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# Modular and diverse synthesis of oxaheterocycles via Pd-catalyzed migratory 1,*n*-cycloannulation of alkenes

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Here, we report a general and modular strategy for the diverse synthesis of oxaheterocycles via a Pd-catalyzed migratory 1,*n*-cycloannulation reaction (MCAR, *n* > 2) of alkenes. Employing readily available (homo)allylphenols and 2-iodophenols as starting materials, this method enables the efficient construction of a broad range of 5- to 8-membered oxaheterocycles with good functional group tolerance. The key to achieving high reactivity and controlling ring-closure is the kinetically favored formation of a *para*-quinone methide (*p*-QM) intermediate rather than an *ortho*-quinone methide (*o*-QM) intermediate during the migration process, which facilitates selective single-site cyclization at the less sterically hindered site and suppresses competing pathways. The synthetic utility of this strategy is further demonstrated by the efficient preparation of several bioactive oxaheterocyclic compounds including a cytotoxic flavan and an MRGPRX4 inhibitor, highlighting its potential in both synthetic and medicinal chemistry.

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Oxaheterocycles represent a privileged and structurally diverse class of heterocycles that are indispensable in diverse natural products and marketed drugs (Scheme 1a).<sup>1</sup> Approximately 19% of the top 200 best-selling small-molecule drugs in 2024 contain at least one oxaheterocyclic unit,<sup>2</sup> including Jardiance, Farxiga, Epoprostenol, *etc.*, which verifies the ubiquity and functional relevance of oxaheterocycles in pharmaceutical pipelines and marketed drugs. Despite their importance, the efficient and modular synthesis of structurally diverse oxaheterocycles from readily available starting materials remains a significant challenge. For example, transition metal catalyzed cycloannulation with alkenes has emerged as a powerful and atom-economical strategy for oxaheterocycle construction due to the wide availability and reactivity of alkenes and amphiphilic coupling partners.<sup>3</sup> However, most existing cycloannulation processes occur at the 1,2-position of alkenes and are largely limited to highly reactive  $\pi$ -systems, such as conjugated dienes,<sup>3*t-n*</sup> allenes,<sup>3*o-q*</sup> or styrenes,<sup>3*r-u*</sup> thereby restricting the scope and structural diversity of accessible oxaheterocycles. Thus, the development of general, flexible, and efficient synthetic

