Pd-Catalysed Migratory 1,1-Cycloannulation Reaction of Alkenes

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One of the central goals of synthetic chemistry is to develop efficient methods for constructing heterocyclic architectures, given their broad distribution in a wide range of natural compounds, pharmaceuticals, agrochemicals, and materials. As a result, methods that allow for the modular and diverse synthesis of heterocyclic compounds via one single approach are in high demand. Here, we report a novel strategy for the preparation of diverse heterocycles via a Pd-catalysed migratory 1,1-cycloannulation reaction (MCAR) of alkenes. Starting from readily available alkenyl amines and alkenyl alcohols, this approach allows the formation of a wide range of heterocycles, including five to seven-membered azaheterocycles and oxaheterocycles with high efficiency and good functional group tolerance. The key to the realisation of this reaction is the use of 4-iodophenol or 2-iodophenol derivatives, where the phenolic hydroxyl group plays a critical role in controlling the direction of migration and the ring-size of the heterocycles through the formation of a quinone methide intermediate. The utility of this strategy in synthetic chemistry and medicinal chemistry were preliminarily demonstrated by the late-stage introduction of heterocycle scaffolds into complex drug molecules, and the efficient preparation of serval bioactive compounds.

Heterocycles are a crucial class of compounds with significant applications and notable biological activities, particularly azaheterocycle and oxaheterocycle, which are widely found in bioactive molecules, pharmaceuticals, pesticides, and natural products (Fig. 1a)[1-3]. From 2015 to 2020, azaheterocycles and oxaheterocycles accounted for 88% and 26%, respectively, in the 164 small-molecule drugs approved by the US Food and Drug Administration (FDA)[4]. As a consequence, extensive studies have focused on

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developing efficient approaches for the preparation of those heterocyclic architectures starting available raw materials.[5-11] In this context, transition metal-catalysed cycloannulation with readily and commercially available alkenes and heteroatom containing amphiphilic partners, including Larock annulation[12-21], Wacker-type cyclization[22-24], dipole cycloaddition[25-27], hetero-Diels-Alder reaction[28-29], [2+2+2] cycloaddition reaction[30-32] etc., represents one of the most efficient and atom-economic methods to accomplish this long-term goal, and has been widely used in the preparation of natural products and bioactive small molecules. Typically, those elegant cyclisation reactions happened at the vicinal 1,2-position across the carbon-carbon double bond, and the majority of the alkenes includes highly reactive styrenes[13], 1,3-dienes[15, 16 ,25 ,27], allenes[17], or strained cyclic alkenes[18, 20], thus limiting the diverse synthesis of various types of heterocycles via one single approach.

Recently, the transition metal-catalysed migratory cycloannulation reaction (MCAR) of unactivated alkenes, where the cycloannulation happens at the non-classic positions (1,n *vs* 1,2) of the alkene[33-38], has been emerging as a promising and innovative strategy for synthesizing a diverse range of cyclic compounds by utilizing the unique capabilities of metal migration on hydrocarbon chains[39-51] (Fig. 1b), inspired by the early contributions by Larock[33-34] and Heck[35]. This approach could serve as an efficient platform for the construction of diverse cyclic compounds with different ring sizes starting from the readily or commercially available unactivated alkenes. However, the transition metal-catalysed migratory cycloannulation reaction (MCAR) is still at its infancy stage, and the migratory cycloannulation with unactivated alkenes remains a big challenge due to the low reactivity, unsatisfying regioselectivity control, and many undesired processes (isomerisation of alkenes, hydrofunctionalisation, Heck process, direct coupling of partners etc.) in transition metal-catalysed alkene functionalization event. In 2022, our group demonstrated a Pd-catalysed migratory 1,n-cycloannulation (n >2) of unactivated alkenes for the efficient synthesis of a series of 6 to 8-membered benzo-azaheterocycles[37]. Very recently, the Patil group have reported an Au-catalysed 1,4-cyloannulation of unactivated alkenes with iodoarenes for the preparation of tetrahydronaphthalene via the cationic relocation[38]. Despite of those progresses, the previous reports on the construction of heterocycles via the MCAR strategy largely limited to aryl halide-containing amphiphiles, thus resulting in the formation of benzo-heterocycles rather than more valuable aliphatic heterocycles, such as pyrrole, piperidine, azepane,

