ORGANIC CHEMISTRY

Catalytic palladium-oxyallyl cycloaddition

Barry M. Trost*, Zhongxing Huang, Ganesh M. Murhade

Exploration of intermediates that enable chemoselective cycloaddition reactions and expeditious construction of fused- or bridged-ring systems is a continuous challenge for organic synthesis. As an intermediate of interest, the oxyallyl cation has been harnessed to synthesize architectures containing seven-membered rings via (4+3) cycloaddition. However, its potential to access five-membered skeletons is underdeveloped, largely due to the thermally forbidden (3+2) pathway. Here, the combination of a tailored precursor and a Pd(0) catalyst generates a Pd-oxyallyl intermediate that cyclizes with conjugated dienes to produce a diverse array of tetrahydrofuran skeletons. The cycloaddition overrides conventional (4+3) selectivity by proceeding through a stepwise pathway involving a Pd-allyl transfer and ring closure sequence. Subsequent treatment of the (3+2) adducts with a palladium catalyst converts the heterocycles to the carbocyclic cyclopentanones.

Cycloaddition reactions are of fundamental importance to organic synthesis, as they provide access to cyclic motifs in an efficient and convergent manner (*1*). Particularly, the capability of cycloaddition reactions to rapidly access fused- and bridged-ring systems has substantially streamlined the synthesis of complex natural products, pharmaceuticals, and agrochemicals. The development of cycloaddition reactions hinges heavily on the design and use of new precursors that can be activated to produce transient and highly reactive intermediates for the subsequent cyclization with acceptors. Among these reactive species, an intermediate of enduring interest is the oxyallyl cation, which consists of a positively charged allyl motif and a negatively charged oxygen atom or, in an alternative resonance structure, a carbocation attached to an enolate (Fig. 1A) (*2*). These diverse structural features have made oxyallyl cations potentially versatile intermediates for cycloaddition, as bond formation can take place at either the two terminal carbons, to afford carbocycles, or one of the carbons and the oxygen site, to produce cyclic ethers.

Conventionally, oxyallyl cations are generated from ketones or enol ethers with α-halo or sulfonyl substituents by using stoichiometric amounts of bases, acids, or reductants. Oxyallyl cations from these precursors were shown to readily react with conjugated dienes to yield seven-membered rings (*3*, *4*). In comparison, cycloadditions between oxyallyl cations and 2π acceptors to afford cyclopentanone or tetrahydrofuran motifs are underdeveloped despite these five-membered rings being ubiquitous in bioactive molecules, functional materials, and their synthetic precursors. The underdevelopment of (3+2) cycloaddition with the oxyallyl cation is largely attributed to the forbidden concerted pathway due to unmatched frontier molecular orbitals, and only a limited number of reactions that operate through stepwise mechanisms have been developed to date (*5*). For example, Noyori and co-workers have pioneered the (3+2) cycloaddition between styrene- or enamine-type olefins with α,α′-dihaloketones to cyclopentanone derivatives by using low-valent iron carbonyl as the reductant (*6*–*8*). A similar cyclopentanone synthesis has also been achieved by the Kuwajima group, with electron-rich olefins, where the oxyallyl cation was generated with aluminum-based Lewis acids from α-acetoxy silyl enol ether (*9*). In both cases, stoichiometric amounts of metal-based reagents were required to generate oxyallyl intermediates.

For the past several decades, palladium catalysts have been found efficient in promoting a wide range of cycloaddition reactions in a chemo- and stereoselective fashion (*10*, *11*). The development and wide application of palladium-stabilized zwitterions (*12*), especially palladium-trimethylenemethane (TMM) in cycloaddition reactions (*13*, *14*), prompted us to consider a Pd-oxyallyl intermediate for the catalytic synthesis of important cyclopentanone and tetrahydrofuran structures. Thus, we devised a bifunctional precursor **1** for the oxyallyl generation that incorporates both an allyl carbonate and a silyl enol ether moiety (Fig. 1B). We hypothesized that once exposed to Pd(0), the allyl carbonate would first be ionized to produce Pd-allyl **2**, and the alkoxide released (together with CO_2) in that process would subsequently remove the silyl group of **2** and generate the proposed Pd-oxyallyl ***3***. However, our and other laboratories' early attempts to access five-membered rings with various 2π acceptors were unsuccessful (Fig. 1C). Instead, Pd-oxyallyl intermediates generated from different precursors were all found to react only with norbornene-type strained alkenes to yield unexpected cyclopropanation products **4** (*15*–*18*). It is proposed that after the migratory insertion of Pd-oxyallyl to norbornene, the reductive elimination of the adducts **5** or **6** toward (3+2) products is intercepted by a proton shift to produce four-membered palladacycle **7**, which upon the C–C reductive elimination, affords the cyclopropane product.