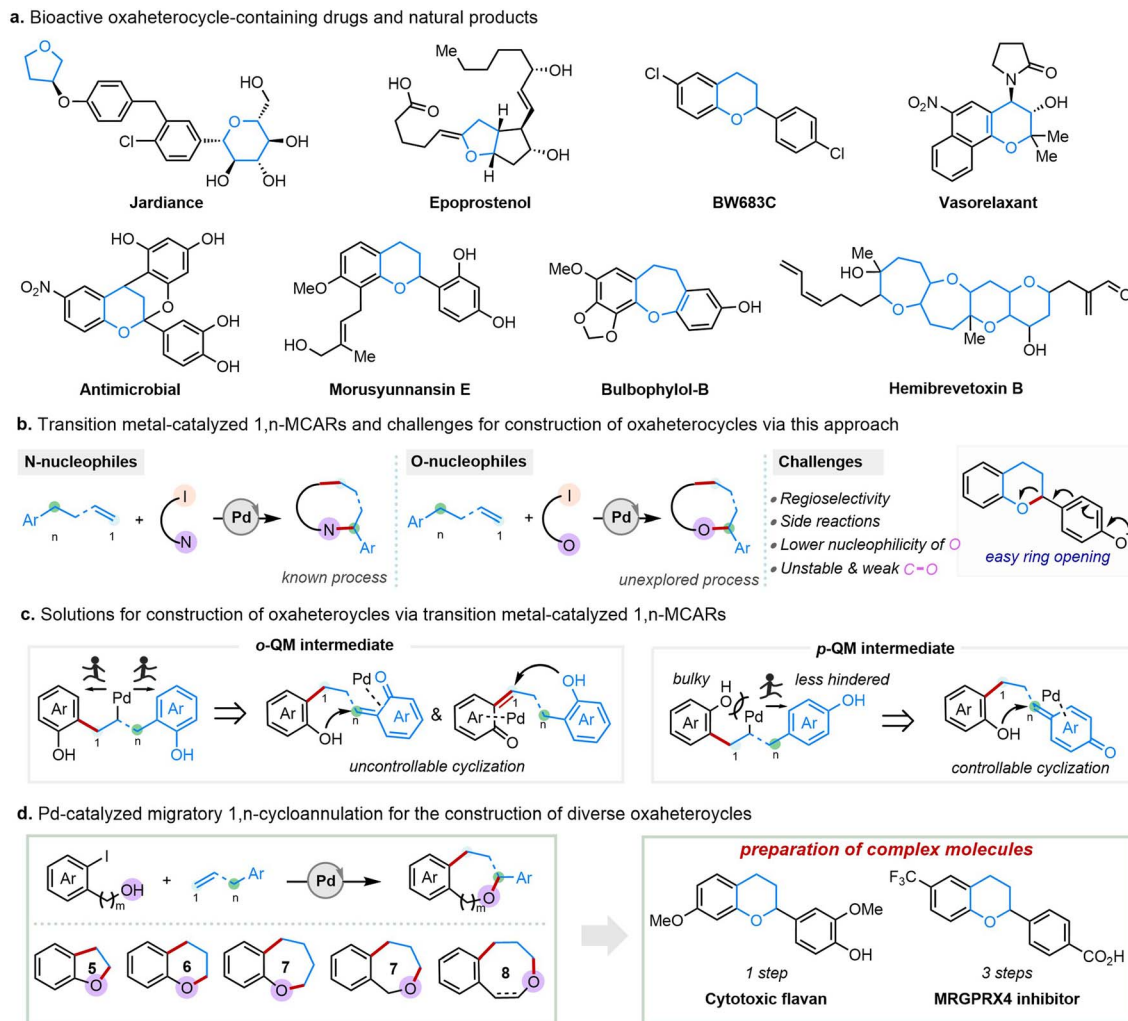
strategies that can rapidly construct a wide range of different-sized oxaheterocycles from simple, readily available building blocks remains a compelling goal in the fields of synthetic and medicinal chemistry.

Recently, transition-metal-catalyzed migratory cycloannulation reactions<sup>4</sup> (MCARs) of unactivated alkenes have garnered increasing attention by taking advantage of the metal-walking process,<sup>5</sup> enabling cyclization at nonclassical positions<sup>6</sup> (1,*n* vs. 1,2) and thus offering new opportunities to construct a variety of cyclic structures with diverse ring sizes and substitution patterns. A major obstacle in migratory cycloannulation reactions (MACRs) is achieving precise control over the cyclization site, which must overcome the formation of thermodynamically disfavored larger metallacycles. In addition, isomerization of unactivated alkenes, the poor regioselectivity control in the migratory insertion step, and catalyst deactivation during the metal-walking process may lead to undesired cycloannulated and Heck-type byproducts, further complicating the reaction outcome. To overcome those challenges, our group has previously introduced quinone methide (QM) intermediates<sup>7</sup> for controlling the migration direction and determining the ring size of the heterocycles, enabling the efficient and diverse synthesis of a series of 6- to 8-membered azaheterocycles via a Pd-catalyzed migratory 1,*n*-cycloannulation (*n* > 2) strategy.<sup>4*a*</sup> However, extending this approach to oxaheterocycles presents distinct challenges due to the inherently lower nucleophilicity of oxygen, the weaker bond energy of C–O bonds relative to C–N bonds,<sup>8</sup> and the formation of indistinguishable quinone methide (QM) intermediates with multiple potential cyclization