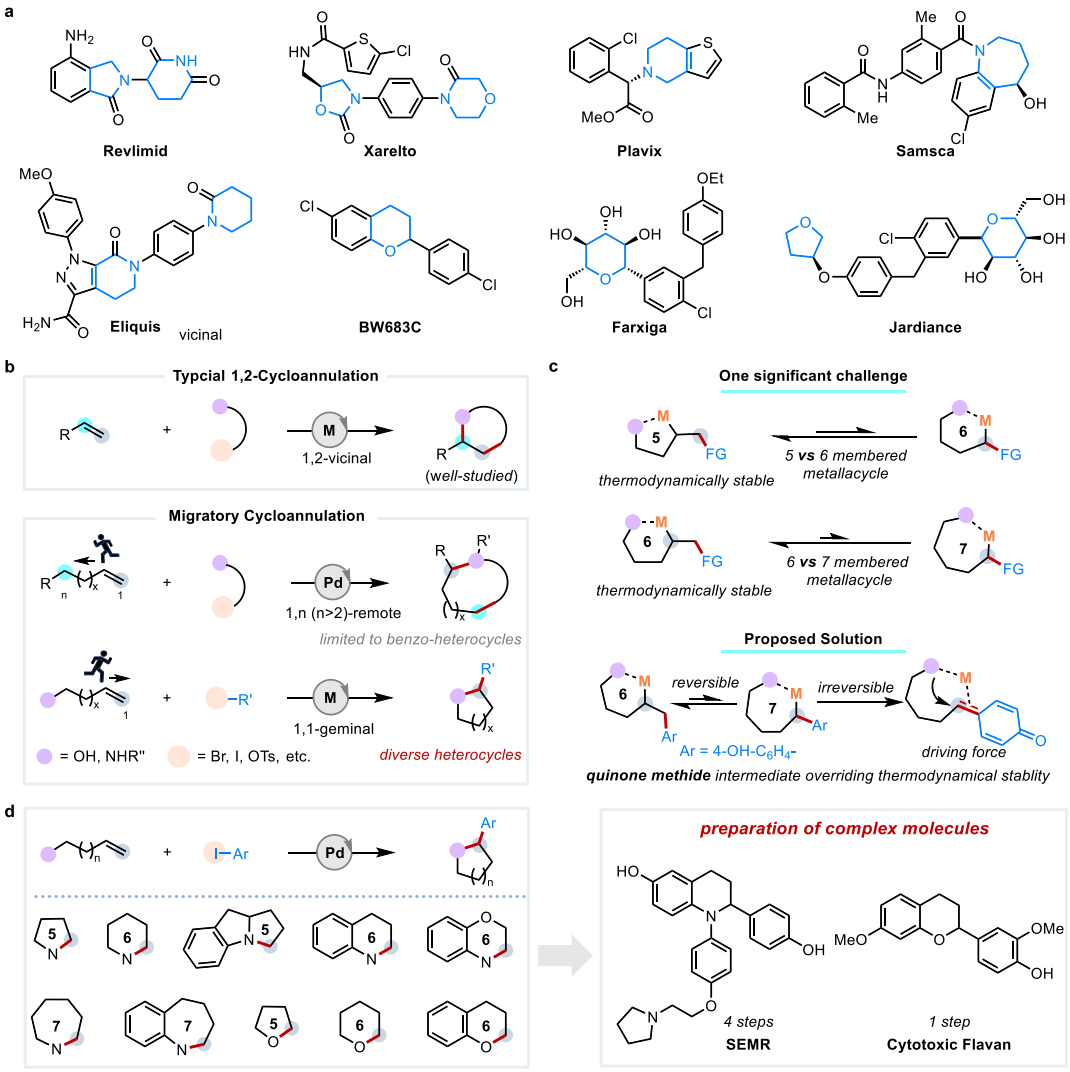


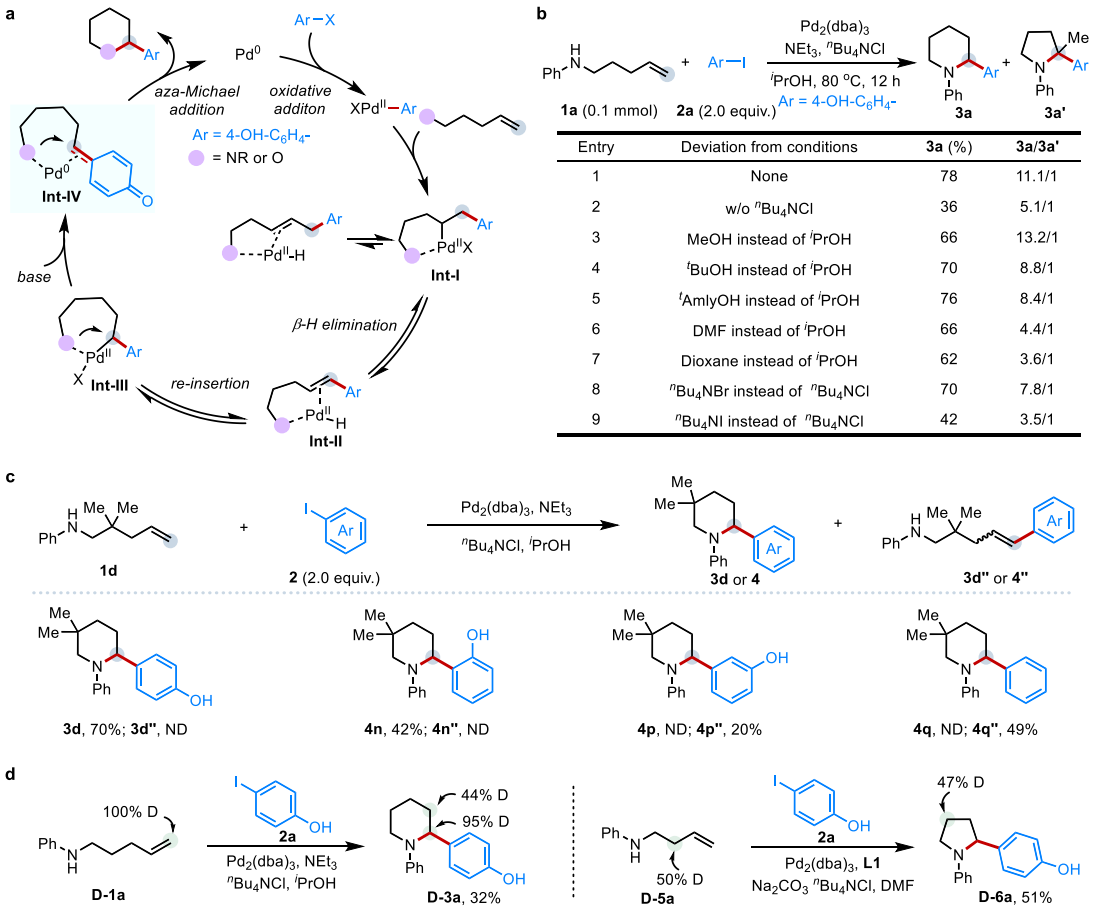
Fig. 1 | Pd-catalysed migratory 1,1-cycloannulation reaction. a, Bioactive heterocycle-containing drugs and natural products. **b,** Transition metal-catalysed cycloannulation with alkenes. **c**, Challenges for transition metal-catalysed migratory 1,1-cycloannulation and proposed solution. **d**, Pd-Catalysed migratory 1,1-cycloannulation for the construction of diverse aza- and oxaheteroycles.

