Facile Generation of *ortho*-Quinodimethanes Toward Polycyclic Compounds

Kazuya Inagaki,[a] Yuna Onozawa,[a] Yuki Fukuhara,[a] Daisuke Yokogawa,[b] Kei Muto,*[c] and Junichiro Yamaguchi*[a]

[a] Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan.

[b] Graduate School of Arts and Sciences, The University of Tokyo, Tokyo 153-8902, Japan.

[c] Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Furo-cho, Chikusa, Nagoya 464-8601, Japan.

ABSTRACT: The Diels–Alder reaction is a cornerstone of organic synthesis, enabling the construction of complex molecular architectures through the cycloaddition of a diene and a dienophile. Among the various dienes employed in this reaction, *ortho*-quinodimethane stands out as an exceptionally powerful intermediate due to its high reactivity, making it particularly effective for constructing benzo-fused polycyclic skeletons found in biologically important molecules such as natural products and pharmaceuticals. [1–3] Although this method has been widely applied in total synthesis,[4–7] the requirement for the laborious preparation of its precursors remains a significant challenge. This study presents a solution through a conceptually distinct palladium-catalyzed generation of *ortho*-quinodimethane via a multicomponent assembly reaction of readily available chemicals, specifically 2-vinylbromoarenes, diazo species, and carbon nucleophiles bearing a dienophile moiety. This approach leads to the synthesis of a diverse range of polycyclic compounds. The key to the present methodology is the unlocking of unprecedented reactivity in a benzyl–palladium intermediate,[8,9] which facilitates distal C–C bond formation on the vinyl group. The synthetic applications of this *ortho*-quinodimethane generation method are demonstrated through the synthesis of a range of polycyclic compounds, including a natural product, highlighting the convergent and diversity-generating nature of this reaction.

The streamlined synthesis of complex and functional molecules from simple and readily available starting materials has long been a fundamental goal in organic synthesis. Polycyclic carbon skeletons are particularly attractive molecular frameworks, as they are prevalent in terpenoids and pharmaceuticals. Among the various strategies and reactions to access these structures,[10] Diels–Alder reaction[11] stands out as one of the most powerful tools, facilitating the [4+2] cycloaddition between a diene and a dienophile to rapidly form six-membered rings. Its ability to create complex cyclic structures with high regio- and stereoselectivity makes it indispensable in synthesizing natural products and bioactive compounds.

Various dienes and dienophiles are known, and reaction development that leverages their exceptional reactivity is ongoing.[12–15] Among these, *ortho*-quinodimethane (*o*QDM) has long been recognized as an outstanding diene due to its reactivity driven by rearomatization[1–3] (Fig. 1A). This unique reactivity allows for the efficient construction of benzo-fused polycyclic skeletons, which are prevalent in biologically important molecules.[4–7] However, *o*QDM's high reactivity can only be unlocked by *in situ* generation from precursors (*e.g.* benzocyclobutenes, benzoheteroles) under harsh conditions. Furthermore, preparing these precursors is often laborious and also limits product diversity, which is a recurring issue in synthetic chemistry. A novel approach to generating *o*QDM from simple, readily available chemicals could address these challenges, enabling a diversity-oriented synthesis of polycyclic compounds in short sequence.[16–19] Despite extensive studies on catalytic methodologies,[20–23], these challenges have persisted for nearly 70 years since *o*QDM was first reported by Cava.[24,25]