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Scheme 1 Pd-catalyzed migratory cycloannulation reaction.

pathways, which can reduce the overall reactivity or complicate ring closure (Scheme 1b). In particular, the weaker C–O bond in oxaheterocycles might promote undesired ring-opening after the initial cyclization, leading to significant amounts of uncyclized byproducts. Additionally, *o*-QM intermediates, which have been previously used in the construction of azaheterocycles, can also result in poorly selective and uncontrollable cyclization processes due to subtle differences in aryl substitutions. To address these issues and further explore the versatility of the migratory 1,*n*-cycloannulation ( $n > 2$ ) strategy in the diverse construction of different-sized oxaheterocycles, we envisioned that a palladium-catalyzed migratory 1,*n*-cycloannulation ( $n > 2$ ) of unactivated alkenes with readily available *ortho*-iodophenols might be realized by the kinetically favored *in situ* formation of a *p*-QM intermediate (*p*-QM vs. *o*-QM), which allows for single-site ring closure at the less sterically hindered site (Scheme 1c).

Herein, we report a general strategy for the modular and diverse synthesis of a wide variety of oxaheterocycles *via* Pd-catalyzed migratory 1,*n*-cycloannulation ( $n > 2$ ) of unactivated alkenes (Scheme 1d). The reaction proceeds through a *para*-

quinone methide intermediate, which plays a pivotal role in guiding the metal-walking process and controlling the site of cyclization. The use of a weak organic base is also essential for suppressing ring-opening events following the initial cyclization, thereby improving overall yield and minimizing the formation of uncyclized byproducts. This reaction features mild conditions, a broad substrate scope and excellent functional group compatibility, making it suitable for the efficient synthesis of 5- to 8-membered oxaheterocycles. The synthetic utility of this approach is demonstrated by the concise preparation of a cytotoxic flavan in one step and an MRGPRX4 inhibitor in three steps. This work not only provides a powerful platform for accessing oxaheterocycles with high structural diversity from simple feedstocks, but also expands the synthetic potential of migratory cycloannulation reactions (MCARs).

To verify the challenges associated with constructing oxaheterocycles *via* Pd-catalyzed 1,*n*-migratory cycloannulation, the reactions of 2-iodophenol with various 2-allylphenol derivatives were initially investigated. The reaction between 2-iodophenol and 2-allylphenol afforded the desired migratory cycloannulated product **3a** in 68% yield with excellent