tetrahydrofuran and tetrahydropyran etc. To address this limitation and further explore the versatility of the MCAR strategy, we environed diverse synthesis of various aliphatic azaheterocycles and oxaheterocyles might be realised via transition metal-catalysed migratory 1,1-cycloannulation by using readily available alkenyl amines and alkenyl alcohols in the presence of commercially available aryl halides. In addition to the aforementioned challenges for MCAR, the most significant obstacle for migratory 1,1-cycloannulation is achieving precise control over the ring-closing position by directing the migration pathway, and

overriding the obstacle though the formation of a thermodynamically unfavourable larger metallacycle[22-24] (Fig. 1c), particularly in the construction of >six-membered heterocycles. Here, we report the efficient construction of a diverse range of aliphatic heterocycles via a Pd-catalysed migratory 1,1-cycloannulation reaction (MCAR) of unactivated alkenes (Fig. 1d). The newly established process offers a powerful tool for the straightforward and efficient construction of azaheterocycles and oxaheterocycles, including pyrrole, piperidine, azepane, tetrahydroquinoline, tetrahydroisoquinoline, tetrahydrobenzo[*b*]azepines, tetrahydrofuran, tetrahydro-*2H*-pyran, and chromane derivatives, with a wide range of ring sizes (5- to 7-membered) utilising readily available alkenyl amines and alkenyl alcohols. The success of this reaction relies on the employment of 4-iodophenol or 2-iodophenol derivatives, where the phenolic hydroxyl group is crucial for controlling the migration direction and determining the ring size of the heterocycles by forming a quinone methide intermediate. The approach could be employed for increasing the molecule complexity via the late-stage incorporation of heterocyclic scaffolds into complex drug molecules, and for the efficient synthesis of serval bioactive compounds. Undoubtably, this new approach has the potential to impact the fields of synthetic and medicinal chemistry significantly by providing a robust, versatile, and efficient strategy for constructing diverse complex heterocyclic structures.

Results and discussion

Inspired by quinone methide intermediate-enabled Pd-catalysed alkene difunctionalisations[37, 52-53], we hypothesized that the control of migratory orientation during chain-walking process might be realized by the irreversible formation of a quinone methide intermediate via the sequential 1,1-migration and Pd–H elimination under basic conditions, thus overcoming the challenges for the diverse synthesis of heterocycles though a thermodynamically unfavourable metallacycle, thus enabling the migratory 1,1-cycloannualation reaction (Fig. 2a). As depicted in Fig. 2a, the palladium catalyst could rapidly migrate to the α-position of benzylic position (**Int-III**) via a rapid β-hydrogen elimination and reinsertion process, following the migratory insertion of alkene into aryl-Pd(II) species generated by the oxidative addition of 4-iodophenol with Pd(0). Subsequently, the intermediate **Int-III** could be rapidly transformed into the corresponding quinone methide intermediate **Int-IV** in the presence of base via Pd–H elimination. The desired



Entry	Deviation from conditions	3a (%)	3a/3a'
1	None	78	11.1/1
2	w/o $^{n}Bu_4NCl$	36	5.1/1
3	MeOH instead of $^{i}PrOH$	66	13.2/1
4	$^{t}BuOH$ instead of $^{i}PrOH$	70	8.8/1
5	$^{t}AmlyOH$ instead of $^{i}PrOH$	76	8.4/1
6	DMF instead of $^{i}PrOH$	66	4.4/1
7	Dioxane instead of $^{i}PrOH$	62	3.6/1
8	$^{n}Bu_4NBr$ instead of $^{n}Bu_4NCl$	70	7.8/1
9	$^{n}Bu_4NI$ instead of $^{n}Bu_4NCl$	42	3.5/1

Fig. 2 | Pd-catalysed migratory 1,1-cycloannulation of unactivated alkenes. a, Proposed catalytic cycle. **b**, Reaction parameters evaluation. **c**, Control experiments with various aryl iodides. **d**, Deuterium experiments. DMF, *N*,*N*-dimethylformamide; Me, methyl; Et, ethyl; Pr, propyl; Ph, phenyl; Bu, butyl; Ar, aryl; dba, dibenzylideneacetone.

