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Pd-catalyzed sequential distal C–H alkenylation and π-allylic amination of arylacetic acids using MBH acetates: access to macrocyclic lactams

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Palladium(II)-catalyzed directed *meta*-selective C–H functionalization of arylacetic acids has been accomplished utilizing Morita–Baylis–Hillman (MBH) acetates as the coupling partner to furnish β-aryl MBH acetates that can be converted into 14-membered macrocyclic lactams employing water as the oxygen source *via* a π-allyl intermediate. The sequential *meta*/*meta*′ C–H difunctionalization can be accomplished with varied coupling partners. Mechanistic investigations underscore the roles of the nitrile-directing template, palladium(II)-catalysis and ligand in *meta*-selectivity. The macrocyclization pathway has been validated through an ^{18}O-labeling experiment and the photophysical studies reveal distinct fluorescence in the selected macrocycles. In addition, the selected lactams exhibited biocompatibility with Vero cells and dose-dependent cytotoxicity against MCF-7 cells, highlighting their therapeutic potential. The substrate scope, functional group tolerance, selectivity, photophysical and biological properties, and the late-stage functionalization of drug molecules as well as natural product derivatives are important practical features.

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Introduction

Transition-metal-catalyzed carbon–carbon bond formation *via* direct C–H functionalization has emerged as a powerful synthetic tool in modern organic chemistry,[1] enabling efficient and straightforward construction of molecular architectures relevant to natural products, pharmaceuticals and advanced materials.[2] In this context, owing to the ubiquity of C–H bonds in organic molecules, achieving site-selective functionalization is a challenging goal.[3] Thus, there has been a significant surge of interest towards developing effective synthetic strategies to functionalize the unreactive C–H bonds.[4] While the directing group (DG) approach has delivered significant outcomes for reactions at proximal C–H bonds,[5] distal functionalization remains a long-standing goal due to thermodynamic instability of the comparatively fluxional metallacycle intermediates.[6] Contextually, subsequent modifications in the geometry as well as the structure and electronic nature of DGs have resulted in several successful distal functionalizations.[7] However, owing to the significant reliance of these approaches on the rigidity of the transition-state, the template-based pathways are mostly confined to relatively shorter chain aryl-alkanoic acids wherein the distal C–H bond is proximal and accessible.[8] In contrast, in the case of substrates with longer alkyl chains, the DG dangles more freely, thereby making it entropically challenging to carry out the activation and functionalization of the C–H bond at a remote site. Interestingly, nitrile-based templates have opened new avenues in distal C–H bond functionalization,[9] and showed promising potential in the synthesis of macrocyclic scaffolds, offering advantages in terms of step and atom economy, highlighting their growing relevance in synthetic applications.[10] However, while previous reports depict the utilization of these templates solely as DGs, which are removed subsequently after the C–H functionalization, their use as a functional handle in achieving macrocyclization remains unexplored. Considering the widespread presence of the arylacetic acid motif in therapeutics such as ibuprofen, ketoprofen, oxybutynin and glycopyrrolate,[11] their utilization to access the less explored macrocyclic chemical space would be valuable. Moreover, C–H functionalization with MBH adducts offers an ideal platform, allowing the conversion of simple and inexpensive building blocks into structurally diverse frameworks. Although, they have been known for their role in *ortho*-selective functionalization,[12] their utilization in distal functionalization is yet to be studied (Fig. 1a). Utilizing MBH adducts for achieving remote alkenylation and exploiting the tethered acetate towards achieving late-stage lactamization would be of wider interest.[13] Recently, the Yu group elegantly showed a Pd-catalyzed *meta*-selective C–H functionalization using an indolyl template for macrocyclization (Fig. 1b),[10] while Yang and co-workers reported a Rh-catalyzed macrocyclization employing the *ortho*-selective C–H functionalization of arenes with MBH adducts