Meanwhile, catalytic multicomponent reactions (MCR)[26,27] offer a convergent, step-economical approach to molecular elaboration by forming multiple bonds in a single step. Although numerous effective MCRs have been developed, including recent examples,[28–30] they require precise control of reactivity, as well as chemo- and regioselectivity. Recently, we reported a series of palladium-catalyzed multicomponent reactions of bromoarenes, diazo compounds, and nucleophiles, achieving dearomative functionalization (Fig. 1B).[31–35] A key mechanistic feature is the unique reactivity of the benzyl palladium intermediate[8,9] generated through these reactions, which typically leads to distal bond formation with nucleophiles on the aromatic ring, resulting in dearomatization.[36,37] We hypothesized that, under the appropriate conditions, this reactivity could be redirected to the terminus of a vinyl group through vinylogous
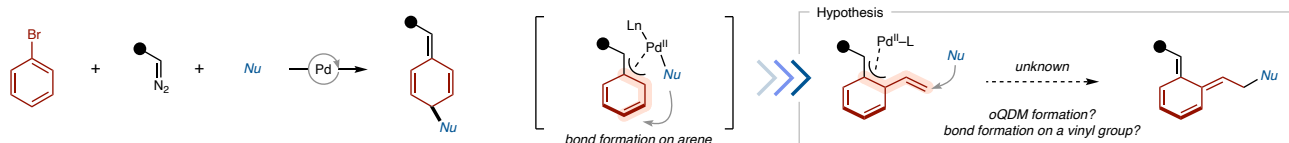
extension, facilitating a nucleophilic attack that leads to *o*QDM generation. This would represent a novel approach to *o*QDM formation via a multicomponent reaction using readily available starting materials. Moreover, we anticipated that by employing a nucleophile that carries a dienophile moiety, the generated *o*QDM could undergo an intramolecular Diels–Alder reaction, leading to the rapid formation of benzo-fused polycyclic compounds in a single step. Herein, we disclose a palladium-catalyzed method for generating *o*QDM from 2-vinylbromoarenes **1**, diazo species **2**, and carbon nucleophiles **3**, enabling the rapid construction of polycyclic carbon skeletons **4** (Fig. 1C).
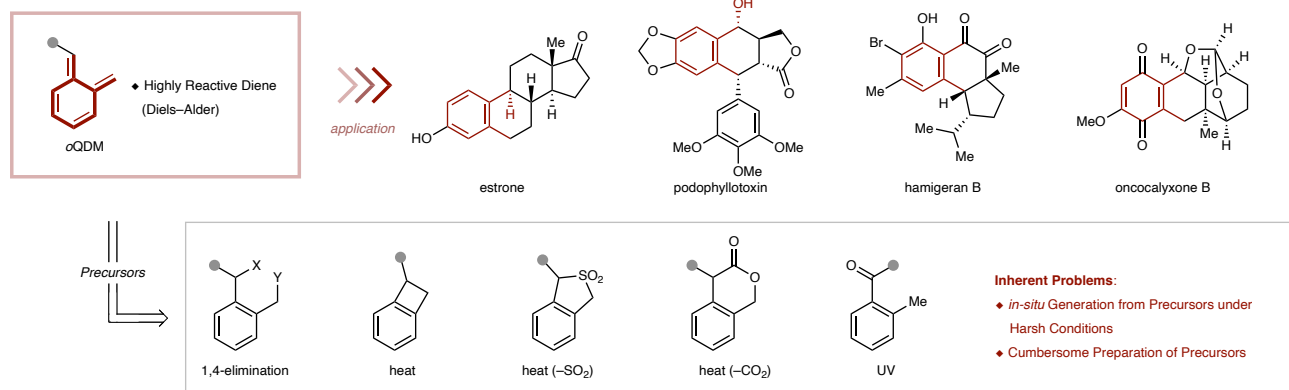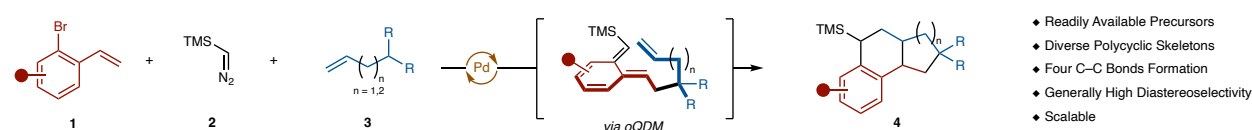

Fig. 1 *ortho*-Quinodimethane chemistry. **A**, *o*QDM, its application to the total syntheses of natural products, and the challenges associated with cumbersome preparation of its precursors. **B**, The unique reactivity of benzyl–Pd species in a dearomative three-component reaction leading to a hypothesis for developing a novel *o*QDM generation methodology. **C**, This work: Pd-catalyzed generation of *o*QDM from 2-vinylbromoarenes, diazo species, and carbon nucleophiles, resulting in the synthesis of polycyclic compounds.

As an initial investigation in this study, we performed the reaction of 2-vinylbromonaphthalene (**1A**) with TMS-diazomethane (**2**) and allyl-substituted malonate **3a** in the presence of Pd/PPh$_3$ catalyst and NaH in toluene at 70 °C (Fig. 2A). Pleasingly, we obtained a polycyclic compound **4Aa** in 65% yield (diastereomer ratio = 86:14), and its structure was confirmed by X-ray crystallographic analysis. **4Aa** was formed through the desired multi-component reaction to generate an *o*QDM intermediate, followed by an intramolecular Diels–Alder reaction. Encouraged by this result, we embarked on condition optimization using 2-bromostyrene (**1B**), **2**, and methallylated malonate **3b** (Fig 2B). Under the same conditions, the reaction gave **4Bb**, albeit in 14% yield with poor diastereoselectivity (Fig 2B, entry 1). The use of *para*-anisylphosphine improved the yield of **4Bb** (Fig 2B, entry 2). Further ligand screening revealed that DPEphos works as an effective ligand, furnishing **4Bb** in 68% yield with high diastereoselectivity (Fig 2B, entry 3). Increasing the temperature to 80 °C improved the yield to 93% (Fig 2B, entry 4). However, other diphosphines such as dppf diminished both the yield and diastereoselectivity (Fig 2B, entry 5). Further exploration of the reaction conditions identified the optimized conditions as Pd(OAc)$_2$/DPEphos catalyst and NaH in toluene at 80 °C (see the Supplementary Information for full details).