1,1-cycloannulation product could be obtained by intramolecular aza- or oxa-Michael addition. To check the feasibility of this approach, 4-iodophenol was employed to react with *N*-(pent-4-en-1-yl)aniline **1a** in the presence of $Pd_2(dba)_3$, $(n\text{-Bu})_4NCl$ in DMF. Although the migratory 1,1-cycloannulation did happen, both six- and five-membered cyclic compounds **3a** and **3a'** were observed with poor regioselectivity (*rr* = 4.4/1.0) (Entry 6, Fig. 2b). The formation of 2-methyl-pyrrolidine **3a'** originates from the poor regioselectivity control in the aryl-Pd(II) insertion step, which further confirmed the challenges for the realization of migratory 1,1-cycloannulation though a thermodynamically unfavourable larger metallacycle. To our great delight, the regioselectivity could be significantly improved when the alcoholic solvents were employed (Entries 1, 3-5), and $^{i}PrOH$ gave the desired six-membered cyclic compounds in 78% yield with a ratio of 11.1/1.0 after systematically evaluation of the reaction parameters (Entry 1). Although the less

steric hindrance MeOH could gave the best regioselectivity (13.2/1.0 *rr*), the yield decreased to 66% (Entry 3). Lower *rr* were observed in ^{t}BuOH and ^{t}Amyl-OH in comparison to MeOH and ^{i}PrOH (Entries 4, 5). With acidic solvent HFIP, the cyclic products were not observed. Moreover, $^{n}Bu_4NCl$ additive plays an important role in reaction efficiency and selectivity, only 36% yield of **3a** and 5.1/1 *rr* were observed in the absence of $^{n}Bu_4NCl$ (Entry 2), and the replacement of $^{n}Bu_4NCl$ by $^{n}Bu_4NBr$ and $^{n}Bu_4NI$ resulted in both lower yields and lower regioselectivities (Entries 7 and 8).

Preliminary mechanistic studies were carried out to shed lights on the mechanism of this Pd-catalysed migratory 1,1-cycloannulation reaction. The migratory cycloannulation reaction could only happen by employing the *para*- and *ortho*-phenoxy substituted aryl iodides, while *m*-iodophenol and simple iodobenzene could only give Heck-type byproducts (Fig. 2b). Those control experiments confirm the importance of phenoxy group, which complies our rational design. Terminal deuterated alkene **D-1a** was performed under the cyclization conditions, the corresponding deuterated product **D-3a** was obtained in 32% yield. The deuterium distributed at the terminal and its adjacent position (Fig. 2d), which illustrates the metal walking process via a β-H elimination and reinsertion process. Besides, when the internal C3-deuterated alkene **D-5a** was employed in this reaction, no deuterium atom migration happened in the target pyrrolidine product **D-6a**. Those deuterated reactions indicated that metal walking process was strongly controlled by the use of 4-iodophenol, which might be explained by the irreversible formation of a quinone methide intermediate.

Following the preliminary exploration of the Pd-catalysed migratory 1,1-cycloannulation reaction, we evaluated the generality of this methodology for preparing a range of azaheterocyclic compounds (Fig. 3). The versatility and efficiency of this approach was demonstrated by the successful synthesis of various heterocycles, including both common and more structurally complex molecules. The reaction successfully generated 2-aryl-substituted piperidine derivatives (**3a-3c**) in high yields, demonstrating the efficiency of the method for constructing six-membered azaheterocycles. Additionally, geminal dialkyl groups on

