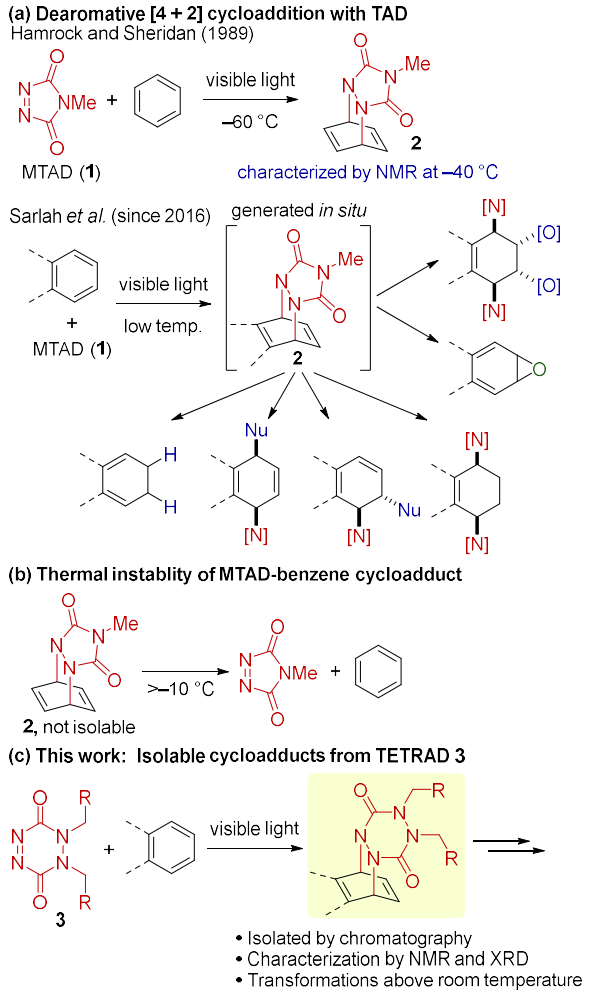
INTRODUCTION

Aromatic compounds with stabilized cyclic π-electron systems such as benzene, naphthalene, pyridine, and quinoline are naturally abundant and readily available feedstocks. As the introduction and their manipulation of functional groups on aromatic rings are well-established synthetic transformations, a wide range of substituted aromatics are also common starting materials in organic synthesis. Based on this background, dearomatization reactions that enable rapid construction of complex non-planar scaffolds from planar aromatic compounds have attracted great attention.[1-4] A major challenge in achieving such transformations derives from the requirement to overcome the stabilization of aromatic systems. While heteroaromatic compounds with attenuated aromaticity[2] and electron-rich phenol derivatives[3] are relatively susceptible to dearomative transformations, simple benzene derivatives are highly challenging substrates to dearomatize due to their high levels of aromaticity. Despite recent advances in dearomatization strategies for synthesizing valuable organic molecules, the development of methodologies that are able to selectively convert benzene rings into the corresponding saturated or partially saturated cyclic carbon skeletons under mild reaction conditions remains formidably challenging tasks.[4]

In 1989, Hamrock and Sheridan reported that 4-methyl-1,2,4-triazoline-3,5-dione (MTAD; **1**) undergoes para-selective [4 + 2] cycloaddition reactions with benzene under visible light irradiation at low temperature (Scheme 1a).[5] Since 2016, this reaction has been revolutionized as a powerful tool for organic synthesis by Sarlah and co-workers.[6-11] They combined dearomative photo-induced [4 + 2] cycloaddition reactions using **1** with various transformations of the resulting alkene functionality, such as oxidation,[7] reduction,[8] transition-metal-catalyzed allylic substitution reactions,[9] and other transformations[10] to provide rapid access to highly functionalized cyclic products. Although this dearomatization strategy based on **1** is highly efficient, the thermal instability of the cycloadduct (**2**) can be a serious obstacle for further understanding the reactivity and expanding the applications of this approach (Scheme 1b). Given that the retro-cycloaddition of **2** proceeds rapidly at temperatures above –10 °C,[5a] its isolation and detailed characterization are difficult. Furthermore, subsequent synthetic transformations must be performed at low temperatures due to the competing thermal decomposition of the intermediate, which can potentially limit the applicable transformations and accessible products.