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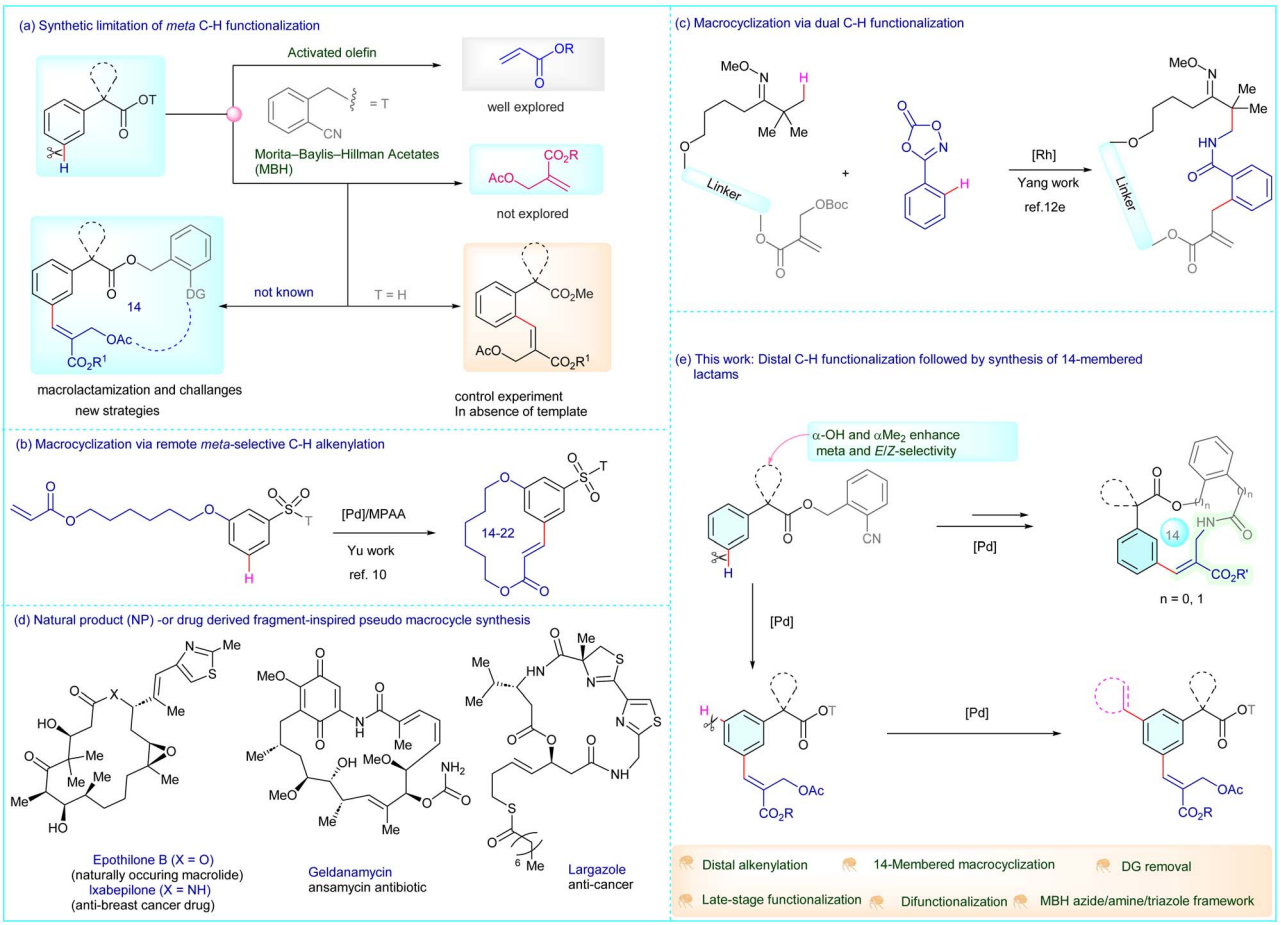


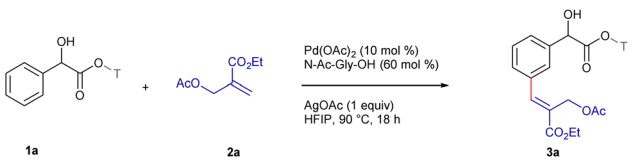
Fig. 1 Pharmaceutical importance of macrocyclic compounds and development of synthetic strategies for macrocyclization.

(Fig. 1c).[12e] This is particularly attractive as they play a crucial role in drug discovery with natural product-based fragments contributing to the progress of therapeutics such as largazole, geldanamycin, epothioline B and Ixabepilone (Fig. 1d).[14] Herein, we report a Pd(II)-catalyzed *meta*-selective C–H functionalization of α-hydroxy arylacetic acids with MBH acetates to afford β-aryl MBH acetates that can be cyclized employing Pd(II)-catalysis to furnish 14-membered lactams. The procedure can be extended for *meta*/*meta*′ C–H difunctionalization with diverse coupling partners (Fig. 1e). The selectivity, substrate scope, functional group tolerance, application to access macrocyclic lactams, difunctionalization and synthetic potential are important practical features.

