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# Rhodium(III)-Catalyzed C−H Alkenylation: Access to Maleimide-Decorated Tryptophan and Tryptophan-Containing Peptides

Jingjing Peng, Chunpu Li, Mirzadavlat Khamrakulov, Jiang Wang,* and Hong Liu*

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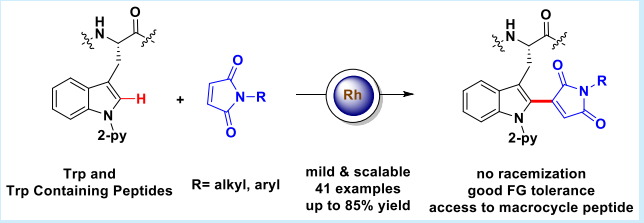
**ABSTRACT:** Maleimide is widely applied in many fields, especially in antibody−drug conjugations and peptide drugs. Herein, we develop a strategy for the C−H alkenylation of tryptophan and tryptophan-containing peptides, providing a synthetic route of decorating maleimide on peptides. The method has a high tolerance of functional groups and protecting groups. Furthermore, this method was applied to prepare peptide conjugation with molecules such as drugs and fluorescence probes. Moreover, macrocyclic peptides were obtained via this reaction.






Maleimide is a useful fragment in medicinal chemistry and biochemistry. It is widely used for bioconjugation as a linker to link biomolecules and other molecules. Trastuzumab emtansine (Kadcyla) is an ADC drug, which is approved by the FDA for the treatment of HER2 positive breast cancer, using maleimide to conjugate emtansine with trastuzumab (Figure 1a).[1] Albuvirtide, a long-acting anti-HIV peptide drug, which is developed by Frontier Biotechnologies Inc., contains a maleimide moiety (Figure 1b). The maleimide moiety can bind with human serum albumin, thus improving the half-life of the peptide.[2] In addition, the maleimide moiety is commonly used in biomolecule labeling as a linker (Figure 1c).

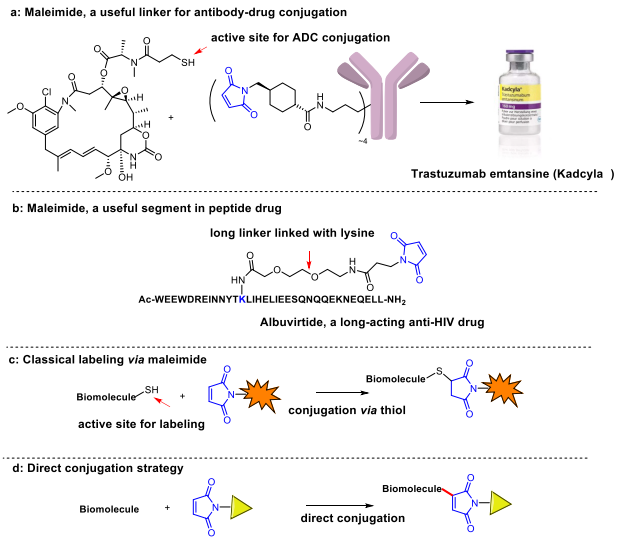



**Figure 1.** Application of maleimide and strategies to install maleimide on biomolecules.

Fluorescence-labeled maleimide can be easily decorated on peptides containing cysteine.[3] However, to conjugate the maleimide moiety with biomolecules, biomolecules should contain active reaction sites like cysteine, thiol, or other linkers. It is important to develop a method to directly decorate maleimide on biomolecules, especially peptides without cysteine (Figure 1d).

Transition-metal-catalyzed C−H activation has provided an efficient route to decorate the maleimide moiety on various organic molecules. Maleimide can be decorated on many useful scaffolds, such as benzene,[4] 8-alkyl quinolines,[5] *N*-sulfonylketimines,[6] 2-amino-1,4-naphthoquinones,[7] and indoles,[8] via this C−H activation strategy, indicating that maleimide is a useful moiety in organic chemistry. In recent years, methods to install maleimide on the C-2 position of indoles have been extensively explored, including using ruthenium,[8a] cobalt,[8b] and manganese[8c] catalysts (Figure 2a). Maleimide can be used as alkylation reagent and also alkenylation reagent in the latest reports via rhodium[8d] and cobalt[8e] catalysts. Maleimide can be decorated on the C-4 position of indoles with Heck-type products obtained (Figure 2b).