A potential approach to switch the chemoselectivity to the desired (3+2) cycloadditions would be the inhibition of the proton transfer process that leads to the cyclopropanation (Fig. 2A). We envisioned that an additional electron-withdrawing group on the oxyallyl intermediate would substantially enhance the acidity of the α proton in **10**, which, in turn, would drive the equilibrium toward the six-membered palladacycles **8** and **9** that lead to the cyclopentanone or tetrahydrofuran products. Thus, a tailored oxyallyl precursor **11** with an ester motif as the electron-withdrawing group was readily synthesized from the corresponding β-keto ester and subsequently examined with a wide range of unsaturated acceptors using palladium catalysts. We found that the desired (3+2) cycloaddition could indeed take place between the oxyallyl precursor and 1,3-cyclohexadiene to produce the bicyclic tetrahydrofuran product **12a** with CpPd(cinnamyl)/tris(*o*-methoxyphenyl) phosphine as the catalyst (Fig. 2B). The cycloaddition turned out to be highly chemoselective, as neither the cyclopropanation product nor the cyclopentanone product from the (3+2) cycloaddition (**22e**, vide infra) was generated. This reaction stands in stark contrast to the conventional oxyallyl cation cycloaddition, in which reactions with conjugated dienes often proceed through (4+3) pathways to produce seven-membered rings (*19*). We propose that the (3+2) cycloaddition described here proceeds through a migratory insertion between the conjugated diene and the Pd-oxyallyl intermediate to generate a zwitterionic intermediate **14** with a newly formed palladium π-allyl motif (*20*, *21*), followed by the reductive elimination to form the five-membered ether (Fig. 2C, bottom). The formal Pd-allyl transfer process is sharply distinct from cycloaddition reactions of analogous Pd-TMM intermediates (Fig. 2C, top), in which a general cyclization pathway involves the addition of Pd-TMM to electron-deficient olefins, generating a new nucleophilic carbanion **13**.

Control reactions using different oxyallyl precursors indicated that the electron-withdrawing substituent was indeed essential for the cycloaddition, as precursors with a phenyl group or without any substitution both failed to yield the (3+2) product (Fig. 2B, entries 1 and 2). The combination of TBS (*tert*-butyl-dimethylsilyl) enol ether and carbonate leaving group was also shown to be important. Replacement of the carbonate leaving group with acetate largely decreased the yield, probably owing to the slower desilylation step with less-basic acetate anion (entry 3). On the other hand, oxyallyl precursors with TIPS

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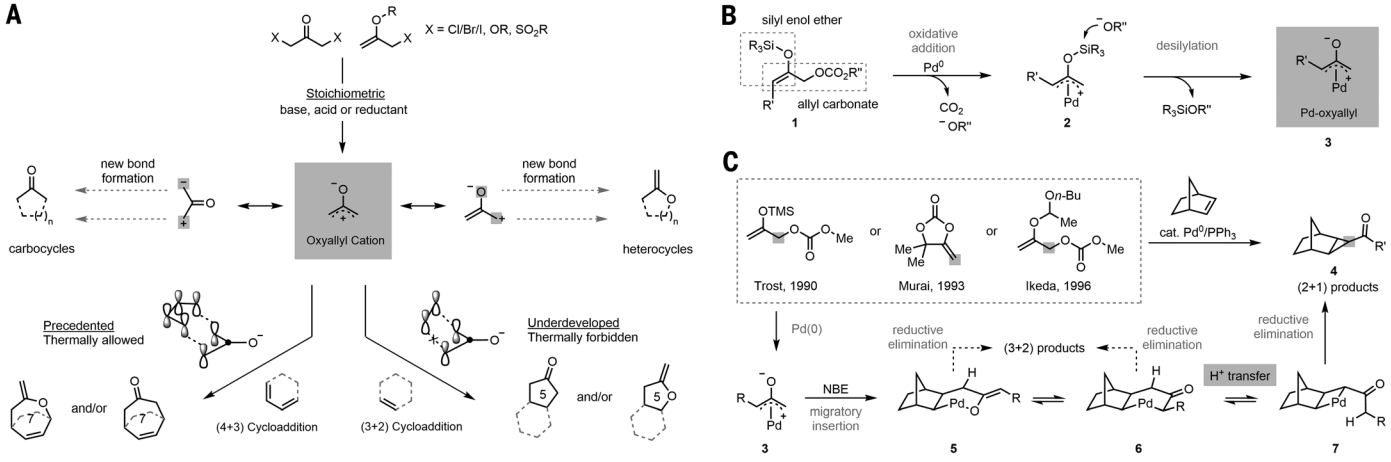