With these optimized conditions in hand, substrate generality was next explored (Fig. 2C). First, we investigated the scope of bromoarenes **1** while keeping constant the other reactants **2** and **3b**. Simple 2-vinylbromobenzene (**1B**) reacted smoothly to provide tricyclic compound **4Bb** in 85% yield with excellent diastereoselectivity. The scalability of this protocol was remarkable, as the gram-scale reaction of **1B**, **2**, and **3b** proceeded without any decrease in efficiency, furnishing over 4 g of **4Bb** in 85% yield. Electron-rich aromatic systems such as alkoxybenzenes **1C–1F** furnished tricyclic compounds **4Cb**, **4Db**, **4Eb**, and **4Fb** in moderate to good yields. Besides methoxy (**1C**), methoxymethoxy (**1D**) and benzyloxy (**1E**) were also applicable. Benzodioxole-fused substrate **1G** led to compound **4Gb** in moderate yield but with great diastereoselectivity. Fluorine- and chlorine-substituted bromoarenes (**1H**, **1I**, **1J**, **1K**) were also viable substrates, furnishing the corresponding tricyclic compounds without the loss of halogen atoms (**4Hb**, **4Ib**, **4Jb**, **4Kb**). These results suggest that the present catalytic system is not significantly affected by modification of the electronics of the starting arenes. *ortho*-Methyl substituted

tricyclic product **4Lb** was generated in moderate yield, indicating that steric factors around the bromine atom does not significantly impact the reaction progress. Similarly, using naphthalene **1A**, **4Ab** was obtained in 75% yield. In these two cases, the relative stereochemistry at the silyl group of **4Lb** and **4Ab** were reversed compared to the other products (*vide infra*). The successful synthesis of thiophene-embedded product **4Mb** is noteworthy because thiophene-based *o*QDMs are rare.[38] It was also found that bromoarene bearing an internal alkene (**1N**) is also a viable substrate, furnishing **4Nb** as a single diastereoisomer, albeit in 38% yield. Regarding the diazo species, while dimethylphenylsilyl diazomethane was applicable, other diazo compounds such as diazo esters and *N*-tosylhydrazones did not furnish the desired products (Fig. S1).

Next, we examined the scope of malonates **3**. The reaction of **1A** and **2** using diethyl allylmalonate (**3a**) furnished **4Aa** in 76% yield as a mixture of *trans*- and *cis*-fused ring systems. Cinnamyl malonate **3c** and unsaturated ester **3d** were also applicable substrates, providing **4Bc** and **4Ad**, respectively. Using prenylated malonate **3e**, we succeeded in synthesizing *gem*-dimethyl tricyclic product **4Ae**, albeit in a low