Results and discussion

We began the optimization studies utilizing α-hydroxy arylacetic acid (mandelic acid, **1a**) with MBH acetate **2a** as the model substrates (Tables 1 and S1–S5, SI). To our delight, the *meta*-selective C–H alkenylation occurred to furnish β-aryl MBH acetate **3a** (template **T1**) in 79% yield with 33 : 1 *E*/*Z*-selectivity as the sole product without affecting the *ortho*-C–H bond, when

Table 1 Optimization of reaction parameters[a]



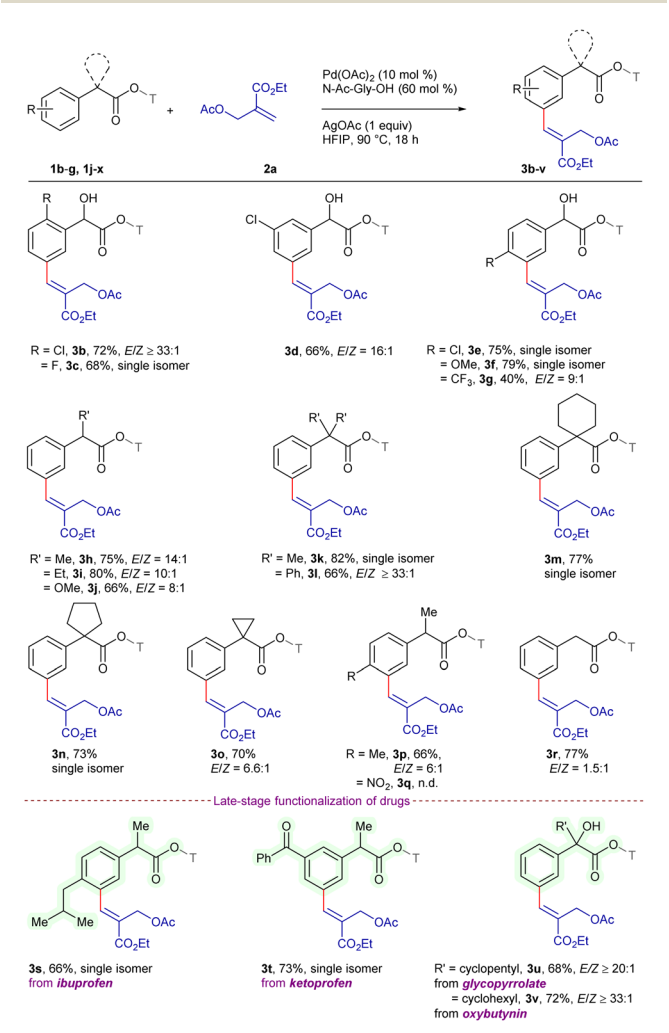
Entry	Deviation from standard conditions	Yield (%)[b] (*E*/*Z*)[c]
1	None	79 (33 : 1)
2	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	35 (33 : 1)
3	N-Ac-L-Leu-OH instead of N-Ac-Gly-OH	40 (33 : 1)
4	Fmoc-Gly-OH instead of N-Ac-Gly-OH	47(25 : 1)
5	Ag_2CO_3 instead of AgOAc	72 (33 : 1)
6	AgTFA instead of AgOAc	51 (33 : 1)
7	$(CH_2Cl)_2$ instead of HFIP	33 (1 : 2)
8	TFE instead of HFIP	Trace

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (60 mol%), AgOAc (0.1 mmol), HFIP (1 mL), 90 °C, 18 h, air, pressure tube. [b] Isolated yield. [c] Determined by 400 MHz ^{1}H NMR. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol. TFE = 2,2,2-trifluoroethanol.

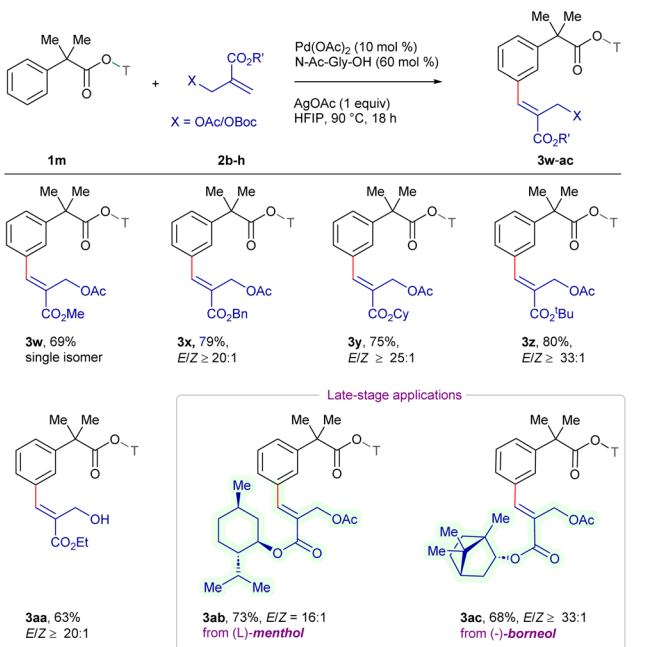
the substrates **1a** and **2a** were stirred with $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (60 mol%) and AgOAc (1 equiv.) at 90 °C for 18 h in HFIP. Among the templates screened, **T1** exhibited the best results, while **T4** and **T5** produced 56% and 59% yields, respectively (Table S1, SI). In contrast, template **T2** without the nitrile DG was an unsuccessful substrate. A similar result was observed with **T3** having the nitrile DG at the third position of the aryl ring. The use of $Pd(TFA)_2$ in place of $Pd(OAc)_2$ led to a drop in the yield to 35% (Entry 2). Of the amino acid ligands studied, N-Ac-Gly-OH, N-Ac-L-Leu-OH and Fmoc-Gly-OH, the former yielded the best outcome (Entries 3 and 4). The reaction utilizing AgOAc was superior to that of Ag_2CO_3 and AgTFA (entries 5 and 6). HFIP was the solvent of choice, whereas $(CH_2Cl)_2$ and TFE gave inferior results (Entries 7 and 8). Control experiments confirmed that the combination of the Pd(II)-catalyst, template and ligand was crucial to achieve selective functionalization.