Fig. 1. Oxyallyl cycloaddition. (**A**) Oxyallyl cation cycloaddition. R, aryl or silyl groups. (**B**) Bifunctional precursor for Pd-oxyallyl intermediate. (**C**) Unexpected (2+1) cyclopropanation. TMS, trimethylsilyl; NBE, norbornene; Me, methyl; Bu, butyl.

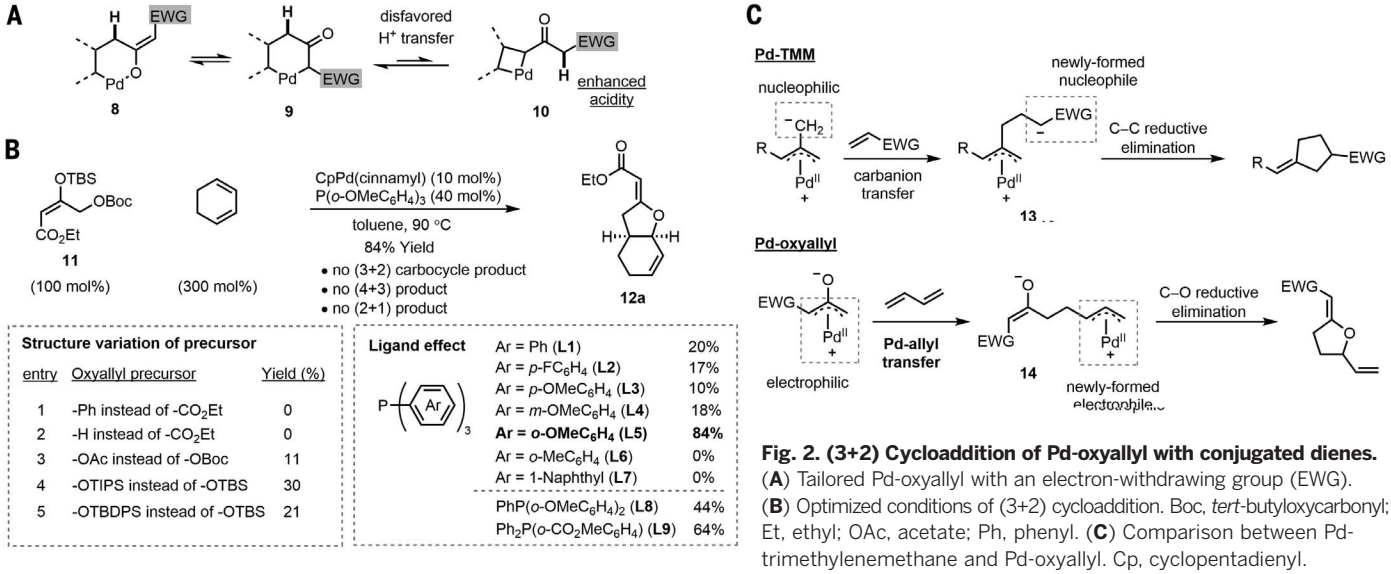

Fig. 2. (3+2) Cycloaddition of Pd-oxyallyl with conjugated dienes. (**A**) Tailored Pd-oxyallyl with an electron-withdrawing group (EWG). (**B**) Optimized conditions of (3+2) cycloaddition. Boc, *tert*-butyloxycarbonyl; Et, ethyl; OAc, acetate; Ph, phenyl. (**C**) Comparison between Pd-trimethylenemethane and Pd-oxyallyl. Cp, cyclopentadienyl.