yield, likely due to steric repulsion between the dimethyl moiety and the TMS group during the Diels–Alder reaction. Introduction of an oxygen functional group as well as chlorine at the bridgehead position of the product was achieved, yielding **4Bf** and **4Bg**. Strikingly, by using one-carbon homologated malonate **3h**, we succeeded in constructing 6-6-6 tricyclic system **4Bh** with good diastereoselectivity. Although the yield was not satisfactory, the use of propagylated **3i** provided cyclic alkene **4Ai**. Beyond malonate, β-ketoesters proved to be reactive substrates in the present reaction system. For example, a reaction with **3j** afforded **4Bj**, albeit as a mixture of diastereoisomers in nearly a 1:1 ratio. Moreover, when a different type of β-keto ester **3k** was used, we obtained 6-6-6 tricyclic ketone **4Bk** (obtained as its enol form) in 34% yield. Of note, carbon skeletons similar to **4Bk** can be observed in abietane terpenoids.[39] Although the yield of **4Bk** is modest, we believe that the success in rapid construction of such a skeleton could potentially be utilized in synthetic and biological studies on related diterpenoids. This varied substrate scope clearly showed that the present methodology can give rise to a wide range of polycyclic skeletons simply by tuning the substituents of these readily available starting materials.
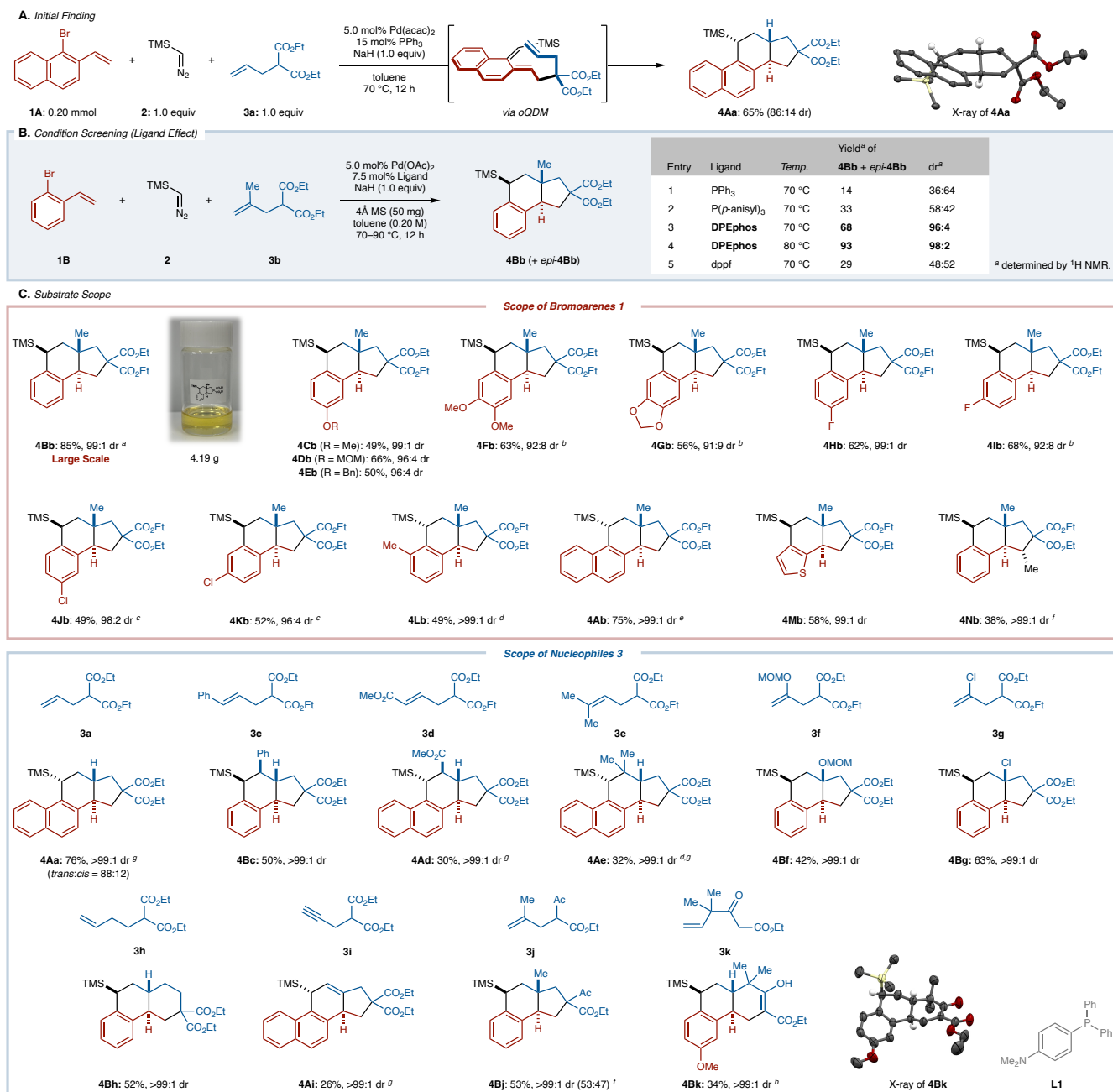
Fig. 2 Development of a catalytic three-component *o*QDM generation reaction. A, Initial study on the reaction of **1A**, **2**, and **3a** to provide polycyclic compound **4Aa**, including the X-ray crystallographic structure of **4Aa**. **B,** Investigation of the ligand effect on the reaction of **1B**, **2**, and **3b**. **C,** Scope of the three-component *o*QDM generation; reactions were performed using **1** (0.20 mmol), **2** (0.20 mmol), **3** (0.20 mmol), Pd(OAc)₂ (5.0 mol%), DPEphos (7.5 mol%), NaH (1.0 equiv), and 4Å molecular sieves (4Å MS, 50 mg) in toluene (1.0 mL) under a N₂ atmosphere at 70–90 °C for 12 h (see the SI for full details). *ᵃ* The reaction was performed on 12 mmol scale. *ᵇ* The reaction was performed on 0.50 mmol scale. *ᶜ* 1.5 equiv of **3** was used. *ᵈ* After the reaction, the mixture was further heated at 120 °C for 6 h. *ᵉ* Pd(acac)₂ (5.0 mol%) and dppf (7.5 mol%) were used instead of Pd(OAc)₂ and DPEphos. *ᶠ* 2.0 equiv of **3** was used. *ᵍ* Pd(acac)₂ (5.0 mol%) and (4-dimethylaminophenyl)diphenylphosphine (**L1**: 10 mol%) were used instead of Pd(OAc)₂ and DPEphos. *ʰ* 3.0 equiv of **3** was used.