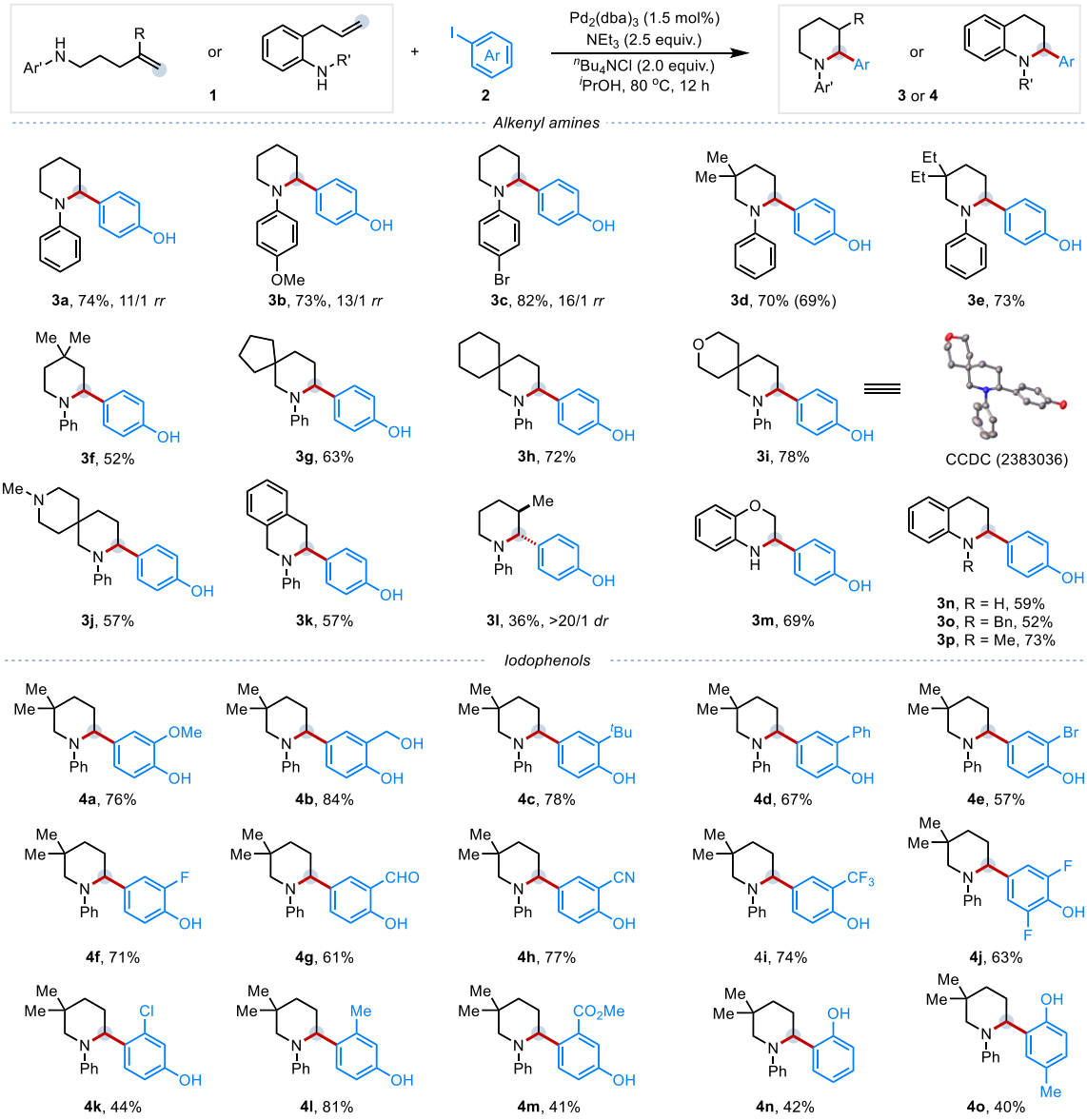


Fig. 3 | The synthesis of six-membered azaheterocycles via Pd-catalysed migratory 1,1-cycloannulation. The values under each structure indicate isolated yields (See Supplementary Information for experimental details). The *rr* and *dr* were determined by ^{1}H NMR analysis of crude product, and *rr* > 20/1 except where noted. Me, methyl; Et, ethyl; Pr, propyl; Ph, phenyl; Bu, butyl; Bn, benzyl; Ar, aryl; dba, dibenzylideneacetone.

different positions of the alkene chain (**3d-3f**) were well-tolerated under the mild reaction conditions, providing the desired products in moderate to good yields (52%-73%). The strategy was also effective for the synthesis of various spirocyclic heterocycles with high regioselectivities and yields, including spiro[4.5]decane (**3g**), azaspiro[5.5]undecane (**3h**), oxa-azaspiro[5.5]undecane (**3i**), and diazaspiro[5.5]undecane (**3j**). These results highlight this method's capacity to construct complex spirocyclic frameworks that are challenging to synthesize through conventional methods. The protocol also

tolerates a 1,1-disubstituted terminal alkene (**1l**), producing the desired product **3l** with excellent diastereoselectivity, albeit with a moderate yield. In addition, benzomorpholine (**3m**) was synthesized in 69% yield, and six-membered tetrahydroquinoline derivatives (**3n**-**3p**) can also be observed in great yields. The substituent effects on the iodophenol moiety were next systematically investigated, revealing that a wide range of substituents, including alkyl (**4c**, **4l**), methoxyl (**4a**), alkanol (**4b**), halogen (**4e**, **4f**, **4j**, **4k**), phenyl (**4d**), trifluoromethyl (**4i**), formyl (**4g**), cyano (**4h**), and ester (**4m**), were all well-tolerated in good to high yields. When 2-iodophenol derivatives (**4n**, **4o**) were evaluated, lower yields were observed probably due to the steric hindrance in the alkene migratory insertion step.