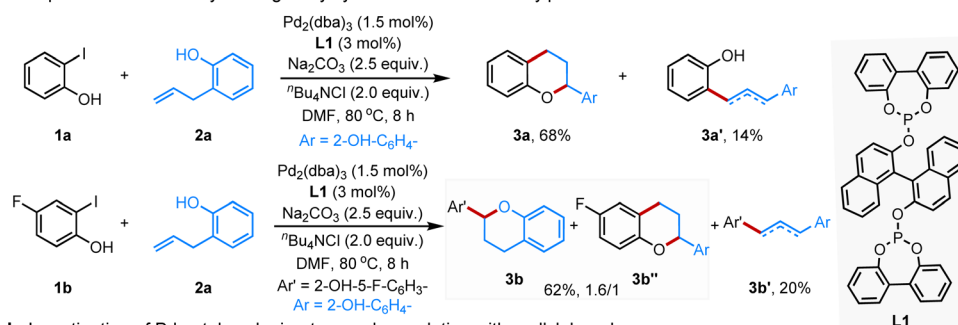


regioselectivity in the presence of  $\text{Pd}_2(\text{dba})_3$  (1.5 mol%), diphosphite ligand **L1** (3.0 mol%),  $n\text{-Bu}_4\text{NCl}$  (2.0 equiv.), and  $\text{Na}_2\text{CO}_3$  (2.5 equiv.) in DMF. However, when 4-fluoro-2-iodophenol was used instead, the reaction with 2-allylphenol produced a mixture of 2-arylchromanes in 62% yield with a 1.6 : 1 ratio, probably due to the formation of two indistinguishable *ortho*-quinone methide (*o*-QM) intermediates in the migratory event followed by uncontrollable cyclization processes (Scheme 2a). These results further illustrate the significant hurdles that remain in the development of Pd-catalyzed 1,*n*-MCAR for efficient oxaheterocycle synthesis. Following our hypothesis that the formation of *p*-QM *via* a kinetically favored migration might enable the single-site ring closure, 4-allylphenol was evaluated under identical reaction conditions. To our great delight, the desired migratory 1,3-cycloannulated product **5a** was obtained in 64% yield, although the 5-membered oxaheterocycle **5a''** (5% yield) and uncyclized Heck-type byproduct **5a'** (15% yield) were formed (Scheme 2b). Encouraged by this lead, systematic screening of the reaction parameters was performed, and the yield of **5a** could be optimized to 86% with 9/1 regioselectivity in the presence of  $\text{Pd}_2(\text{dba})_3$ ,  $\text{NET}_3$ , and  $n\text{-Bu}_4\text{NCl}$  in dioxane (Scheme 2c, Entry 1). Although a high regioselectivity was observed in DMF (10/1) compared to dioxane (9/1), it gave a lower yield (Entry 2). When THF was employed instead of dioxane, both the yield and regioselectivity decreased (Entry 3),

indicating that the solvent plays a critical role in this migratory cycloannulation reaction. The choice of base also affects the reaction outcome, and the use of a strong inorganic base normally gave inferior outcomes probably due to the undesired ring-opening after the initial cyclization. For instance, replacing  $\text{NET}_3$  with  $\text{Na}_2\text{CO}_3$  led to a lower yield but a slightly higher regioselectivity (Entry 4). The use of DIPEA also resulted in lower efficiency and regioselectivity (Entry 5). Notably, the presence of the  $n\text{-Bu}_4\text{NCl}$  additive was found to be essential for both reaction efficiency and regioselectivity. Neither the desired cyclized product nor the Heck-type byproducts were observed in the absence of  $n\text{-Bu}_4\text{NCl}$  (Entry 6). The replacement of  $n\text{-Bu}_4\text{NCl}$  with  $n\text{-Bu}_4\text{NBr}$  and  $n\text{-Bu}_4\text{NI}$  led to diminished yields and regioselectivities (Entries 7 and 8). These results highlight a significant anion effect, likely stemming from the strong coordination ability of chloride, which may facilitate the oxidative addition of the aryl halide and stabilize key Pd intermediates during the catalytic cycle.

Under the optimized reaction conditions, we investigated the generality of this methodology for the preparation of a diverse range of oxaheterocyclic compounds. In general, this protocol demonstrated broad functional group tolerance and excellent regioselectivity, enabling the efficient construction of various functionalized dihydrobenzofuran, chromane, tetrahydrobenzo[*c*]oxepines, and tetrahydrobenzo[*b*]oxepines. In

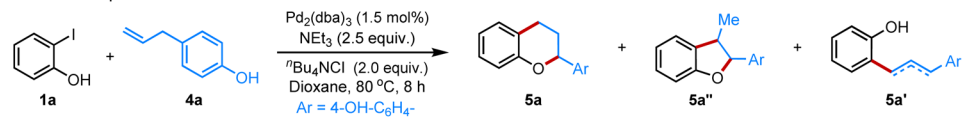
#### a. Exploration of Pd-catalyzed migratory cycloannulation with *o*-allylphenol