To gain insight into the mechanism of the present reaction, several control experiments were performed. First, to determine whether radicals are involved, we conducted a reaction with TEMPO as a radical scavenger (Fig. 3A). As a result, no significant inhibition by TEMPO and no TEMPO-adducts were observed, with **4Bb** being obtained in 68% yield. This result ruled out the involvement of radical

species in this reaction. Our next focus was the mechanism of the *o*QDM-generation step. As an alternative to the initially hypothesized mechanism (Fig. 1), a reaction pathway involving 4-*exo-trig* carbopalladation was considered possible (Fig. 3B).[40] If the 4-*exo-trig* carbopalladation pathway were involved, a control experiment without nucleophilic counterparts would furnish *exo*-methylidenecyclobutene **5**.

However, **5** was not generated and starting material **1B** was recovered, which suggests that the 4-*exo-trig* carbopalladation pathway is not operative.

Computational studies were conducted to further clarify the *o*QDM-generation step (Fig. 3C). We calculated the activation free energy from benzylpalladium **Int4**. The calculation suggested that the coordination of malonates to **Int4** would generate **Int5**, which can then undergo C–C bond formation through transition state **TS56**, leading to **Int6**. The activation energy barrier for this inner sphere mechanism was estimated to be rather high at 38.5 kcal/mol. This result led us to consider another possibility, where **Int4** migrates to π-allyl–Pd species **Int5α**, upon which Tsuji–Trost-type C–C bond formation delivers **Int6** through transition state **TS56α**. Our DLPNO-CCSD(T)[41] calculations indicated that this alternative pathway requires a lower activation energy of 31.9 kcal/mol. To validate this experimentally, we designed a control experiment to determine whether the isomerization of monodeuterated styrene **6** occurs (Fig. 3D). Treatment of **6** with a catalytic amount of palladium(0) species indeed induced H/D isomerization, supporting the generation of π-allyl intermediate **Int5a**.[42,43]

Next, utilizing nucleophile **3l**, which lacks a dienophile moiety, in the reaction of **1A** with **2**, we confirmed the formation of naphthocyclobutene **8** as a sole *cis*-isomer (Fig. 3E). This result can be understood by considering that the π-benzylpalladium intermediate favors conformer **9B** likely due to steric repulsion between the TMS group and the C8 proton on the naphthalene ring, leading to the formation of *Z,Z-o*QDM **10**. Finally, **10** can undergo thermal 4π electrocyclization to form **8**.