Building upon the aforementioned success on the synthesis of piperidine derivatives, further investigations focused on expanding the scope to synthesize a variety of azaheterocycles and oxaheterocycles with different sizes and types (Fig. 4). Five-membered cyclisation product **6a**, (4-(1-phenylpyrrolidin-2-yl)phenol, was obtained in lower yield starting from *N*-(but-3-en-1-yl)aniline with 4-iodophenol under the standard conditions (See Supplementary Information for more details). When BINOL-derived bisphosphate **L1** was employed as ligand, Na_2CO_3 as base in DMF, the five-membered cyclization product **6a** was given as the single cyclization product in 65% yield. This comprehensive exploration revealed this method's broad applicability and remarkable functional group tolerance, providing access to diverse five- and seven-membered heterocycles. Various substituted aryl amines were efficiently converted into their corresponding five-membered pyrrole derivatives (**6a-6z**) under the optimized conditions, generally yielding moderate to high yields. Substrates bearing various halogen substituents, including bromide, fluoride, and chloride (**6b-6d**), gave the desired products in moderate yields with complete retention of the halogen, demonstrating the mildness of the reaction conditions. Both electron withdrawing and electron donating substituents can be tolerated under the mild conditions giving corresponding pyrrole derivatives in high yields, including *t*-butyl (**6e**), trifluoromethyl (**6f**), ester (**6g**), nitro (**6h**) and piperonyl (**6i**). Alkenyl amines bearing more complex aryl group gave the desired products in 50%-56% yields, including mesityl (**6j**) and tetrahydronaphthalen-1-yl (**6k**), 1-naphthalenyl (**6l**), and 2-naphthalenyl (**6m**). The excellent compatibility with a wide range of heteroaryl groups is also noteworthy,

including indole (**6n**), quinoline (**6o**, **6p**), pyridine (**6q**), and oxazole (**6r**). These substrates yielded the desired heterocycles efficiently, showcasing the versatility of the method.