(triisopropylsilyl) or TBDPS (*tert*-butyl-diphenylsilyl) groups both afforded the desired cycloaddition product, albeit in lower yields compared with the TBS group (entries 4 and 5).

Ligand screening demonstrated that the (3+2) cycloaddition reactions were promoted by monodentate triarylphosphine ligands (Fig. 2B, right column). Whereas simple triphenylphosphine (**L1**), as well as its meta- and para-substituted derivatives with different electronic properties (**L2** to **L4**), afforded the product in low yields, an *ortho*-methoxy substituent (**L5**) was found to substantially boost the efficiency of the cycloaddition reaction. Similarly improved yields were also observed with other analogous ligands with *ortho*-methoxy (**L8**) and *ortho*-carboxylic ester groups (**L9**). Nevertheless, ligands with noncoordinating ortho-substituents (**L6** and **L7**) were completely ineffective for the cycloaddition, excluding the increased steric hindrance of **L5** as a contributing factor for the improved reactivity. In addition, bidentate phosphine ligands were also incompatible with the reaction (fig. S1). On the basis of these results, we propose that the *ortho*-methoxy and ester groups of the ligand stabilize the palladium intermediates and facilitate the cycloaddition by providing secondary coordination, though their Lewis basicity is not strong enough to block the reaction site by chelation (*22*).

The cycloaddition reaction was readily scalable, and only a slight decrease of yield was observed when the catalyst loading was halved (Fig. 3A, **12a**). Different types of esters, including benzyl (**12b**) and *tert*-butyl esters (**12c**), could all facilitate the (3+2) cycloaddition reaction as electron-withdrawing groups. The cycloaddition reaction was also found to be compatible with an oxyallyl precursor bearing a Weinreb amide motif (**12d**), which can be further transformed to various ketones with corresponding metal-based nucleophiles.

When cyclohexadienes with a terminal substituent were used as acceptors, the cycloaddition reactions occurred chemo- and regioselectively at the less-hindered olefin with C–C bond formation at the terminal carbon (Fig. 3B). The bicyclic tetrahydrofuran product from 1-methylcyclohexadiene (**12e**) shares the skeleton with a number of monoterpene lactones and thus would be a potential synthetic intermediate to access these bioactive natural products (*23*). Cyclohexadienes with a wide range of other functional groups at the terminal position, such as phenyl (**12f**), acetate