Having optimized the reaction conditions, we next explored the substrate scope using a series of α-substituted arylacetic acids utilizing **2a** as the standard substrate (Scheme 1). Notably, the substrates bearing *ortho*-substituents such as chloro **1b** and fluoro **1c** reacted to deliver the *meta*-alkenylated products **3b** and **3c** in 72% and 68% yields, respectively, with ≥33 : 1 *E*/*Z*-selectivity. The reaction of *meta*-chloro substituted **1d** gave **3d** in 66% yield with an *E*/*Z* ratio of 16 : 1, while the substrates having chloro **1e** and methoxy **1f** groups at the *para*-position reacted to furnish **3e** and **3f** in 75% and 79% yields, respectively, with *E*-selectivity. Furthermore, 4-trifluoromethyl-substituted **1g** coupled to furnish **3g** in moderate yield with a 9 : 1 *E*/*Z* ratio, which might be due to the electron withdrawing nature of the substituent. However, the substrates with methyl **1j**, ethyl **1k** and methoxy **1l** substituents at the α-position delivered the target scaffolds **3h–j** in 66–80% yields with ≥8 : 1 *E*/*Z*-selectivity. In addition, bulky α-substituents, dimethyl **1m**, diphenyl **1n**, spirocyclohexyl **1o**, spirocyclopentyl **1p**, spirocyclopropyl **1q**, and α-methyl-4-methyl **1r** were compatible, furnishing **3k–p** in 66–82% yields with ≥6 : 1 *E*/*Z*-selectivity. In contrast, the reaction of α-methyl-4-nitrophenylacetic acid **1s** failed to deliver **3q**, which might be due to the chelation of the nitro group with the Pd-catalyst. However, arylacetic acid **1t** underwent reaction to afford **3r** in 77% yield, albeit, with an *E*/*Z* ratio of 1.5 : 1. This may be attributed to the absence of α-substitution on the arylacetic acid, thereby leading to greater DG-*meta* distance. Furthermore, the reaction of substrates bearing ibuprofen **1u** and ketoprofen **1v** furnished **3s** and **3t** in 66% and 73% yields, respectively, with *E*-selectivity, while the reaction of glycopyrrolate and oxybutynin afforded **3u** and **3v** in 68% and 72% yields, respectively, with ≥20 : 1 *E*/*Z*-selectivity.

The scope of the procedure was extended for a series of MBH acetates **2b–h** using **1m** as the standard substrate (Scheme 2).



Scheme 1 Scope of α-substituted arylacetic acids.[a,b,c,d] [a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (60 mol%), AgOAc (0.1 mmol), HFIP (1 mL), 90 °C, 18 h, air, pressure tube. [b]Isolated yield. [c]Determined by 400 MHz ^{1}H NMR. [d]n. d. = not detected.



Scheme 2 Scope of MBH acetates.[a,b,c] [a]Reaction conditions: **1m** (0.1 mmol), **2** (0.12 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (60 mol%), AgOAc (0.1 mmol), HFIP (1 mL), 90 °C, 18 h, air, pressure tube. [b]Isolated yield. [c]Determined by 400 MHz ^{1}H NMR.