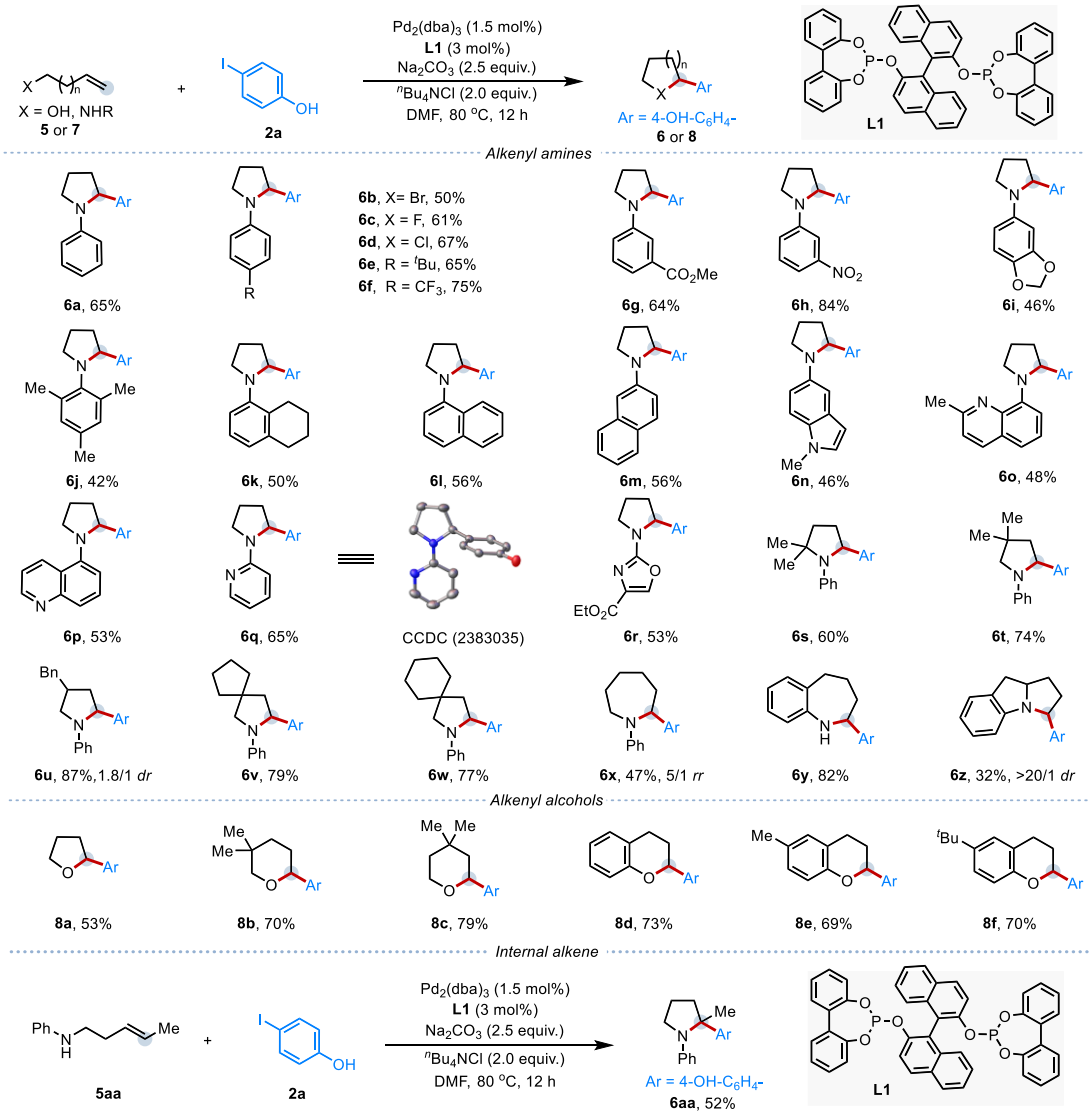


Fig. 4 | The synthesis of azaheterocycles and oxaheterocycles via Pd-catalysed migratory 1,1-cycloannulation. The values under each structure indicate isolated yields (See Supplementary Information for experimental details). The *rr* and *dr* were determined by ^{1}H NMR analysis of crude product, and *rr* > 20/1 except where noted. DMF, *N*,*N*-dimethylformamide; Me, methyl; Et, ethyl; Ph, phenyl; Bu, butyl; Ar, aryl; dba, dibenzylideneacetone.

Various alkyl substitutions on the alkene chain were also tolerated in high efficiency, including *gem*-dimethyl (**6s**, **6t**), benzyl (**6u**), cyclopentyl (**6v**), and cyclohexyl (**6w**) groups. Similar to the synthesis of spirocyclic piperidines, this method is also suitable for the synthesis of spirocyclic pyrrole derivatives, including azaspiro[4.5]decane (**6v**) and azaspiro[4.4]nonane (**6w**), from simple starting materials. To our great delight, seven-membered azepane (**6x**) and tetrahydrobenzo[*b*]azepine (**6y**) could also be synthesized

in 47% and 82% yields respectively, further illustrating the method's utility for synthesizing larger ring systems. Tricyclic compound tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (**6z**) was synthesized in 32% yields with >20/1 *dr*. More importantly, internal alkene is effective in this reaction, providing the corresponding pyrrole derivative (**6aa**) bearing a tertiary carbon centre in 52% yield.

To further demonstrate the applicability of this methodology for the preparation of oxaheterocycles, a series of alkenyl alcohols and phenols were investigated. Five-membered 2-aryl-substituted tetrahydrofuran (**8a**), six-membered tetrahydropyran (**8b**-**8c**), six-membered chromane (**8d**-**8f**) could be easily accessed via the current Pd-catalysed migratory 1,1-cycloannulation of unactivated alkenes. The exploration of oxaheterocycles further underscores the robustness of this approach, expanding its potential applications in the synthesis of complex bioactive molecules and materials.

Given the importance of aliphatic heterocycles in drug discovery by enhancing the pharmacokinetic and binding properties of therapeutic compounds, we have conducted the installation of azaheterocycles into the marketed drugs and bioactive molecules. As showed in Fig. 5a, a pyrrole motif was efficiently introduced into aminoglutethimide (**10a**), apixaban (**10b**), coumarin (**10c**) and a bioactive molecule GRL067 (**10d**). Moreover, this newly developed methodology could provide more efficient, and sustainable routes to construct complex molecular architectures, enabling the rapid discovery and optimisation of pharmaceuticals, agrochemicals, and materials. For instance, 2-aryl tetrahydroquinoline derivative **13** could be efficient synthesized in two steps using our method as the key step, which could efficiently convert to a selective estrogen receptor modulator (SERM)[54] **16** in two steps. Furthermore, ERβ ligands **17** and **18**[55] were obtained by the oxidative aromatization of 2-aryl tetrahydroquinoline derivative **13**, respectively. Notably, oxaheterocycle-containing bioactive molecule cytotoxic flavan **21** was synthesized within one step by taking advantage of our Pd-catalysed MCAR reaction[56]. Similarly, oxazolinylflavan **24** with antipoliovirus activity could be efficiently synthesized in three steps starting from commercially available 2-allyl-4-chlorophenol[57].