Here we report that 1,2-dihydro-1,2,4,5-tetrazine-3,6-diones (TETRAD; **3**), the six-membered analogues of TADs,[12] undergo visible-light-promoted [4 + 2] cycloaddition reactions[13-15] with benzenes, naphthalenes, and several *N*-heteroaromatic compounds, and the generated cycloadducts are stable enough to be isolated via chromatographic purification (Scheme 1c). The isolated adducts were characterized using single-crystal X-ray diffraction and used for further transformation reactions at room temperature or above. DFT calculations suggested that the thermal retro-cycloaddition of the benzene–MTAD adduct proceeds via a synchronous mechanism, while that of the benzene-TETRAD adduct features a mechanism in which two C–N bonds are asynchronously cleaved with a concomitant large conformational change of the *p*-urazine moiety from the adduct to the transition state (TS).

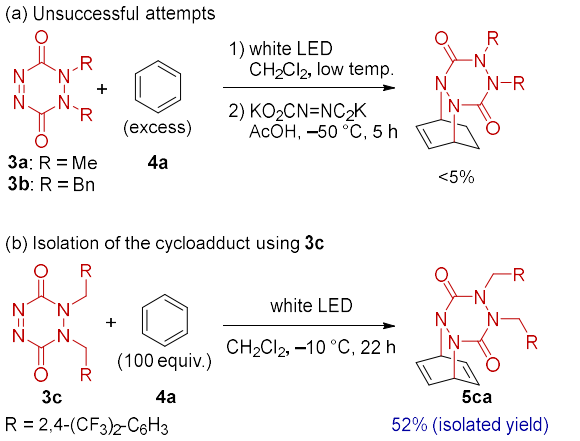
Scheme 1. Dearomative [4 + 2] cycloaddition under visible light irradiation.



RESULTS AND DISCUSSION

Dearomatization of Benzene and Evaluation of the Thermal Stability of the Cycloadduct. We have recently reported the synthesis and reversible covalent bonding properties of TETRAD **3**.[12] We then became interested in whether a dearomative [4 + 2] photo-cycloaddition of TETRAD **3** with benzene would be feasible. With the report by Sarlah and coworkers in mind,[8a] we first attempted to obtain the cycloadduct after reduction from TETRAD **3** bearing Me (**3a**) or Bn (**3b**) substituents and benzene (**4a**), which were used in our previous study. However, no promising results were observed under any reaction conditions (Scheme 2a). To improve the reactivity and stability,[16] a TETRAD bearing 2,4-bis(trifluoromethyl)benzyl groups (**3c**) was newly synthesized and examined for the dearomative cycloaddition with **4a** (Scheme 2b). Gratifyingly, the desired reaction proceeded at –10 °C under visible light irradiation. To our surprise, the corresponding cycloadduct (**5ca**) was stable at around 0 °C and could be isolated without reduction via column chromatography on silica gel using a cooled column and eluent, which enabled its detailed characterization (Figure 1). The desired reaction scarcely proceeded at lower temperatures (<–20 °C) probably due to the attenuated reactivity of TETRAD **3** compared with MTAD.

Scheme 2. Dearomative [4 + 2] cycloaddition using TETRAD 3.