Our next investigation focused on the Diels–Alder process, specifically to determine whether the generated *o*QDM is in equilibrium with its cyclobutene form. To assess this, we conducted two low-temperature reactions: one is the three-component reaction of **1A**, **2**, and **3a**, and the other is the reaction of naphthocyclobutene **11** prepared separately (Fig. 3F). The former reaction afforded **4Aa** in 52% yield, whereas the latter delivered **4Aa** in a low yield irrespective of the presence of a palladium catalyst. These results suggest that the Diels–Alder reaction of *in situ*-generated *o*QDM is faster than its isomerization to the cyclobutene form. Based on these studies and previous reports,[31–35] a plausible mechanism was conceived (Fig 3G). Oxidative addition of **1B** to palladium(0), followed by reaction with **2**, forms Pd-carbene species **II**. Upon aryl migration forming benzyl–Pd **III**, isomerization to π-allyl–Pd species **IV** occurs. From species **IV**, sodium malonate **3b·Na** induces C–C formation at the vinyl moiety, releasing *o*QDM **V**, which subsequently undergoes a Diels–Alder reaction to form **4Bb**.
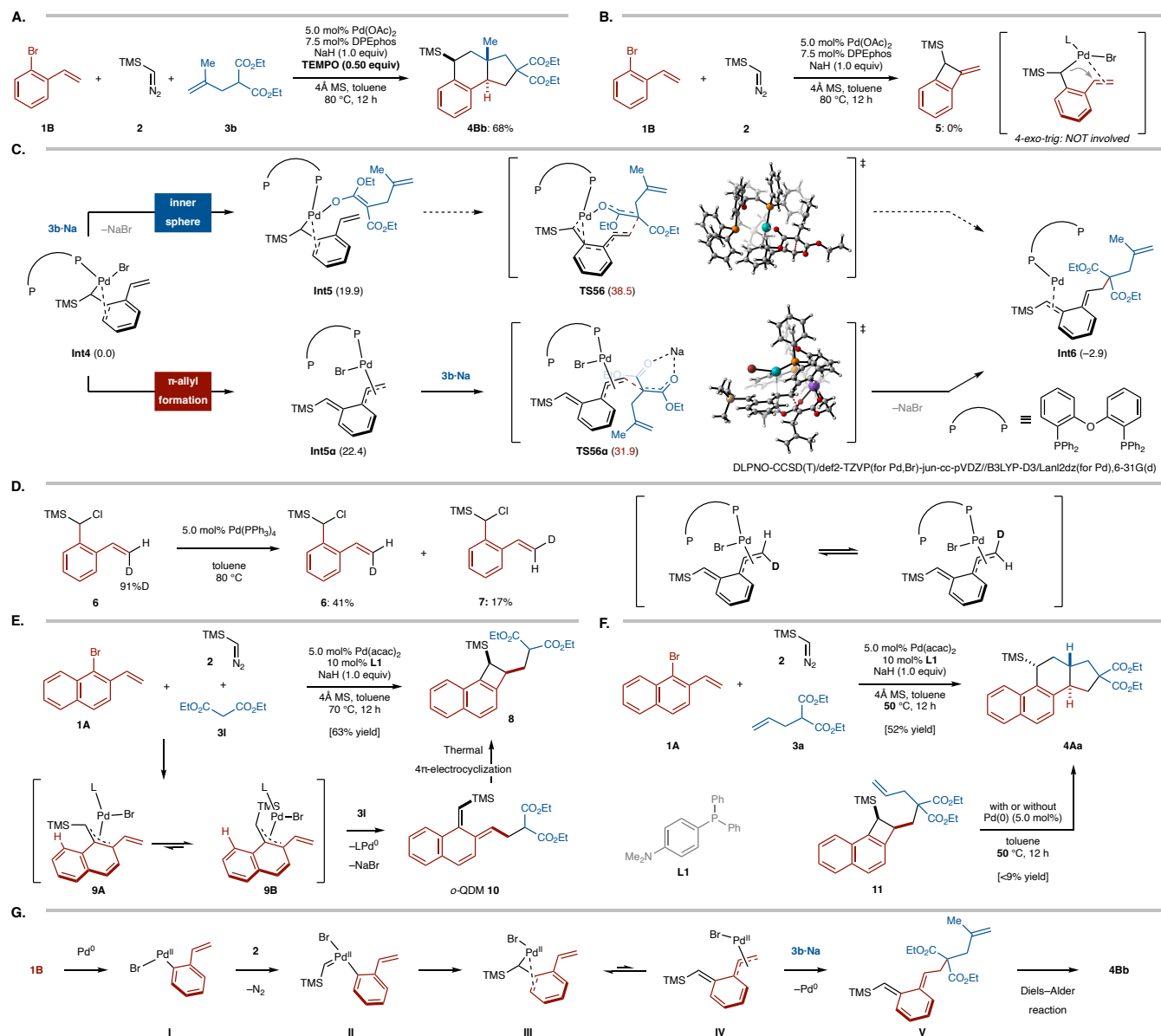
Fig. 3 Mechanistic studies. A, Radical scavenger experiment. **B,** Reaction without nucleophile **3**. **C,** Computational studies on the vinyl C–C bond formation. **D,** Observation of the isomerization of deuterated styrene **6**. **E,** A reaction using **3l** without a dienophile moiety. **F,** Insight on the Diels–Alder reaction of *in situ*-generated *o*QDM. **G**, A plausible reaction mechanism.