#### b. Investigation of Pd-catalyzed migratory cycloannulation with *p*-allylphenol



#### c. Reaction parameters evaluation



| Entry | Deviation from conditions                          | <b>5a</b> (%) | <b>5a/5a''</b> | <b>5a/5a'</b> | Entry | Deviation from conditions                                      | <b>5a</b> (%) | <b>5a/5a''</b> | <b>5a/5a'</b> |
|-------|----------------------------------------------------|---------------|----------------|---------------|-------|----------------------------------------------------------------|---------------|----------------|---------------|
| 1     | none                                               | 86            | 9/1            | 22/1          | 5     | DIPEA instead of $\text{NET}_3$                                | 74            | 6/1            | 12/1          |
| 2     | DMF instead of Dioxane                             | 78            | 10/1           | 11/1          | 6     | w/o $n\text{-Bu}_4\text{NCl}$                                  | ND            | ND             | ND            |
| 3     | THF instead of Dioxane                             | 74            | 6/1            | 19/1          | 7     | $n\text{-Bu}_4\text{NBr}$ instead of $n\text{-Bu}_4\text{NCl}$ | 50            | 4.2/1          | 13/1          |
| 4     | $\text{Na}_2\text{CO}_3$ instead of $\text{NET}_3$ | 64            | 11/1           | 4/1           | 8     | $n\text{-Bu}_4\text{NI}$ instead of $n\text{-Bu}_4\text{NCl}$  | 30            | 4/1            | 4/1           |

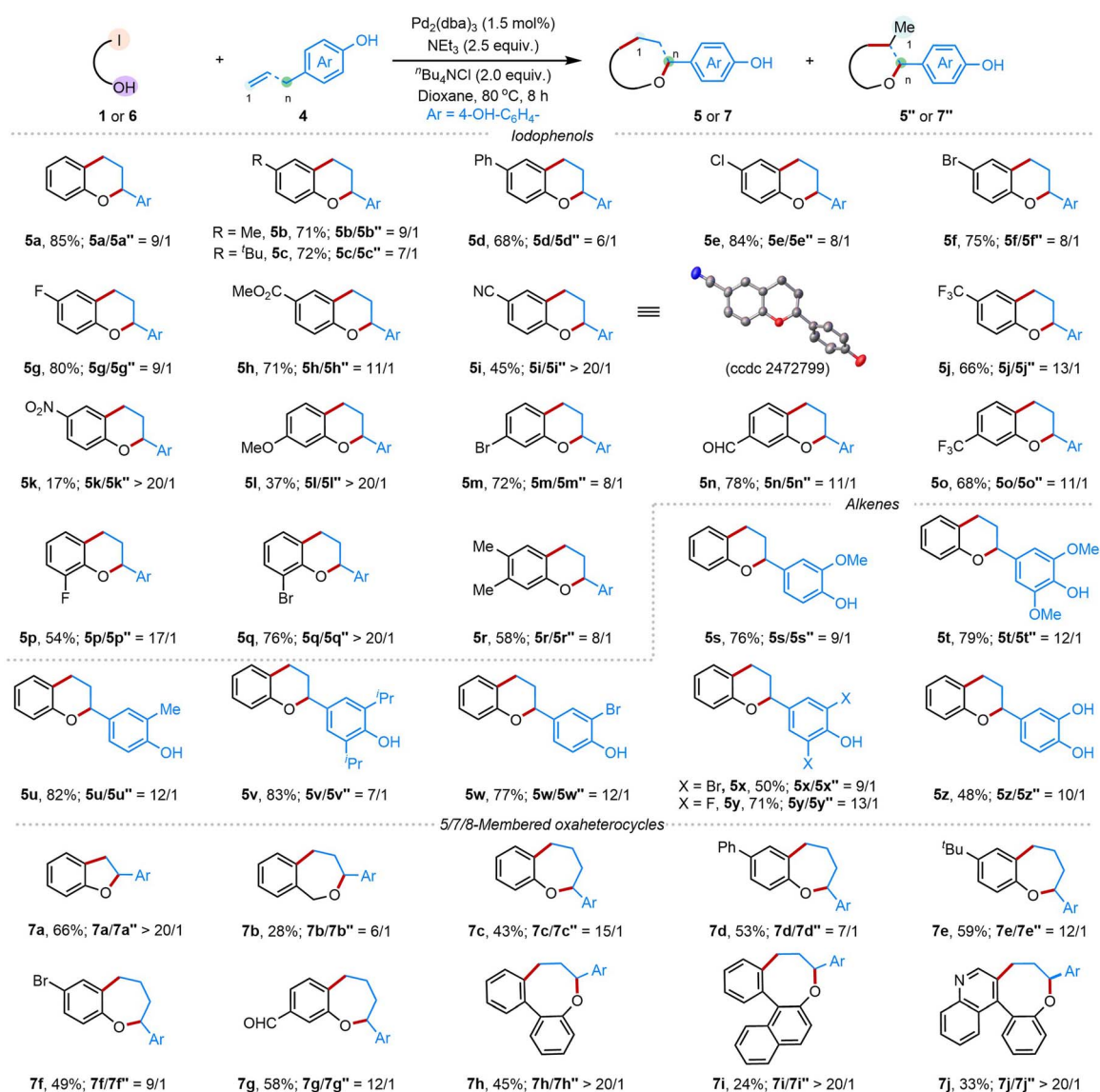
Scheme 2 Pd-catalyzed migratory 1,*n*-cycloannulation of unactivated alkenes.