The improved thermal stability of **5ca** allowed us to prepare a single crystal for X-ray diffraction analysis. The obtained solid-state structure is shown in Figure 1a. The length of the two C–C bonds of the carbocycle (1.316/1.317 Å) clearly indicates their double-bond character. The *p*-urazine moiety adopts a twisted-boat-like conformation, which is similar to the structures reported for other related compounds.[12,17]

We have examined the thermal stability of isolated **5ca** by ^{1}H NMR analysis in different deuterated solvents (Figure 1b). In $CDCl_3$, the retro-cycloaddition was very slow at 0 °C ($t_{1/2}$ > 800 h), while it proceeded at a moderate rate at room temperature ($t_{1/2}$ = 17.7 h). While the retro-cycloaddition in C_6D_6 proceeded at a similar rate, it was significantly accelerated in DMSO-d_6. The half-life of the corresponding benzene–MTAD adduct (**2**) has been reported to be 1 h at 0 °C.[5a] A comparison of our results and the reported instability of **2** clearly suggests higher thermal stability for **5ca** compared to that for **2**.

The improved stability of **5ca** was quite unexpected for us because we originally designed TETRAD **3** based on the hypothesis that the *p*-urazine form might be destabilized due to the twisted-boat-like structure.[12] To gain insight into the reason for the slower retro-cycloaddition reaction of **5ca** compared with that of **2**, we performed DFT calculations on the thermal retro-cycloaddition reactions of **5ca** and **2** (Figure 1c). In addition to the retro-cycloaddition of **5ca** (**C**), those of benzene–MTAD adduct **2** (**A**) and a benzene–dimethyl-substituted TETRAD adduct (**B**) were calculated. For **C**, two conformations were examined (**adduct** and **adduct′**). The conformation observed in the X-ray structure is slightly favored (**adduct**) over the other (**adduct′**), albeit that the latter conformation is slightly favored in the corresponding TS for the retro-cycloaddition. The activation barriers of the retro-cycloaddition of **A** (18.8 kcal/mol) and **C** (22.7 kcal/mol) reasonably explain the difference in their thermal stability. More importantly, the structures of their TSs show distinctive features. In the case of benzene–MTAD adduct ($\mathbf{TS_A}$), the two breaking C–N bonds have almost the same length, indicating a concerted and synchronous retro-cycloaddition mechanism. On the other hand, $\mathbf{TS_C}$ exhibits significantly different C–N bond distances (2.59/1.66 Å), which indicates that the cleavage of one C–N bond precedes the other, commensurate with a highly asynchronous reaction. The observed solvent effects (Figure 1b) could be attributed to the partially ionic nature of $\mathbf{TS_C}$.[18] While highly asynchronous, the pathway of the

