Marine Furanocembranoids-Inspired Macrocycles Enabled by Pd-catalyzed Unactivated C(sp3)-H Insertion Reaction of Donor/Donor Carbenes

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Article

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Abstract
Biomimetic modularization and function-oriented synthesis of structurally diversified natural product-like macrocycles in a step-economical fashion is highly desirable. Inspired by marine furanocembranoids, herein, we unprecedentedly synthesized diverse alkenes substituted furan-embedded macrolactams via a modular biomimetic assembly strategy. The success of this assembly is the development of crucial Pd-catalyzed carbene coupling between ene-yne-ketones as donor/donor carbene precursors and unactivated Csp3‒H bonds which represents a great challenge in organic synthesis. Notably, this method not only obviates the use of unstable, explosive, and toxic diazo compounds, but also can be amenable to allenyl ketones carbene precursors. DFT calculations demonstrated that a 1,4-Pd shift could be involved in the mechanism. Moreover, the collected furanocembranoids-like macrolactams showed significant anti-inflammatory activities against TNF-α, IL-6, and IL-1β and the low cytotoxicity is comparable to Dexamethasone.

Introduction
Many natural macrocyclic small-molecules have evolved to interfere with protein-protein interactions, and often have been harnessed as probes for target validation and starting points for lead compounds for drugs discovery.1–7 For example, marine cembranoids or furanobutenolide-based cembranoids exhibit a wide range of biological activities, e.g. antitumoral, antimicrobial and anti-inflammatory (Fig. 1A). A deeper examination into their scaffolds reflects that alkene substituted furan is of crucial importance for the biological activities. Despite these valuable function, gene expression limitations of soft corals and difficulty of resupply could hamper the sustainability of them. Therefore, the development of new strategies and methods to expeditiously access and enrich diverse natural furanocembranoids-like chemical space is highly desirable.8–14 Inspired by natural products or privileged scaffold15 and our interest in developing new coupling reactions,16–19 we set out to create polysubstituted alkene furan-embedded macrolactams via a short and modular biomimetic strategy, which simply utilizes either the fundamental building blocks from living organism’s endogenous ligands or mimics, such as amino acids or unnatural amino acids.20–21 A retrosynthetic analysis indicated that a successive and concise Csp3‒H carbene coupling, and amidation could assemble these readily available building blocks, such as aryl bromides, natural or unnatural amino acids and enynones, faithfully into the target molecules (Fig. 1B).

Over the past decade, transition-metal (e.g., Pd, Rh, Ir)-catalyzed carbene cross-coupling22 has emerged as a powerful tool for organic chemists to construct polysubstituted alkenes that might be difficult to synthesize by other methods. Concomitant with the rapid growth of this field is the combination of C‒H activation23–25 and carbene cross-coupling due to the remarkable advantage in atom- and step-economy. In this context, the functionalizations of Csp2‒H substrates by using diazo esters as acceptor carbene precursors are highly advanced.26–29 While a few carbene cross-couplings of Csp3‒H substrates with diazo esters have been developed, they are mainly limited to the activated positions (benzyllic, allylic, α-to heteratoms).30–35 Significant progress has been made in carbene cross-couplings of unactivated Csp3‒H
bonds from Davies\textsuperscript{36–41} and Martin.\textsuperscript{42} Notably, all of these reported protocols exclusively employed the donor-acceptor metal carbenoid generated from diazo esters. To the best of our knowledge, the carbenic cross-couplings of unactivated Csp\textsuperscript{3}–H bonds with non-diazo donor/donor carbenoid precursors have never been documented, although they are more environmentally friendly and could hold great promise for the exploration of chemical space. Expanding this carbenic chemistry to unactivated Csp\textsuperscript{3}–H bonds with non-diazo donor/donor carbenoid is elusive for several reasons. First, metal-mediated cleavage of unactivated Csp\textsuperscript{3}–H bonds is often significantly slower than Csp\textsuperscript{2}–H bonds. Second, the electrophilic capacity of donor/donor carbenoid is relatively weak compared to the acceptor carbenoid. Finally, the key C–C bond-forming event requires metal carbenoid intermediate. Such intermediates are frequently plagued by competing oxidation and dimerization.\textsuperscript{41}

Herein, we report the first Pd-catalyzed intermolecular unactivated Csp\textsuperscript{3}–H bond insertion reactions by choosing ene-yne-ketones and allenyl ketones as donor/donor carbenoid precursors.\textsuperscript{43–51} Accordingly, these reactions are distinguished by their high stereoselectivity and wide substrate scope including several drug derivatives. DFT mechanistic studies reveal that a 1,4-Pd shift could be involved.\textsuperscript{52–61} The unique features of these alkenes substituted furans are illustrated as novel building blocks for the construction of anti-inflammatory\textsuperscript{62} macrocyclic targets.