particular, a variety of 2-aryl-substituted chromane derivatives (**5a–5r**) were synthesized in moderate to high yields (Scheme 3). The reaction also tolerated a wide array of substituents at the 6-position, including alkyl groups such as methyl (**5b**), *tert*-butyl (**5c**), phenyl (**5d**), and halogens (**5e–5g**), and strong electron-withdrawing groups such as ester (**5h**), cyano (**5i**), trifluoromethyl (**5j**), and nitro (**5k**). Notably, the structure of the products for this migratory cycloannulation reaction was confirmed by X-ray single-crystal diffraction analysis of oxaheterocycle **5i**.<sup>9</sup> Moreover, substituents at the 7-position were also well tolerated, including methoxy (**5l**), bromo (**5m**), formyl (**5n**), and trifluoromethyl (**5o**), affording the corresponding cyclized products in moderate yields with excellent regioselectivity. Substitution at the 8-position likewise gave highly regioselective outcomes, with fluoro (**5p**) and bromo (**5q**) substituents

furnishing products in 54% and 76% yields, respectively. Additionally, a polysubstituted methylated chromane substrate underwent successful cyclization to give **5r** in 58% yield with an 8 : 1 regioselectivity ratio. These results collectively highlight the robustness and synthetic utility of the Pd-catalyzed cycloannulation strategy for accessing structurally diverse and functionally rich heterocycles with high regioselectivity.

Next, the substituent effects on the 4-allyl-phenol moiety were systematically investigated. Our strategy proved to be effective across a variety of functional groups, showing excellent regioselectivity and moderate to high yields. For example, commercially available eugenol can be readily transferred to six-membered oxaheterocycle **5s** in 76% yield and 9/1 regioselectivity. A range of 3,5-disubstituted allyl-phenols bearing methoxy (**5t**), isopropyl (**5v**), bromo (**5x**) and fluoro (**5y**) groups



**Scheme 3** The synthesis of oxaheterocycles via Pd-catalyzed migratory 1,*n*-cycloannulation. The values under each structure indicate isolated yields (see the SI for experimental details). The ratios of **5/5''** and **7/7''** were determined by <sup>1</sup>H NMR analysis of the crude product.



were compatible under the standard conditions, giving the corresponding 2-aryl chromane derivatives with high yields and excellent regioselectivity. In addition, allylphenols bearing 3-methyl (**4u**) and 3-bromo (**4w**) substituents were well tolerated, affording the desired products in 82% and 77% yields, respectively. Notably, bromo substituents, which are typically reactive under transition-metal catalysis, were well retained under the migratory cyclization conditions (products **5f**, **5m**, **5w**, and **5x**). The compatibility with the bromo group is particularly valuable, as it can serve as a versatile handle for subsequent transition-metal-catalyzed cross-coupling reactions, enabling further molecular diversification. Furthermore, even substrates containing an additional free phenolic hydroxyl group were compatible with Pd-catalyzed cyclization, as exemplified by the formation of **5z** in 48% yield with excellent regioselectivity (10 : 1).