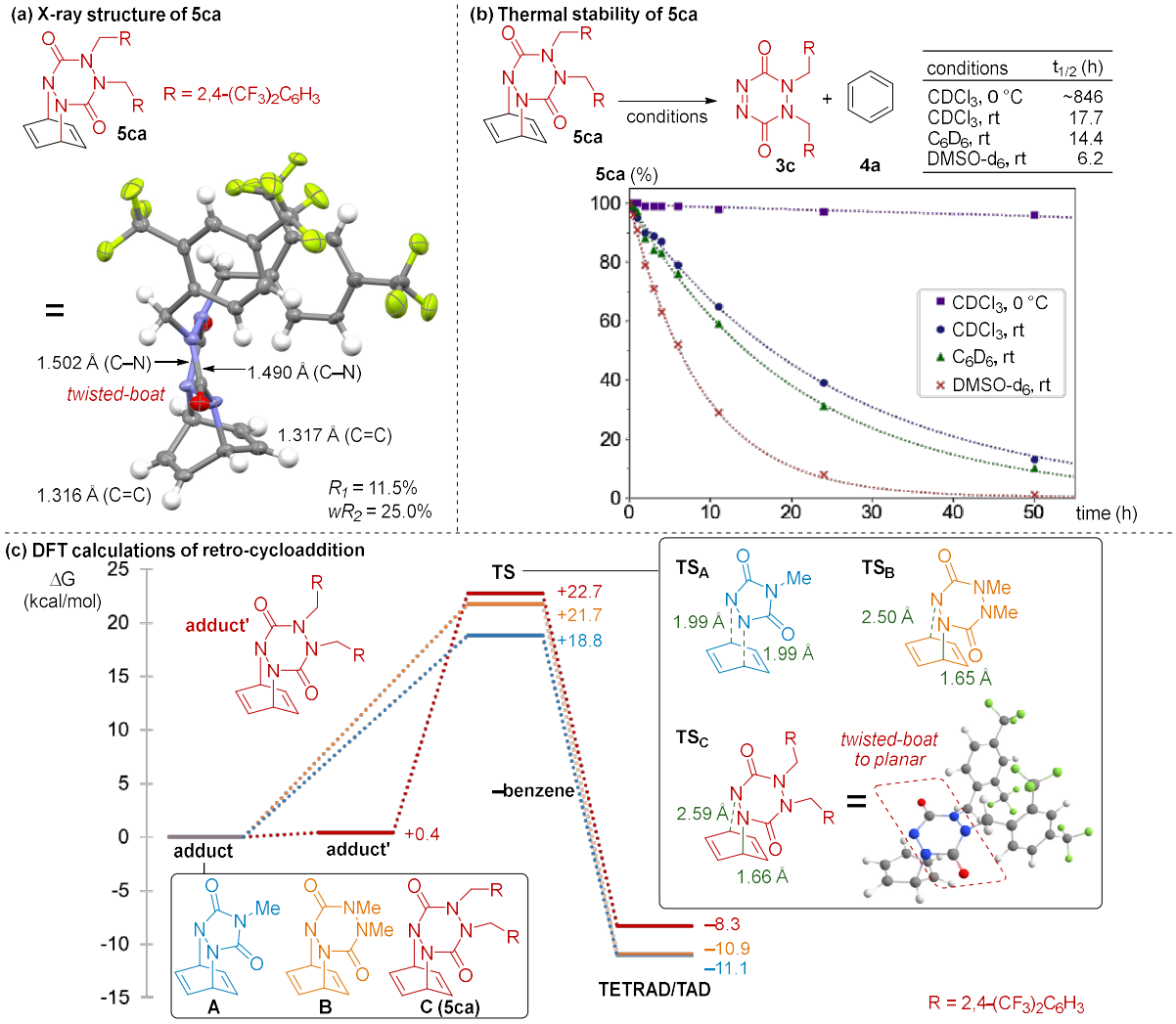


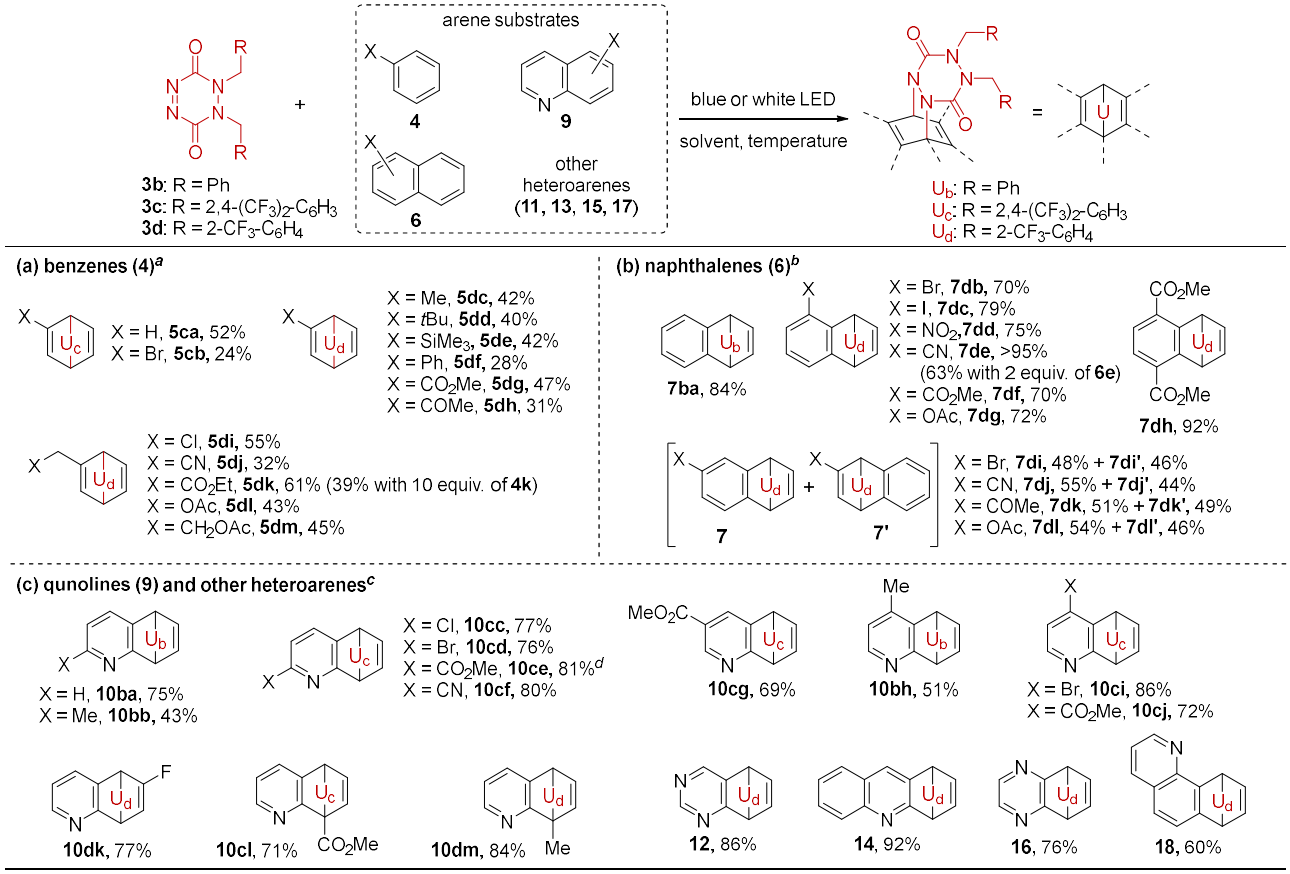
Figure 1. Characterization and thermal stability of **5ca**. (a) X-ray structure of **5ca**. (b) Thermal stability of **5ca** evaluated by ^{1}H NMR analysis in different solvents at 0 °C or room temperature. (c) Computational studies on retro-cycloaddition reactions at the DSD-PBEP86/def2-TZVPP+SMD(benzene)//M06-2X/def2-SVP level of theory.

retro-cycloaddition of **C** remains concerted; we could not locate any zwitterionic intermediate. Furthermore, it is noteworthy that the six-membered *p*-urazine ring of the TETRAD in **TS**$_C$ is almost planar (sum of the internal angles: 712°) and more planar than that in **adduct′** (sum of the internal angles: 692°). At this point, we speculate that the asynchronous nature,[19] as well as the conformational change from twisted boat (**adduct′**) to planar (**TS**$_C$) for **C** might lead to the higher activation barrier compared to that for **A**. As the TS structure and activation barrier for **B** are more similar to those for **C** than to those for **A**, the aforementioned differences are mainly due to the differences between the TAD and TETRAD scaffolds, and are not dominated by the different *N*-substituents.

Substrate Scope. Subsequently, we examined the scope of the dearomative cycloaddition of benzene derivatives **4** with TETRADs **3**, and the results are summarized in Scheme 3a. In addition to **3c**, we used **3d**, which carries 2-trifluoromethylbenzyl groups on the nitrogen atoms, for the reactions with substituted benzenes due to the slightly improved reaction outcome. Although the yields were moderate in most cases, various substituted benzenes reacted with **3**, and the cycloadducts **5** were successfully isolated and characterized. It is noteworthy that benzenes that bear a strongly electron-withdrawing carbonyl group afforded the desired products (**5dg** and **5dh**) because these substrates have been reported to be unreactive when using MTAD.[7a] While a large excess of arenes was used for the investigation of the substrate scope, we also trialed a reaction with a reduced amount of ethyl phenylacetate (**4k**; 10 equiv.), which afforded the desired cycloadduct (**5dk**), albeit in somewhat diminished yield (39%).