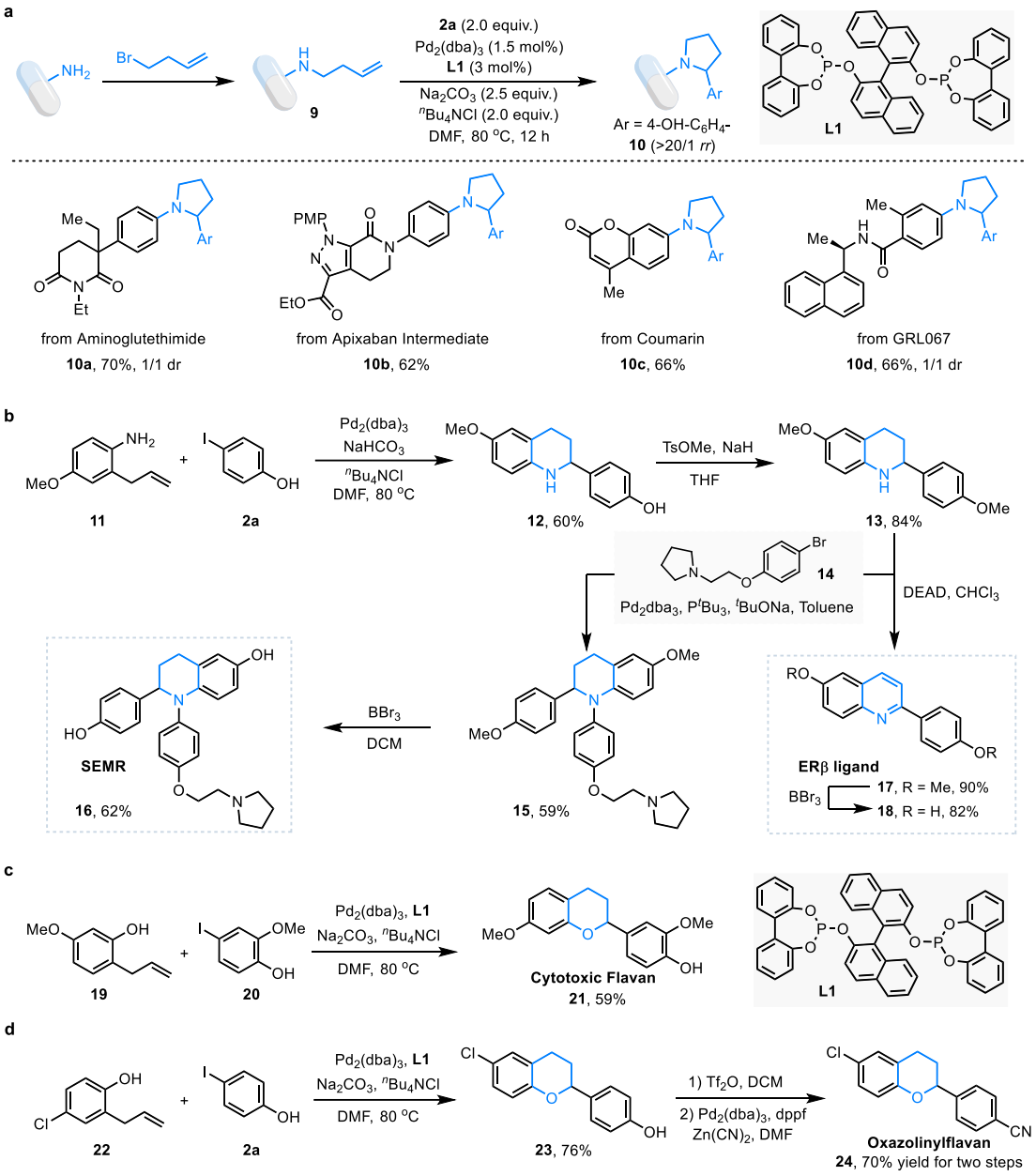


Fig. 5 | Synthetic applications of Pd-catalysed migratory 1,1-cycloannulation. a, Late-stage installation of azaheterocycle motif in bioactive scaffolds. **b**, Synthesis of a potential selective estrogen receptor modulator (SERM) and ERβ ligands. **c**, Preparation of cytotoxic flavan. **d**, Preparation of oxazolinylflavan. DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; DCM, dichloromethane; dppf, 1,1-bis(diphenylphosphino)ferrocene; Me, methyl; Et, ethyl; Ph, phenyl; Bu, butyl; dba, dibenzylideneacetone; Ts, *para*-toluenesulfonyl; Tf, trifluoromethanesulfonic; PMP, 4-methoxyphenol.

In summary, we have developed a palladium catalysed migratory 1,1-cycloannulation of unactivated alkenes to efficiently construct a variety of five to seven-membered azaheterocycles and oxaheterocycles. The hydroxyl group plays a pivotal role in the determining the ring size of the heterocycles by controlling migratory steps and enabling the formation of quinone methide intermediates. The ability to tolerate various substituents and functional groups under mild conditions, combined with high efficiency and

regioselectivity, underscores the potential of this method as a valuable tool in both synthetic and medicinal chemistry for the preparation of complex bioactive molecules.

Methods

General procedure for Pd-catalysed 1,1-migratory cycloannulation of unactivated alkenes: To a 10 mL tube in a glovebox, iodophenols (0.4 mmol), $Pd_2(dba)_3$ (2.8 mg, 1.5 mol%), and $^{n}Bu_4NCl$ (111.2 mg, 0.4 mmol) were added. The tube was sealed with a cap fitted with a PTFE liner and transferred outside of the glovebox. Then, isopropanol ($^{i}PrOH$, 2.0 mL) was added to the mixture, followed by the addition of NEt_3 (70 μL, 0.5 mmol) and alkenes (0.2 mmol). The reaction mixture was stirred at 80 °C for 12 hours. After the reaction mixture was cooled to room temperature, it was diluted with ethyl acetate (EtOAc) and filtered through a pad of silica to remove any insoluble material. The organic phase was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel or preparative thin-layer chromatography (TLC), as indicated. Full experimental details and the characterization data for all new compounds can be found in the Supplementary Information.

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Data Availability

All information relating to optimization studies, experimental procedures, mechanistic studies, NMR spectra and high-resolution mass spectrometry are available in the Supplementary Information. X-ray structural data of compound **3i** (CCDC (2383036) and **6q** (CCDC (2383035) are available free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. All other data are available from the corresponding authors upon request.

Supplementary Information is available in the online version of the paper.

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