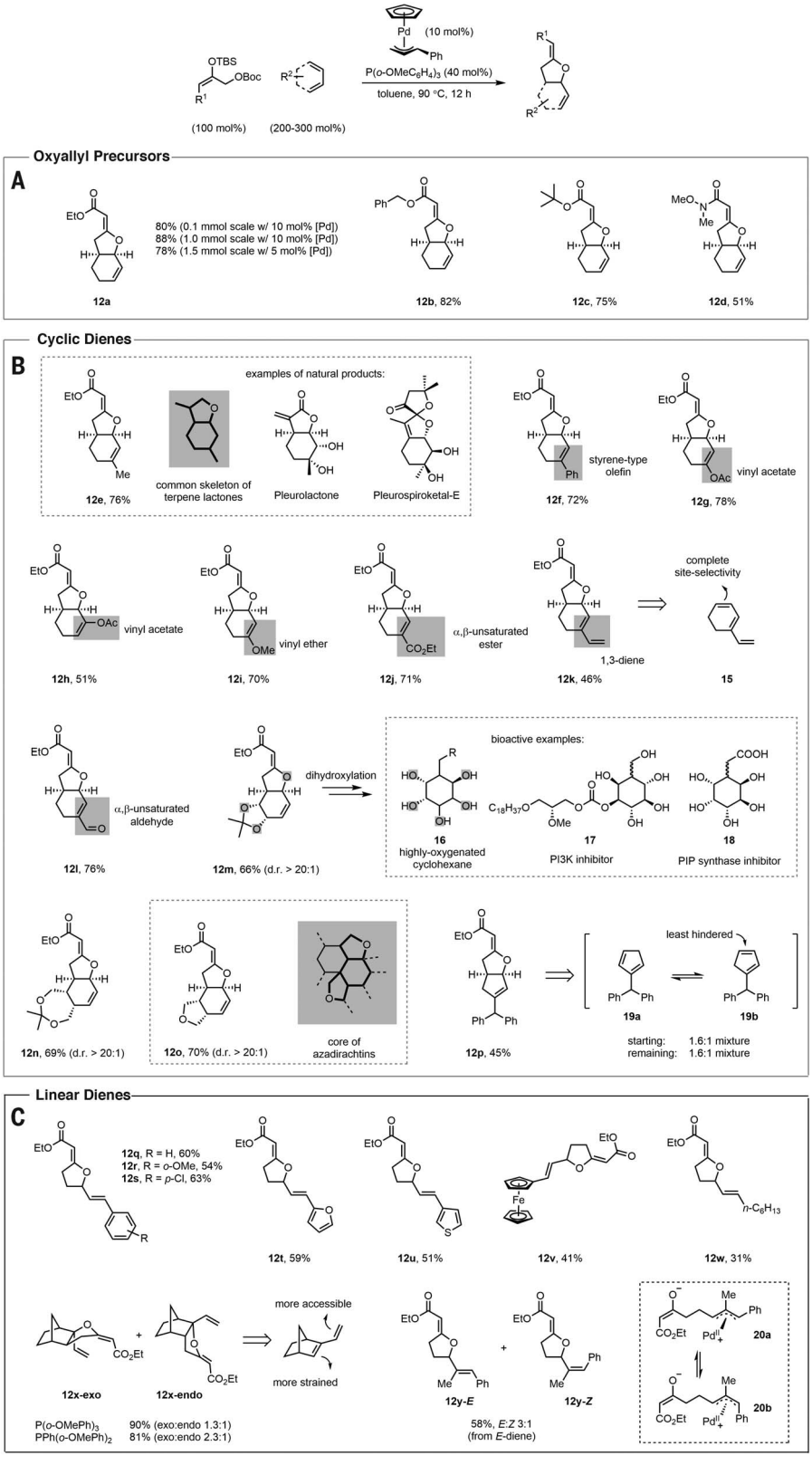

Fig. 3. Scope of the (3+2) cycloaddition of Pd-oxyallyl with conjugated dienes. (**A**) Cycloaddition with different oxyallyl precursors. (**B**) Substrate scope of cyclic dienes. PI3K, phosphatidylinositol 3-kinase; PIP, phosphatidylinositol phosphate; d.r., diastereomeric ratio. (**C**) Substrate scope of linear dienes. Unless otherwise noted, cycloaddition reactions were run with 10 mol % CpPd(cinnamyl), 40 mol % tris(*o*-methoxyphenyl)phosphine, 0.1 mol of oxyallyl precursors, and 200 to 300 mol % dienes at 90°C for 12 hours. The data are reported as isolated yields.

(**12g**), methoxy (**12i**), and ester (**12j**), were also suitable substrates and afforded cyclic olefins with diverse structural and electronic properties that can serve as versatile handles for further modification of the bicyclic ring systems. The extraordinary chemoselectivity was also manifested in the case of the substrate bearing an aldehyde, which produced adduct **12l** in a good yield. Cyclohexadiene with a C-2 acetate substituent also participated in the cycloaddition smoothly to afford the corresponding bicycle (**12h**), albeit in a lower yield compared with its C-1–substituted counterpart. 1-Vinylcyclohexadiene **15**, a conjugated triene substrate with mono-, di-, and trisubstituted olefins, cyclized with oxyallyl selectively at the cyclic and less-substituted olefin instead of the least sterically accessible site (**12k**), probably driven by the more-efficient orbital overlap of the cyclic diene. Additionally, we found that the (3+2) cycloaddition reaction was able to build a variety of complex fused-ring structures rapidly by using easily available cyclohexadienes with multiple functional groups. For example, the 5-6-5 fused-ring system (**12m**) could be readily assembled with high diastereoselectivity through the cycloaddition with the bicyclic diene that originates from the microbial dearomative dihydroxylation of benzene (*24*). The trans relationship between the acetal ring and the tetrahydrofuran ring supports an inner-sphere cycloaddition pathway in which the new bonds form at the same and, in this case, the less-hindered face of the diene coordinating the palladium. The remaining olefin in **12m** could potentially be further dihydroxylated to produce pentaoxygenated derivatives **16**, which would be an advanced synthetic intermediate toward a number of bioactive compounds, especially enzyme inhibitors related to phosphatidylinositols (e.g., **17** and **18**) (*25*). The (3+2) cycloaddition also enabled the synthesis of a cyclohexene derivative with two fused tetrahydrofuran rings (**12o**), a motif that resembles the core structure of azadirachtins and related tetranortriterpenoids (*26*). In addition to cyclohexadienes, cyclopentadiene derivatives can also participate in the (3+2) cycloaddition reaction. When a dynamic mixture of cyclopentadienes **19a** and **19b** reduced from 6,6-diphenylfulvene was employed, the cis-fused 5-5 ring **12p** was obtained as the only product, indicating a preference for the less-hindered olefin.