The silyl group introduced by TMS-diazomethane (**2**) and the diester moiety at the nucleophilic site may seem synthetically superfluous, but they have been demonstrated to be useful in several transformations (Fig. 4A). Specifically, treatment of **4Bb** with TBAF can remove the TMS group, yielding **12**. Additionally, heating **4Bb** at 60 °C under an oxygen atmosphere can give ketone **13**. Furthermore, when the TMS group was replaced with a Me₂PhSi group (Fig. S1), the Tamao–Fleming oxidation proceeded smoothly, providing alcohol **14** with retention of stereochemistry. In the case of the TMS group, it was possible to convert the compound into an alcohol at –78 °C, albeit as a diastereomeric mixture, using the method reported by Yoshino and Matsunaga.[44] Interestingly, when this reaction is carried out at a higher temperature (–40 °C), iodination also proceeds, and subsequent oxidation of the resulting alcohol allows for the synthesis of iodinated compound **15**, where the iodine atom

serves as a functional handle. Besides these silyl group transformations, we found that site-selective desaturation of **4Bb** can be achieved with DDQ oxidation, furnishing **16** in an acceptable yield. As for the diester moiety, it can be converted to compound **17** through reaction with urea, and typical hydrolysis followed by decarboxylation smoothly converts it to carboxylic acid **18**.

In addition to the three-component reaction, we found that similar chemistry can be performed in a reaction between benzyl electrophiles **19** and malonate **3b** (Fig. 4B).[45,46] Under slightly modified palladium-catalyzed conditions (Pd(acac)₂/P(3,5-xylyl)₃ catalyst, NaH, and 3Å MS in cyclohexane), naphthylmethyl phosphinate **19a** and **3b** reacted to give **20** in 35% yield. In this bimolecular reaction, in addition to DPEphos, monophosphine ligands such as P(3,5-xylyl)₃ also work as an effective ligand. This implies that DPEphos facilitates the reaction of diazo species after

the oxidative addition of bromoarenes in the three-component reaction (Table. S12). Using secondary alcohol derivative **19b** also produced tetracyclic compound **21** in 67% yield, albeit as a mixture of diastereomers (80:20).

Next, using **3l** as a nucleophile, we conducted a one-pot four-component reaction involving **1A**, **2**, **3l**, and dienophile (Fig. 4C). After performing the three-component reaction to give **8**, methallyl bromide was added to the same vessel. As a result, we obtained **4Ab** in 56% yield. Similarly, employing cyclohexenyl bromide furnished pentacyclic compound **22** in 58% yield as a single isomer. The above three-component reaction using malonate bearing a cyclohexenyl group as a dienophile did not furnish **22**, likely due to steric hindrance (Fig. S1). In contrast, the one-pot four-component reaction can be used as a complementary protocol for the synthesis of such sterically congested products, avoiding the need to prepare dienophile-substituted malonates. Trapping the generated *o*QDM by an intermolecular Diels–Alder reaction with *N*-methylmaleimide was also feasible, producing **23** in 73% yield.

This one-pot four-component reaction was applied to the synthesis of a classic natural product, equilenin (**31**), which is used in menopausal hormone therapy (Fig. 4D).[47] Equilenin (**31**) was the first synthesized steroid, dating back to the work of Bachmann in 1939.[48] Our synthesis followed the above one-pot four-component reaction. We first performed the palladium-catalyzed reaction of vinylnaphthalene **24**, **2**, and **3l**, leading to naphthocyclobutene **25**. To the same vessel, methacryloyl chloride (**26**) and Mg(OEt)$_2$ were added to generate tricarbonyl **27**. After removing the volatiles *in vacuo*, the mixture was heated at 90 °C in toluene/H$_2$O, delivering tetracyclic compound **29** in 57% yield. Finally, decarboxylation and desilylation smoothly produced **29**, a known synthetic intermediate toward **30**,[49] thereby accomplishing the formal synthesis of equilenin (**31**).