**Results**

Stimulated by the challenges of our synthetic target macro lactams, we first examined the module assembly by optimizing unactivated Csp\textsuperscript{3}–H olefination. 1-Bromo-2-(tert-butyl)benzene and 3-(4,4-dimethylpent-2-yn-1-ylidene)pentane-2,4-dione were selected as the model substrates and a number of reaction parameters such as base, ligand, Pd catalyst, and solvents were screened. After considerable experimentation, we were pleased to discover that a simple cocktail containing [PdCl(allyl)]\textsubscript{2} (5 mol%), \textsuperscript{1}BuXphos (30 mol%), and NaOAc in DMF at 100 °C in 1,4-dioxane established the reaction conditions, affording compound 3aa in 76% isolated yield with high stereoselectivity after 4 h (Table 1, entry 1). This Csp\textsuperscript{3}–H olefination is distinctive from Martin and co-workers’ recent work,\textsuperscript{42} in which they described an interesting Pd-catalyzed [4+1] cycloaddition of diazo esters. A series of control experiments were also conducted to validate the role of each parameter. Not surprisingly, the examined parameters were all essential for this transformation. The use of either DIPEA or KOAc did not further improve the yield of the desired product 3aa (Table 1, entries 2 and 3). Notably, the ligand appears to be important, as replacing \textsuperscript{1}BuXphos with Xphos or Brettphos provided 3aa in a much lower yield and no reaction occurred in the absence of ligand (Table 1, entries 6, 7, and 8). In addition, a diminished yield was observed when Pd(MeCN)\textsubscript{4}(OTf)\textsubscript{2} or Pd(OAc)\textsubscript{2} was employed (Table 1, entries 9 and 10). The influence of the solvents was also investigated. While similar efficiency was obtained using DMA, only traces of product were obtained in THF and no detectable amount of 3aa could be found in acetonitrile (Table 1, entries 13 and 14).
After determining the optimal reaction conditions, we turned our attention to evaluate the scope of this Pd-catalyzed intermolecular unactivated Csp\(^3\)‒H bond insertion reaction with ene-yne-ketones as donor/donor carbene precursors. As shown in Table 2, our Csp\(^3\)‒H carbene olefination method turned out to be widely applicable regardless of the electronic variations at the para and meta positions on the aromatic ring of the aryl bromides (3aa-3ea). Likewise, the naphthyl bromide employed for the synthesis of 3fa served well as a partner in the reaction. Gratifyingly, functional groups on the tertiary alkyls including cyano and ester are compatible (3ga-3ha), although aryl, secondary, and primary alkyls are not reactive probably due to steric hindrance or β-H elimination.\(^{63-66}\) Particularly interesting was the observation that the aryl bromide substrate substituted with free amine did not interfere, providing 3ja in a good yield without traces of the N‒H bond carbene insertion product being observed. Remarkably, the ene-yne-ketones containing ketone, ester, and heterocyclic ring can be successfully transformed into corresponding products (3ab-3ad) in good to excellent yields (77-91%).

To evaluate the generality of the protocol, alternatively, we investigated this Csp\(^3\)‒H carbene olefination process using allenyl ketones as donor/donor carbene precursors.\(^{47}\) As illustrated in Table 3, a wide range of allenyl ketones with electron-donating or -withdrawing substituents were well tolerated and a series of alkenes derivatives substituted with dihydrofurans were obtained. Generally, reactions of allenyl ketones with electron-donating substituents attached to a phenyl ring proceeded in higher yields than those having electro-withdrawing groups (5ab, 5ac, 5ad, 5ah). Moreover, the relative configuration of 5ab was unambiguously assigned by the X-ray crystal structure analysis. Particularly, substrates bearing furanyl and thienyl functional groups were also amenable to the standard conditions, which provided the pharmaceutical bis-heterocyclic compounds in decent yields with excellent stereoselectivities.

The identification of lead compounds greatly benefits from fragment-based drug design and the ability to directly modify the privileged scaffolds. Therefore, to highlight the potential application of these Csp\(^3\)‒H bond carbene coupling reactions in medicinal chemistry, late-stage cyclization/olenification of complex and bioactive molecules was subjected to our established protocol. Remarkably, the alkenes substituted with furans and dihydrofurans products derived from Repaglinide, Ioxepac, Mycophenolic acid, Adapalene and Dehydrocholic acid were synthesized in moderate to excellent yields (Table 4). For example, Repaglinide, an antidiabetic drug used to control blood sugar in type 2 diabetes mellitus, had also been installed with 1-bromo-2-(tert-butyl)benzene and subjected into this protocol, gave access to the product 3ka in an excellent 92% yield. Notably, starting from Ioxepac, a non-steroidal anti-inflammatory drug with analgesic activity, which was successfully converted to new furan or dihydrofuran-containing Ioxepac (3la, 5lc) in 84% and 74% yield, respectively.