Linear dienes could also undergo the (3+2) cycloaddition reaction, producing 2-alkylidene-5-vinyl-tetrahydrofuran products (Fig. 3C). In particular, terminally substituted aromatic dienes with different substituents on the arene all afforded the corresponding cycloaddition products in good yields (**12q** to **12s**). Dienes with heterocycles, including furan and thiophene, as well as a ferrocene moiety, were also compatible with the (3+2) cycloaddition (**12t** to **12v**). Nevertheless, alkyl-substituted linear dienes showed much lower reactivity compared with their cyclic analogs, probably due to the lack of the confined *s*-cis conformation that lowers the entropy of activation for the transition state of

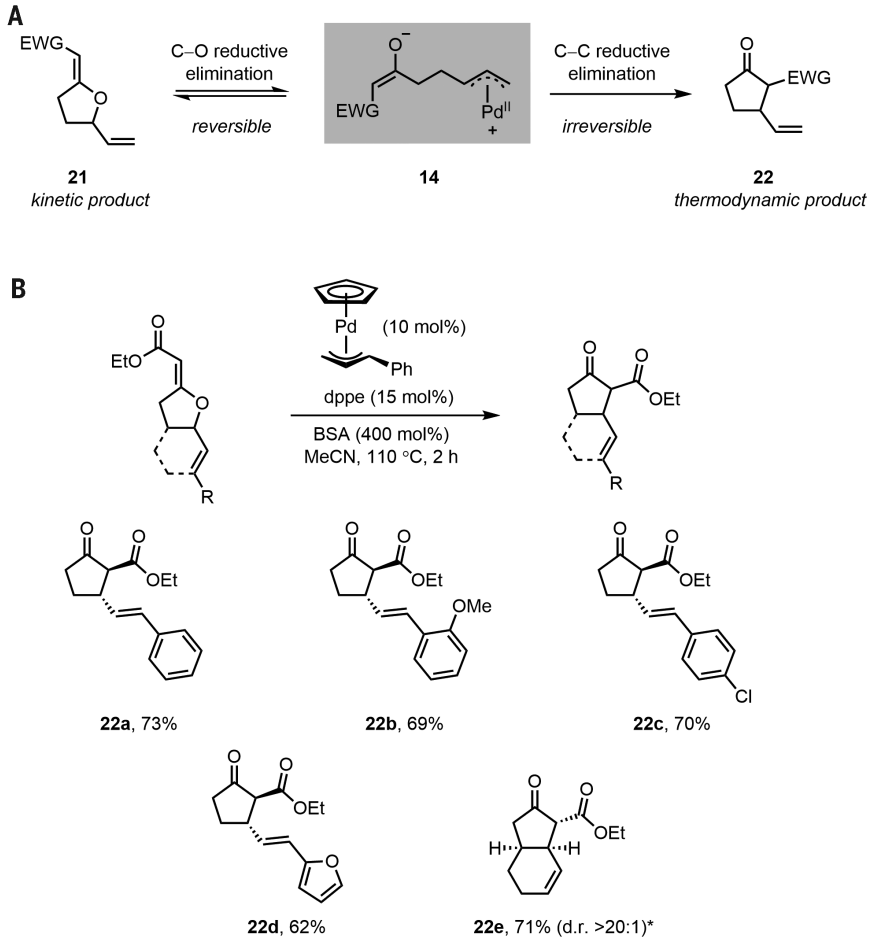

Fig. 4. Isomerization of tetrahydrofuran to cyclopentanone products. (**A**) Pathways to different (3+2) cycloaddition products. (**B**) Scope of [1,3] O-to-C rearrangement. Unless otherwise noted, the isomerization reactions were run using 10 mol % CpPd(cinnamyl), 15 mol % dppe, 400 mol % *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and 0.1 mol of tetrahydrofuran substrate in acetonitrile at 110°C. The data are reported as isolated yields. The asterisk indicates a reaction performed at 80°C in the absence of BSA and with 20 mol % of RuPhos instead of dppe.