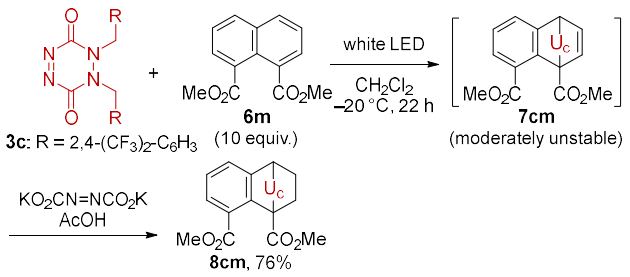
We also examined the dearomatization of naphthalene derivatives **6** using TETRADs **3b** or **3d** (Scheme 3b). Naphthalenes **6** were generally more reactive than benzenes **4**, and the corresponding cycloadducts **7** were much more stable than **5**. Various 1-substituted and 1,4-disubstituted naphthalenes selectively underwent the cycloaddition at the unsubstituted side (**7db**–**7dh**) in good-to-high yield. We attempted to reduce the amount of 1-cyanonaphthalene (**6e**) in the synthesis of **7de**, and the corresponding product was obtained in acceptable yield (63% with 2 equiv. of **6e**). When we used 2-substituted naphthalenes as the substrate, regioisomers (**7** and **7′**) were formed in an approximate 1:1 ratio and good yield.[20] The dearomatization of the sterically hindered side of 2-substituted naphthalenes has not been reported using MTAD, and the

Scheme 3. Substrate scope for dearomative cycloaddition reactions with TETRAD 3.



[a]Reaction conditions: benzenes **4** (100 equiv.), white LED, CH_2Cl_2 or neat, –10 °C, 22–88 h. [b]Reaction conditions: naphthalenes **6** (10 equiv.), white LED, CH_2Cl_2, –20 °C, 22 h. [c]Reaction conditions: quinolines **9**, quinazoline **11**, acridine **13**, quinoxaline **15**, or benzo[*h*]quinoline **17** (5 equiv.), blue LED, AcOEt, –40 °C, 7–42 h. [d]Solvent: AcOEt/CH_2Cl_2. For detailed reaction conditions for each substrate, see the Supporting Information.

Scheme 4. Dearomative cycloaddition of 1,8-substituted naphthalene 6m.