Once the crucial connection of the aryl bromides and enynone building blocks was successfully established, we next selected different natural or unnatural amino acids and attempted to assemble them
to the macrolactams via a short and modular biomimetic strategy. With 6-8 steps, eight novel
polysubstituted alkene-embedded macrolactams (6a-6h) were efficiently assembled (Scheme 1). To
explore whether these alkene-embedded macrolactams could successfully exhibit pharmacologically
relevant features, the macrolactams 6a-6h were investigated for the inhibitory effects on inflammatory
mediators by LPS-induced inflammatory responses in RAW 246.7 macrophages. The results showed that
6g exhibited prominent inhibitory effects on the production of TNF-α, IL-6, and IL-1β with IC50 values of
0.45, 1.59, and 0.59 μM, respectively. It should be noted that these pro-inflammatory cytokines are
critically involved in the process of inflammation, immunity, cell survival and apoptosis, and metabolic
diseases.67-69 Both 6g and 6h were approximately 10 times more potent in the inhibitory activity on IL-6
than the drug Dexamethasone, the widely used corticosteroid medication to relieve inflammation (see the
Supporting Information). More importantly, they did not show obvious cytotoxicity at the indicated
concentrations compared to Dexamethasone. We further examined the effects of 6g on the levels of
phosphorylation of NF-κB and IkB-α induced by LPS in RAW 246.7 cells. As expected, 6g could abrogate
the phosphorylation of NF-κB and IkB-α, an NF-κB inhibitory protein, whose phosphorylation results in its
degradation and promotes subsequent translocation of NF-κB into nucleus and transcription of
inflammatory genes (Figure 2B).70 The current preliminary pharmacological results indicated a promising
prospect of 6g to be developed as a novel anti-inflammatory agent, with competitive potency and safety
advantage.

Apart from the scope of these conversions and intriguing anti-inflammatory activities, we were also
interested in the reaction mechanism. Two possible catalytic cycles are shown in Scheme 2. To gain
insight into the proposed catalytic cycles and see which cycle is more favorable, we carried out DFT
calculations to investigate the detailed mechanism. Although the similar mechanistic pathways have
been proposed by others,42 the DFT calculations of Pd(II) shift are still uncovered to date.

Figure 3 shows the energy profiles calculated. Considering the sizes of ligand and substrate, we start with
the complex A in which the Pd (0) metal center coordinates with the ligand L and the substrate aryl
bromide [Figure 3(a)]. Oxidative addition (OA) followed by concerted metalation deprotonation (CMD)
gives the key palladacycle intermediate IM4. The barrier for the OA is small while the barrier for the CMD
process is 33.4 kcal/mol.

From the key palladacycle intermediate IM4, two possible paths (consideration of the two cycles shown
in Scheme 2) were calculated (Figure 3(b)). Path A involves alkyne-activation cyclization followed by
migratory insertion (Cycle A in Scheme 2), while Path B engages protonation first and then alkyne-
activation cyclization (Cycle B in Scheme 2). Clearly, Path A requires to pass through a very high-lying
transition state (TS6-7A) for the migratory insertion. The high-lying TS6-7A structure is a result of the
unfavorable migration step that involves weakening/breaking of the two strong Pd-C bonds in the 5-
membered ring of IM6A.
Figure 3(c) shows that when the migration insertion occurs on the carbene structure IM7B without a 5-membered ring moiety, a very small barrier of 7.5 kcal/mol is calculated. After the migratory insertion, which is highly exergonic, β-hydride elimination occurs easily (almost barrierless), followed by reductive elimination and ligand (aryl bromide) coordination to regenerate the active species A.

The calculation results suggest that Cycle B is favorable. From Figure 3, we can also see that the CMD transition state structure TS₂-₃ (Figure 3(a)) and the protonation transition state structure TS₄-₅B (Path B in Figure 3(b)) show similar stability, although the latter lies slightly higher than the former. On the basis of the results, TS₄-₅B (Path B in Figure 3(b)) is the rate-determining transition state, and therefore, the overall reaction barrier is 34.1 kcal/mol, corresponding to the energy difference between IM1 and TS₄-₅B.

The calculated overall energy barrier is moderately high, which is understandable in view of the fact that the reaction temperature is 100 °C. In Figure 3, the series of transformation from IM2 to IM5B corresponds to a 1,4-Pd-shift.

Apart from all of the calculations mentioned above, we also calculated a pathway, which is closely related to Path A but starts from IM4B (instead of IM4) to react with 2a. The calculation results (Figure S1) indicate that this pathway is slightly favorable than Path A, but still less favorable than Path B.

**Conclusion**

In summary, we have developed two types of Pd-catalyzed intermolecular unactivated Csp³-H bond insertion reactions by choosing ene-yne-ketones and allenyl ketones as donor/donor carbene precursors, allowing for the construction of a diversity of alkenes substituted with furans and dihydrofurans. These two carbene cross couplings exhibit high efficiency and stereoselectivity, which can be applied to late-stage cyclization/olefination of different therapeutic drugs. DFT mechanistic studies supported that a unique 1,4-Pd shift was involved in the catalytic cycle. Furthermore, alkenes substituted with furans as novel building blocks were successfully assembled via a short and modular biomimetic strategy into macrolactams, which showed significant anti-inflammatory activity with less cytotoxicity.

**Declarations**

**Data availability**

All relevant data are available in Supplementary Information, Supplementary Data and from the authors.

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Author contributions

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**Tables And Schemes**

Due to technical limitations, full-text HTML conversion of the tables and schemes could not be completed. However, they can be downloaded and accessed in the Supplementary Files.