Building on the aforementioned success in synthesizing six-membered chromane derivatives, we further explored the versatility of this strategy by extending to the synthesis of oxaheterocycles with diverse ring sizes. Under the optimized conditions, five-membered dihydrobenzofuran derivative **7a** was obtained in 66% yield with excellent regioselectivity. It is worth mentioning that the reaction with styrene under similar conditions did not provide the desired cyclic product (see the SI for more details). Additionally, seven-membered tetrahydrobenzo[*c*]oxepine derivative **7b** was successfully prepared *via* the coupling of 2-iodobenzyl alcohol and 4-allylphenol under Pd-catalyzed migratory cycloannulation conditions, affording the desired product in 28% yield with 6 : 1

regioselectivity. Additionally, seven-membered tetrahydrobenzo[*b*]oxepine **7c** could also be obtained in 40% NMR yield under the standard conditions employing 4-(but-3-en-1-yl)phenol and 2-iodophenol as substrates, albeit with unsatisfactory regioselectivity (*rr* = 2.5/1.0). Upon systematic optimization, the yield and regioselectivity of **7c** were significantly improved by employing DIPEA as the base and *t*-AmylOH as the solvent (for details, see the SI). With modified conditions in hand, a variety of phenol substrates bearing diverse substituents including *tert*-butyl, bromo, and formyl groups on the aromatic ring were well tolerated, affording the corresponding oxepine products (**7d**–**7g**) in good yields with high regioselectivity. Remarkably, when 2-[2'-iodophenyl]phenol was employed as the amphiphilic coupling partner, the reaction enabled the formation of eight-membered 7,8-dihydro-6*H*-dibenzo[*b,d*]oxocine derivatives (**7h**–**7j**) in good yields and excellent regioselectivity. For the preparation of medium-sized oxaheterocycles, uncyclized Heck-type products were observed as the major byproducts alongside the desired cyclized products, which may suggest that the Pd–H active species dissociates from the alkenes due to the slow ring-closure step caused by ring strain. Moreover, attempts to synthesize larger (>8-membered) oxaheterocycles using this method yielded exclusively Heck-type products. This demonstrates the capability of the developed Pd-catalyzed migratory cycloannulation strategy to construct medium-sized oxaheterocycles, which are typically challenging to access through conventional methods.



Scheme 4 Synthetic applications of Pd-catalyzed migratory 1,*n*-migratory cycloannulation.





Scheme 5 Mechanistic studies and proposed mechanism.

After systematically investigating the generality of the Pd-catalyzed 1,*n*-migratory cycloannulation reaction (MACR), we further explored the synthetic applicability and scalability of this methodology (Scheme 4). This reaction could be scaled up to a 5.0 mmol scale, affording desired product **5a** in 87% yield and 9/1 regioselectivity (Scheme 4a). The phenolic hydroxy group in chromane derivative **5a** was readily transformed into the corresponding aryl triflate **8** in 93% yield (Scheme 4b). This versatile intermediate could then undergo a series of transition metal catalyzed cross-coupling reactions, including borylation (**9**), amination (**10**), Suzuki–Miyaura coupling (**11**), and alkynylation (**12**), enabling rapid access to structurally diverse and functionally complex molecules. Moreover, the synthetic utility of this methodology was showcased by the concise, one-step synthesis of the bioactive cytotoxic flavan **15** in 59% yield from simple precursors using our Pd-catalyzed MACR reaction (Scheme 4c).<sup>10</sup> Similarly, the MRGPRX4 inhibitor **17** was efficiently constructed in three steps with an overall yield of 50%, starting from 2-iodo-4-(trifluoromethyl)phenol and 4-allylphenol (Scheme 4d). Notably, this route is significantly shorter than the previously reported six-step synthesis,<sup>11</sup> underscoring the potential of our method for streamlining complex molecule construction.