The work presented herein addresses the long-standing challenge in *o*QDM chemistry that required multi-step preparation of precursors, enabling the efficient synthesis of benzo-fused polycyclic compounds. The high scalability and ability to synthesize a diverse range of molecular skeletons demonstrate significant potential for future applications in synthetic chemistry.
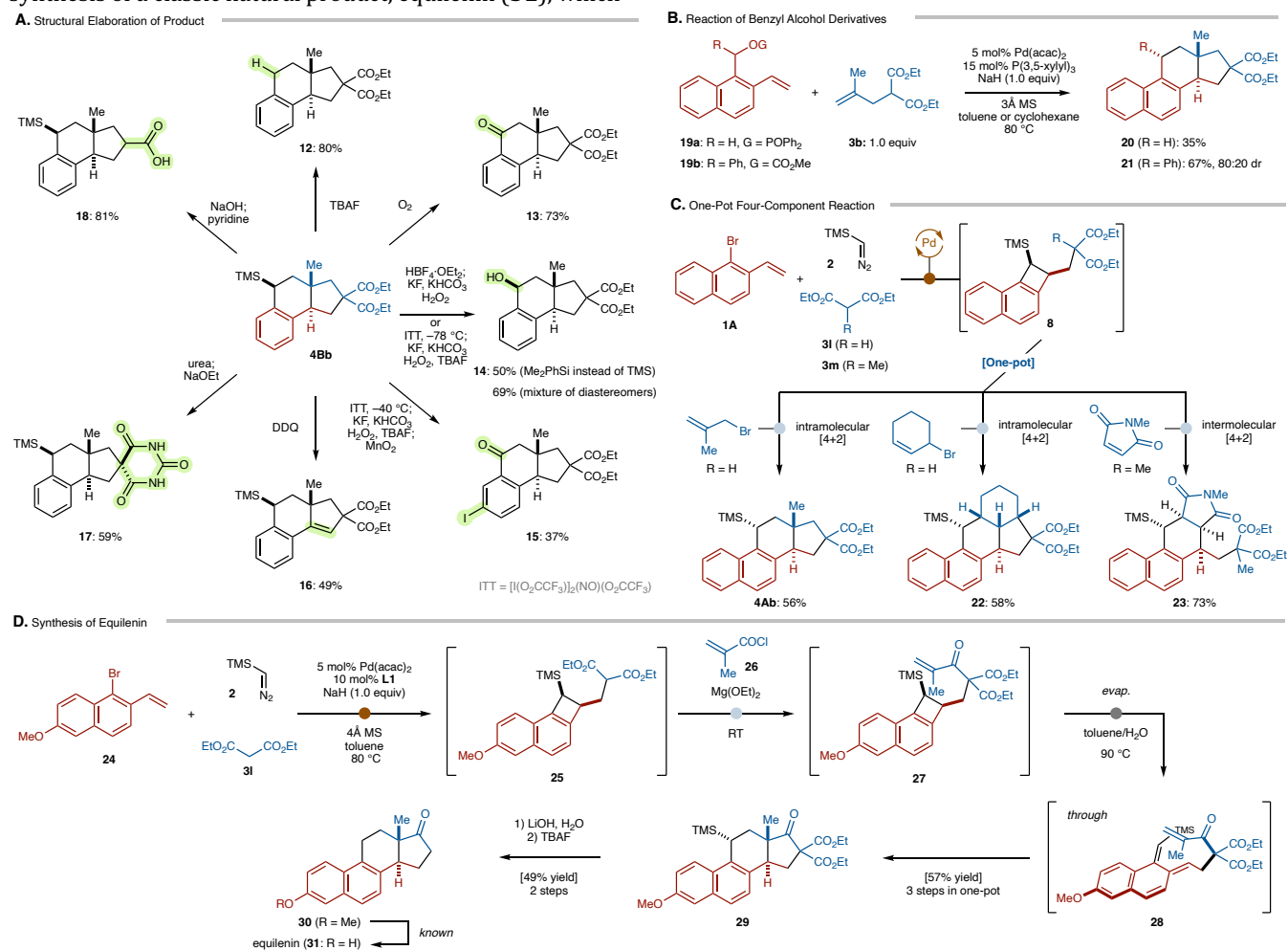

Fig. 4 Synthetic applications A, Structural elaboration of product. **B,** Reaction of benzyl alcohol derivatives with malonate **3b**. **C**, One-pot four-component reaction. **D**, Synthesis of equilenin.

ASSOCIATED CONTENT

Supplementary Information

The crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under reference no. CCDC-2376437 (**4Aa**) and 2376438 (**4Bk**). All other data supporting the findings of this study are available in the manuscript and its Supplementary Information.

AUTHOR INFORMATION

Corresponding Author

Kei Muto –Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Chikusa, Nagoya 464-8601, Japan; orcid.org/0000-0001-8301-4384; Email: muto.kei.v4@f.mail.nagoya-u.ac.jp
Junichiro Yamaguchi – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan; orcid.org/0000-0002-3896-5882; Email: junyamaguchi@waseda.jp

Author Information

Kazuya Inagaki – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan.
Yuna Onozawa – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan.
Yuki Fukuhara – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan.
Daisuke Yokogawa – Graduate School of Arts and Sciences, The University of Tokyo, Tokyo 153-8902, Japan; orcid.org/0000-0002-7574-0965

Author Contributions

K.M. conceived this project. K.I., Y.O, Y.F, and K.M. performed the experiments and analyzed the data. K.M. and D.Y. performed the computational studies. K.M. and J.Y. cowrote the manuscript with feedback from all authors. K.M. and J.Y. directed the project.

Notes

The authors declare no competing financial interest.

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