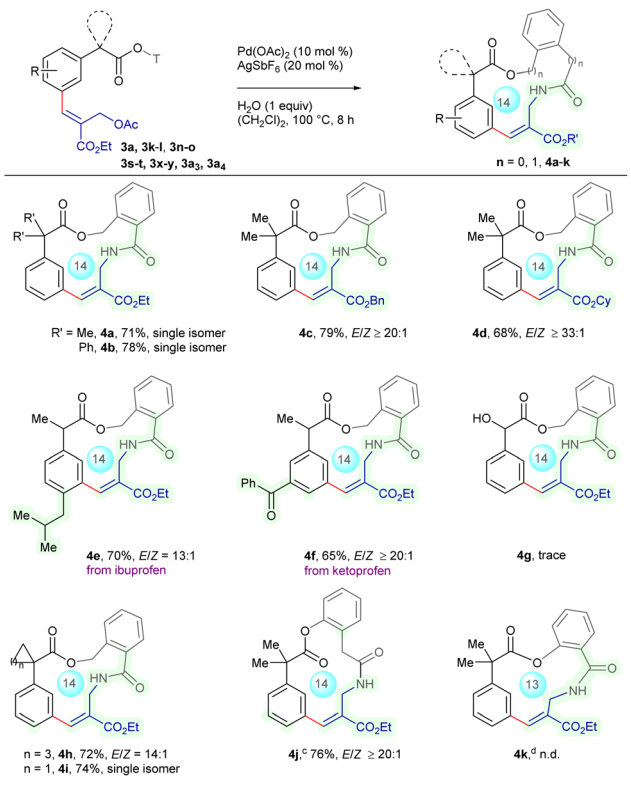
MBH acetates bearing alkyl groups such as methyl **2b**, benzyl **2c**, cyclohexyl **2d** and *tert*-butyl **2e** demonstrated excellent compatibility, furnishing **3w–z** in 69–80% yields with ≥20 : 1 *E*/*Z*-selectivity. Furthermore, Boc-protected **2f** reacted to deliver **3aa** in 63% yield, where the protecting group underwent hydrolysis to yield the alcohol. In addition, the reaction of MBH acetates derived from naturally occurring L-menthol **2g** and (−)-borneol **2h** gave **3ab** and **3ac** in 73% and 68% yields with ≥16 : 1 *E*/*Z*-selectivity, showcasing the synthetic potential for diversification of natural product derivatives.

Having established the *meta*-selective C–H functionalization, we turned our attention towards macrocyclic lactamization incorporating the arylacetic acid motif (Scheme 3). Gratifyingly, the macrocyclization proceeded employing $Pd(OAc)_2$ (10 mol%), $AgSbF_6$ (20 mol%) and H_2O (1 equiv.) in $(CH_2Cl)_2$ at 100 °C for 8 h to deliver **4a** in 71% yield with *E*-stereochemistry (Table S6, SI). A similar result was observed with α-disubstituted **3l** to afford **4b** in 78% yield with *E*-selectivity. This strategy could be extended to the substrates with benzyl **3x** and cyclohexyl **3y** substituents to produce **4c** and **4d** in 79% and 68% yields, respectively, with ≥20 : 1 *E*/*Z*-selectivity. Moreover, α-substituted arylacetic acids derived from ibuprofen **3s** and ketoprofen **3t** analogues reacted to produce **4e** and **4f** in 70% and 65% yields, respectively, with ≥13 : 1 *E*/*Z*-selectivity, whereas attempts to introduce structural complexity by replacing the α-methyl group with a hydroxy group resulted in a trace amount of **4g**, which might be due to an unfavorable electronic effect impeding the cyclization. Furthermore, α-spirocyclopentyl **3n** and α-spirocyclopropyl **3o** underwent cyclization to afford **4h** and **4i** in 72 and 74% yields, respectively, with ≥14 : 1 *E*/*Z*-selectivity, highlighting the compatibility with sterically hindered spirocyclic substrates. Moreover, substrate $\mathbf{3a_3}$ cyclized to deliver **4j** in 76% yield with ≥20 : 1 *E*/*Z* selectivity, whereas $\mathbf{3a_4}$ failed to furnish **4k**, possibly due to less efficient formation of the key π-allyl palladium intermediate.

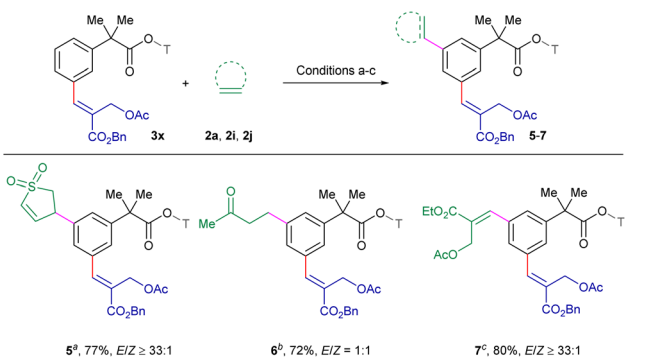
The scope of the procedure was further examined for the sequential *meta*/*meta*′ C–H difunctionalization employing **3x** as a representative example to expand the synthetic utility (Scheme 4). Delightfully, 2,5-dihydrothiophene-1,1-dioxide **2i** reacted to deliver **5** in 77% yield with ≥33 : 1 *E*/*Z*-selectivity. In addition, alkylation employing but-3-en-2-ol **2j** furnished β-aryl ketone **6** in 72% yield with a 1 : 1 mixture of *E*/*Z*-isomers, which might be due to the non-conjugated nature of the alkyl group, while the reaction with **2a** produced **7** in 80% yield with ≥33 : 1 *E*/*Z*-selectivity, demonstrating the versatility of procedure across multiple class of electrophiles.