Preliminary mechanistic studies were carried out to shed light on the mechanistic insights of this Pd-catalyzed migratory 1,*n*-cycloannulation reaction. A terminal deuterated alkene **D-4a** was subjected to the standard cyclization conditions, affording the corresponding deuterated product **D-5a** in 84% yield (Scheme 5a). The deuterium is mainly distributed at the terminal position, with only 8% appearing at its adjacent position. In contrast, when the internally deuterated alkene (**D-4a'**, labelled at the C3 position) was used, the product (**D-5a'**) was obtained in 57% yield. In this case, the deuterium was retained at the original position (86%) and partially transferred to the adjacent position (50%), supporting the involvement of a metal-walking process *via*  $\beta$ -hydride elimination and

reinsertion. Moreover, these results suggest that metal migration is likely directed by 4-allylphenol, which plays a crucial role in controlling the metal walking direction. This control may arise from the irreversible formation of a *p*-QM intermediate, which stabilizes the intermediate and channels the reaction along the desired pathway. No desired cycloannulation product was observed when a *para*-methoxy-protected allylphenol was used, which strongly supports our hypothesis (Scheme 5b). The migratory cycloannulation reaction could only happen by employing the *para*-allylphenol and *ortho*-allylphenol substituted aryl alkenes, consistent with our proposed quinone methide intermediate during the cyclization process. To further understand the pathway for the formation of the five-membered oxaheterocycle **5a''**, internal alkene **4a'** was subjected to the standard reaction conditions but failed to produce the five-membered azaheterocycle **5a''** (Scheme 5c). This result indicates that **5a''** is not formed *via* isomerization of **4a** to **4a'** followed by direct Ar–Pd(II) insertion and instead originates from an initial migratory insertion event. Based on the aforementioned mechanistic studies and our previous reports, a plausible catalytic cycle is depicted in Scheme 5d. The reaction begins with oxidative addition of 2-iodophenol with Pd(0), generating intermediate **Int-I**. Subsequent coordination, migratory insertion of the alkene into the aryl–Pd(II) species and the metal-walking process ( $\beta$ -hydride elimination and reinsertion) afforded intermediate **Int-II**. Under basic conditions, Pd–H elimination leads to the formation of a *p*-QM intermediate (**Int-IV**). Finally, an intramolecular oxa-Michael addition delivers the 1,*n*-cyclized product.

## Conclusions

In conclusion, we have developed a palladium-catalyzed migratory 1,*n*-cycloannulation of unactivated alkenes that enables the efficient construction of a wide range of five- to eight-membered oxaheterocycles. The *para*-hydroxyl group on



the alkene substrate plays a pivotal role in determining the ring size of the heterocycles by directing the metal migration pathway *via* the formation of a *p*-QM intermediate rather than an *o*-QM intermediate. This strategy exhibits a broad substrate scope and excellent functional group tolerance and operates under mild reaction conditions, making it a practical and versatile tool for the synthesis of structurally diverse oxaheterocycles.

## Author contributions

P. W. conceived the concept and directed the project. J.-P. W. conducted the experiments and developed the reactions. Y. W. and P. W. co-wrote the manuscript. All authors contributed to the discussion.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

CCDC 2472799 (5i) contains the supplementary crystallographic data for this paper.<sup>9</sup>

Supplementary information: materials and methods, experimental procedures, characterization data, and NMR spectra. See DOI: <https://doi.org/10.1039/d5sc06539a>.

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