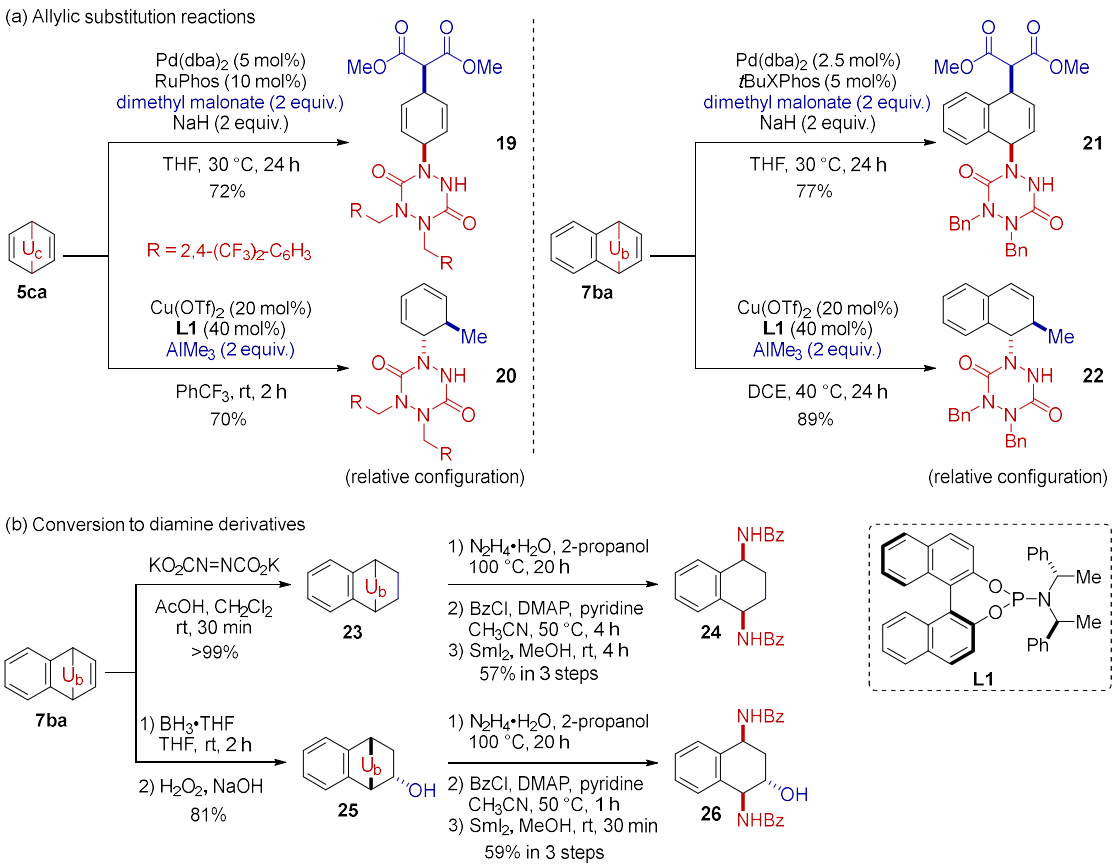


formation of isomers **7′** would be characteristic of TETRAD **3**. This finding prompted us to investigate dimethyl naphthalene-1,8-dicarboxylate, which carries substituents on both six-membered rings (Scheme 4, **6m**). Gratifyingly, it reacted with **3c** under the standard conditions to give the product possessing a tetrasubstituted bridgehead carbon (**7cm**). Although the clean isolation of **7cm** was difficult due to its moderate thermal instability, the product was isolated after the reduction of the resulting olefin (**8cm**, 76%).[8a]

We next investigated the dearomatization of quinolines **9** (Scheme 3c). In this case, the use of ethyl acetate as the solvent was slightly beneficial, and the corresponding dearomatized cycloadducts (**10**) were generally obtained in good yield. The optimal substituents on TETRAD **3** depend on the substrate structure. In addition to various non-, 2-, 3-, and 4-substituted quinolines (**10ba**, **10bb**, **10cc**–**10cg**, **10bh**, **10ci**, and **10cj**), quinolines that bear a substituent at the 6- and 8-position were suitable substrates for the dearomative cycloaddition (**10dk**, **10cl**, and **10dm**). In contrast to the instability of **7cm** in Scheme 4, **10cl** and **10dm**, which possesses a tetrasubstituted bridgehead carbon center, were stable enough to undergo chromatographic purification. We further investigated other extended *N*-heteroaromatic compounds as substrates. Quinazoline (**11**), acridine (**13**), quinoxaline (**15**), and benzo[*h*]quinoline (**17**) all underwent the desired dearomatization to furnish the cycloadducts in 60–92% yield.

Transformation Reactions. Finally, transformation reactions of the isolated cycloadducts were examined, and the results are shown in Scheme 5. We first focused on transition-metal-catalyzed allylic substitution reactions. While the allylic substitution reactions of the dearomative cycloadducts derived from MTAD were studied in depth by Sarlah and co-workers,[9] allylations of active methylene compounds have not been reported, although they are frequently used in allylic substitution reactions. We hypothesized that this limitation could potentially be due to the thermal instability of cycloadducts based on

Scheme 5. Transformation reactions of the dearomative cycloadducts.[a]



[a]For the determination of the relative configurations of **20**, **21**, and **26**, see the Supporting Information. Those of **19** and **22** were analogously assigned.