To assess the scalability of the procedure, the reaction of **1m** with **2c** was investigated as a representative example on 1 mmol scale (Scheme 5). The reaction occurred to deliver **3x** in 76% yield (304.8 mg). Furthermore, to demonstrate the removability of the nitrile template, hydrolysis of **3w** was carried out utilizing LiOH in a mixture of THF, MeOH and H_2O to provide carboxylic acid **8** in 78% yield, which can be hydrogenated to furnish *meta*-alkylated **9** in 80% yield. Moreover, the cross-coupling of **3x** with phenyl boronic acid replaced the acetate moiety to afford **10** in 73% yield with an *E*/*Z*-selectivity of 5.2 : 1, while the acetate group was substituted with HFIP using NaOTf to furnish ether-linked **11** in 86% yield. In addition, the Pd-catalyzed azidation of **3k** with NaN_3 afforded **12** in 86% yield, which could be reduced *via* a Staudinger reaction to deliver amine derivative **13** in 69% yield, while a Cu(I)-catalyzed click reaction with phenylacetylene afforded triazole scaffold **14** in 89% yield.

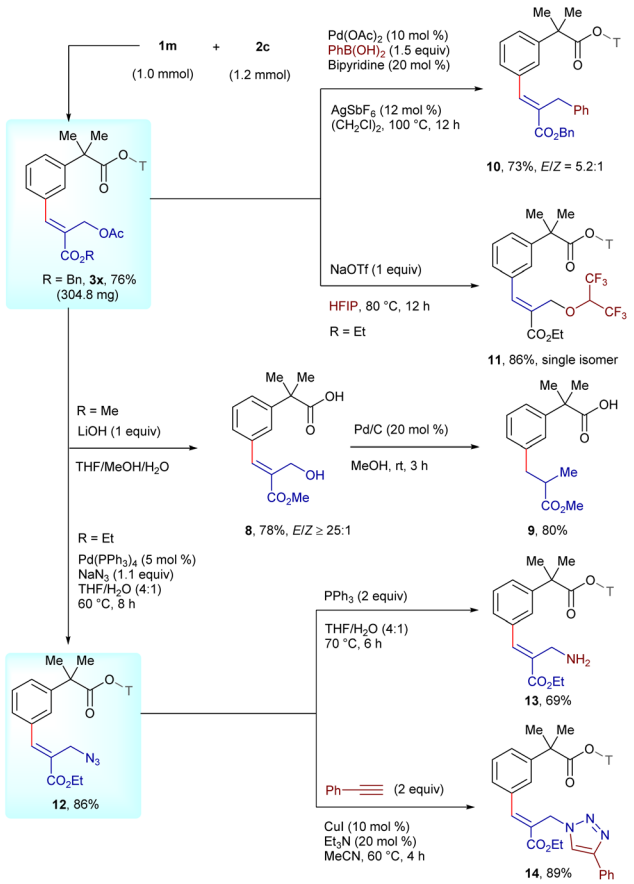
To gain insight into the reaction pathway, deuterium labeling and kinetic isotope experiments were performed