π-allyl palladium generation. On the other hand, the absence of extra stabilization from adjacent arenes for the linear alkyl dienes also leads to their underperformance compared with dienes with aromatic substituents. When 1-vinylnorbornene was submitted to the reaction, (3+2) cycloaddition occurred site-selectively at the more-strained cyclic olefin instead of the terminal one (**12x**), and cyclopropane products from (2+1) cycloaddition were not obtained. Both endo and exo cycloaddition products were formed. The use of a less-reactive bis(*o*-methoxyphenyl)phenylphosphine ligand resulted in a lower yield but a higher selectivity toward the exo isomer. Reaction of 1-phenyl-2-methylbutadiene with exclusive E-geometry yielded a mixture of E and Z isomers as the cycloaddition product (**12y**). This observation is consistent with the formation of a new π-allyl palladium (i.e., **20a** and **20b**) after the addition of Pd-oxyallyl to the diene substrate, as the bond rotation during the π-σ-π isomerization of Pd-allyl would alter the olefin geometry and form the Z-product.

Although the current cycloaddition reactions produce tetrahydrofuran rings exclusively, it is equally important to devise an expeditious synthesis of cyclopentanone derivatives using the (3+2) cycloaddition of Pd-oxyallyl intermediate. We envisioned that the product-forming C–O bond reductive elimination should be a reversible process (Fig. 4A), as the β-keto ester anion is weakly basic, well-stabilized, and thus a good leaving group for the palladium π-allyl formation. Therefore, we anticipated that an isomerization reaction from the tetrahydrofuran **21** to more thermodynamically stable cyclopentanone **22** via intermediate **14** should be feasible by using palladium catalysts that can facilitate the irreversible C–C bond reductive elimination (*27*–*29*). Indeed, the desired [1,3] O-to-C rearrangement of cycloaddition products from linear dienes was found to proceed and afford α,β-disubstituted cyclopentanones (**22a** to **22d**) using CpPd(cinnamyl)/1,2-bis(diphenylphosphino)ethane (dppe) as the catalyst under elevated temperature. The bicyclic tetrahydrofuran product **12a** was also suitable for the isomerization, in which 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos), a prominent ligand for promoting palladium-mediated oxidative addition and reductive elimination (*30*), was employed and fused cyclopentanone **22e** was obtained in good yield and high diastereoselectivity.

Together, the synthetic methods described here toward these two important classes of five-membered cyclic motifs are expected to serve as useful tools for synthesis of complex molecules, particularly those with fused-ring systems. The presence of the ketoester motif especially provides a powerful intermediate for extensive structural elaboration.

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ACKNOWLEDGMENTS

We thank C. Kalnmals for proofreading the manuscript and providing several synthetic intermediates. **Funding:** We thank the NSF (CHE-1360634) and the NIH (GM033049) for support of our programs. We are also grateful to the Tamaki Foundation for financial support.

G.M.M. acknowledges the SERB Indo-U.S. Postdoctoral Fellowship for additional financial support. **Author contributions:** B.M.T. conceived of and designed the project, Z.H. and G.M.M. carried out the experiments, B.M.T. and Z.H. wrote the manuscript, and all authors analyzed the data and discussed the results. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** All data, including experimental details, spectroscopic data, and additional information about the optimization of reaction conditions, are in the supplementary materials.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/362/6414/564/suppl/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S3
NMR Spectra
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14 June 2018; accepted 5 September 2018
10.1126/science.aau4821

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Science **362** (6414), 564-568.
DOI: 10.1126/science.aau4821

Steps to smaller rings

Certain ring-forming reactions in organic chemistry are efficient because the orbital symmetries match up in the reactants and products. Oxyallyl ions tend to react with dienes in this paradigm to form seven-membered rings. Under palladium catalysis, Trost *et al.* redirected this reaction toward more common five-membered tetrahydrofuran rings by appending an ester to the diene. Although that pathway is symmetry-forbidden, the electron-withdrawing ester appears to stabilize a key intermediate along a stepwise route to the smaller ring.

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