MTAD, and that the improved stability of **5** and **7** could enable the use of a weakly nucleophilic active methylene compound for allylic substitution reactions. We found that the reaction between dimethyl malonate and a dearomatized cycloadduct of benzene (**5ca**) proceeded in 72% using a Pd/RuPhos catalyst (Scheme 5, **19**). Additionally, a copper-catalyzed allylic substitution reaction using $AlMe_3$ as the nucleophile proceeded to provide *trans*-substituted product **20** in 70% yield when a phosphoramidite ligand (**L1**) was used.[4e] As these transformation reactions were performed at room temperature or above, the use of benzene–MTAD cycloadducts would be unsuitable due to their thermal instability. The same allylic substitution reactions of naphthalene–TETRAD adduct **7ba** using a Pd catalyst and dimethyl malonate and a Cu catalyst and $AlMe_3$ were also successful under slightly modified reaction conditions, providing the products **21** and **22**, respectively.

Based on the previous reports using MTAD,[6-10] we examined the fragmentation of the *p*-urazine moiety of the cycloadduct to afford diamine derivatives. For this study, naphthalene–TETRAD adduct **7ba** was reduced to give **23**,[8a] which was used as a model substrate. After intensive tuning of the reaction conditions, a three-step sequence involving hydrazinolysis, benzoyl protection, and reductive N–N bond cleavage using SmI_2 was found to furnish the desired protected diamine **24** in 57% yield (over 3 steps). To further demonstrate the synthetic utility of the stable cycloadduct **7ba**, we investigated a hydroboration/oxidation reaction. While the hydroboration of an MTAD–naphthalene adduct has been reported,[10a] an expensive rhodium catalyst was required. On the other hand, hydroboration of **7ba** was readily performed under very standard conditions (BH_3•THF, rt), and the corresponding alcohol **25** was obtained in 81% after oxidation. The *p*-urazine moiety of **25** was successfully fragmented under the optimized conditions, affording protected diaminoalcohol **26**. The relative configuration of **26** was determined via single-crystal XRD analysis (for details, see the Supporting Information).

CONCLUSION

In summary, we have discovered that dearomative [4 + 2] cycloaddition reactions of TETRAD **3** with simple arenes, naphthalenes, quinolines, and other *N*-heteroaromatic compounds under visible light irradiation afford isolable adducts, whose structure was revealed by single-crystal X-ray diffraction analysis. The cycloadduct of benzene–TETRAD **5ca** exhibited higher thermal stability ($t_{1/2}$ =17.7 h in $CDCl_3$ at rt) than a benzene–MTAD adduct. The retro-cycloaddition proceeds via an asynchronous concerted mechanism, and the conformational change of the *p*-urazine moiety might lead to the destabilization of the corresponding transition state. The cycloadducts are able to undergo several synthetic transformations, including palladium-catalyzed allylic substitutions with a malonate nucleophile, copper-catalyzed allylic substitutions with $AlMe_3$, and a non-catalytic standard hydroboration/oxidation reaction, which were carried out above room temperature and would thus be unsuitable for benzene–MTAD

cycloadducts. The resulting *p*-urazine moiety can be converted into the corresponding diamine functionality via hydrazinolysis and SmI_2-mediated N–N bond cleavage. These findings may facilitate further fundamental studies and synthetic applications of the photochemical dearomatization of arenes using not only TETRAD, but also TAD and related azo compounds.

ASSOCIATED CONTENT

Supporting Information.
Details for experimental procedures, characterization of the synthesized compounds, DFT calculations, and NMR spectra (PDF).

Cartesian coordinates of calculated structures (XYZ)

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Notes

The authors declare no competing financial interest.

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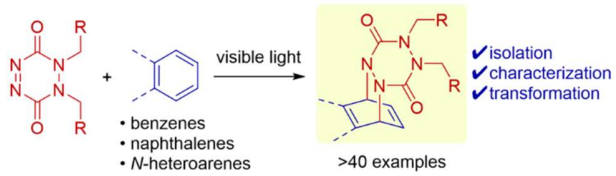
visible light
• benzenes
• naphthalenes
• N-heteroarenes
>40 examples
✔isolation
✔characterization
✔transformation