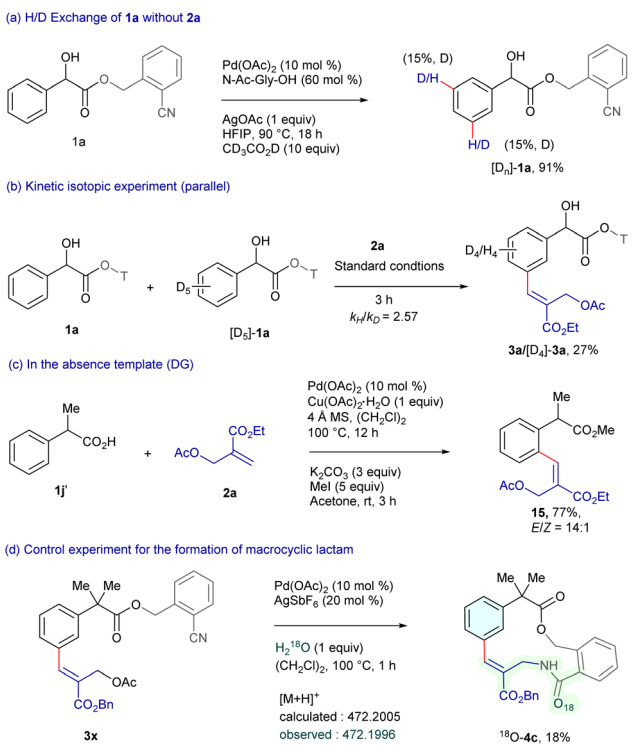
Scheme 3 Scope of macrocyclic lactams.[a,b,c,d,e] [a]Reaction conditions: **3** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), $AgSbF_6$ (20 mol%), H_2O (0.1 mmol), $(CH_2Cl)_2$ (1 mL), 100 °C, 8 h, air, pressure tube. [b]Isolated yield. [c]$\mathbf{3a_3}$ has been used (please see Table S1). [d]$\mathbf{3a_4}$ has been used (please see Table S1). [e]Determined by 400 MHz ^{1}H NMR.



Scheme 4 Scope of sequential distal C–H functionalization. [a]Reaction conditions: **3x** (0.1 mmol), **2i** or **2a** (0.12 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (20 mol%), AgOAc (0.1 mmol), HFIP (1 mL), 90 °C, 18 h, air, pressure tube. [b]**3x** (0.1 mmol), **2j** (0.12 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (20 mol%), Ag_2CO_3 (0.25 mmol), HFIP (1 mL), 90 °C, 18 h, air, pressure tube. [c]Isolated yield.



Scheme 5 Removal of the template and synthetic utilities.



Scheme 6 Mechanistic studies.

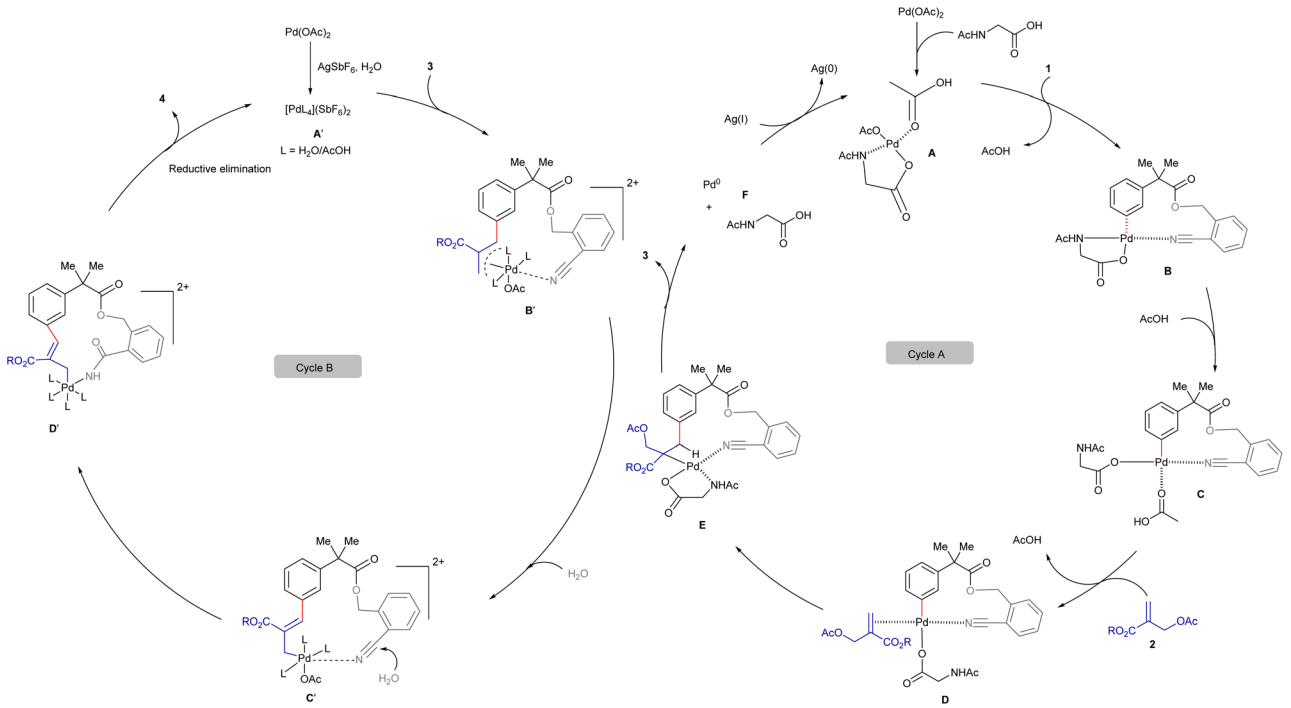
(Scheme 6). Treatment of substrate **1a** with CD_3CO_2D resulted in 15% deuterium incorporation at the *meta*-position, indicating that C–H bond cleavage might be reversible (Scheme 6a). Furthermore, the intermolecular kinetic isotope experiment (KIE) of **1a** with [D_5]-**1a** exhibited $k_H/k_D = 2.57$, suggesting that C–H bond cleavage might be the rate-limiting step (Scheme 6b). Moreover, the reaction of arylacetic acid **1j′** with **2a** employing 10 mol% $Pd(OAc)_2$ and 1 equiv. $Cu(OAc)_2 \cdot H_2O$ in $(CH_2Cl)_2$, followed by *in situ* esterification furnished **15** in 77% yield (Scheme 6c).[15] This outcome suggests that the nitrile template plays a crucial role in selective C–H functionalization. In addition, the $H_2{}^{18}O$ experiment (detected *via* HRMS) suggests that water acts as the oxygen source in the macrocyclic lactam formation (Scheme 6d).

The observed experimental results and literature precedent[16] suggest that the substrate **1** can undergo a weak chelation with the Pd(II)-complex **A** to form **B**, bringing the metal in close proximity to the *meta*-C–H bond (cycle **A**, Scheme 7). Subsequently, the cleavage of the C–H bond can lead to the formation of palladacycle **C** *via* a concerted metalation and deprotonation (CMD) process. The coordination of **C** with the double bond of **2** can produce **D** that can lead a 1,2-migratory insertion to furnish **E**. The β-hydride elimination can yield the alkenylated **3** and Pd(II)-species, which can undergo reductive elimination to generate the Pd(0) species **F** and HX as a by-product. However, β-acetate elimination was not observed, likely due to the geometric and electronic constraints of metallacycle **E** (ref. 16*c*, 16d, 16f and 16g). The external oxidant AgOAc plays a crucial role in oxidizing Pd(0) to Pd(II), thereby facilitating the regeneration of the active Pd(II)-catalyst for the subsequent catalytic cycle.

The second catalytic cycle of the macrocyclization is depicted in cycle **B** (Scheme 7).[17] Initially, the Pd(II)-species **A′** reacts with **3** to produce the Pd-π-allyl-complex **B′** that can lead to the formation of the palladacycle **C′**. Hydration of the chelated C–N triple bond can produce **D′** that can undergo reductive elimination to deliver the 14-membered lactam **4**, concurrently regenerating the Pd(II)-species **A′**.

The photophysical properties of the selected macrocyclic lactams were investigated due to their conjugated framework. UV-vis and fluorescence studies (in CH_3CN) revealed emission maxima at λ_{em} 340 nm (Fig. S2, SI), indicating the high-energy excited state characteristic of the aromatic macrocycles. Notably, lactam **4a** exhibited a red-shifted emission, which suggests the intramolecular charge transfer (ICT), while the products **4c–f** showed negligible shifts, implying the limited ICT contributions.[18]

Furthermore, the biocompatibility and cytotoxicity of **4a** and **4e–f** were evaluated as representative examples using MTT assays against Vero and MCF-7 cells. Vero cells showed no significant morphological changes or viability loss up to 200 μg mL^{-1}, revealing their non-toxic nature, while the cytotoxicity assays on MCF-7 cells showed dose-dependent morphological changes and reduced viability at higher concentrations. Overall, the lactams were biocompatible with normal cells yet cytotoxic to cancer cells, highlighting their therapeutic potential (Fig. S3–5 and Table S7, SI).



Scheme 7 Proposed catalytic cycle.

Conclusion

In summary, we have developed a Pd-catalyzed directed *meta*-selective C–H functionalization of α-substituted arylacetic acids with MBH acetates. The β-aryl MBH acetate can subsequently be cyclized to produce 14-membered macrocyclic lactams. The procedure can be extended to achieve difunctionalization with varied coupling partners. The substrate scope, *meta*-selectivity, functional group diversity, photophysical properties, biological activities and post-synthetic applications are the important practical features.

Author contributions

P. M.: designed, performed, analysed the experiments and writing the manuscript. P. K. M., V. T. and S. K.: analysed the experiments and writing the manuscript. T. P.: conceptualization, funding acquisition, investigation, project administration, supervision, visualization, writing – original draft, review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures, additional figures, tables, photophysical study, cytotoxicity study and spectral data. See DOI: **https://doi.org/10.1039/d5sc08286b**.

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