In the past few years, various transition-metal-catalyzed modifications of peptides have been reported by the groups of Lavilla and Albericio,[9] Corey,[10] Chen,[11] Daugulis,[12] Yu,[13] Ackermann,[14−17] Shi,[18] James,[19] Waser,[20] and Fairlamb,[21] among others.[22] Of all the reported literature, the Ackermann group contributes a lot to the modification of tryptophan and tryptophan-containing peptides. Diaryliodonium salts as arylation reagents for C-2 arylation were obtained via a noble-

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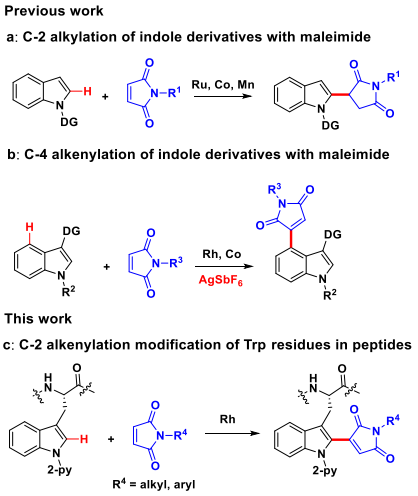


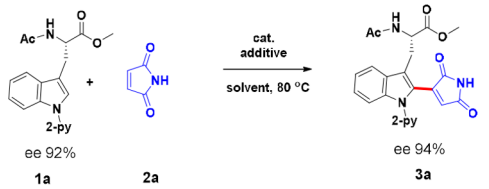

**Figure 2.** Transition-metal-catalyzed strategies to install maleimide on indoles, tryptophan and tryptophan-containing peptides.

metal palladium catalyst.[14b,c] However, palladium is expensive and toxic as a catalyst, whereas the use of less expensive and less-toxic cobalt and manganese catalysts are a better choice for peptide C−H activation. Alkynylation,[15] cyanation,[16] and allylation[17] of tryptophan-containing peptides were reported. Considering that C−H activation has been successfully used in peptide modification and that maleimide is a useful linker in medicinal chemistry, we begin to think if maleimide could be directly decorated on tryptophan and tryptophan-containing peptides and afford Heck-type products via a transition-metal-catalyzed C−H activation reaction (Figure 2c).

To test our hypothesis, we chose tryptophan **1a** and maleimide **2a** as the model substrates. We initiated our studies by exploring reaction conditions for the rhodium(III)-catalyzed C−H alkenylation (Table 1). Different kinds of Ag additives were explored (entries 1−3). When $Ag_2CO_3$ was used, **3a** can be obtained in 40% yield (entry 1), whereas AgOAc and $Ag_2O$ shared similar yields (49 and 44%, respectively, entries 2 and 3). The yield of **3a** could slightly improve when the concentration of **1a** increases to 0.2 M (entry 4). To investigate the role of the silver additive, 10 mol % of $Ag_2O$ was replaced with 0.9 equiv of AgOAc, and the yield continued to improve to 55% (entry 5). Various metals such as cobalt, manganese, ruthenium, and iridium were explored, but no product was obtained (see the Supporting Information, Table S1), indicating the importance of the rhodium catalyst. To further optimize the reaction, different solvents were selected (entries 6−8 and Table S1). MeCN was the best solvent for the titled transformation, resulting in 76% yield of **3a** (entry 8). To further improve the product yield, we tried to increase the amount of AgOAc additive (entry 9). Finally, reaction time was also investigated (entry 10). It was shown that shortening the reaction time had no effect on this reaction. To investigate the role of a 2-pyridine directing group, two control experiments were designed. When **1a** was replaced with Ac-Trp-OMe (**S1a**) and Ac-Trp(Ph)-OMe (**S1b**) (see the Supporting Information, brief mechanistic investigation), no product could be obtained, thus indicating that the 2-pyridine directing group was crucial in this reaction. In summary, we finally chose tryptophan **1a** and maleimide **2a** in the presence of $[RhCp^*Cl_2]_2$ catalyst and $Ag_2O$ and AgOAc as additives in 1 mL of acetonitrile as the best reaction condition.

With the optimal conditions for the rhodium(III)-catalyzed C−H alkenylation identified, we examined its versatility by first

**Table 1. Optimization of the Rhodium(III)-Catalyzed C−H Alkenylation**[a,b]

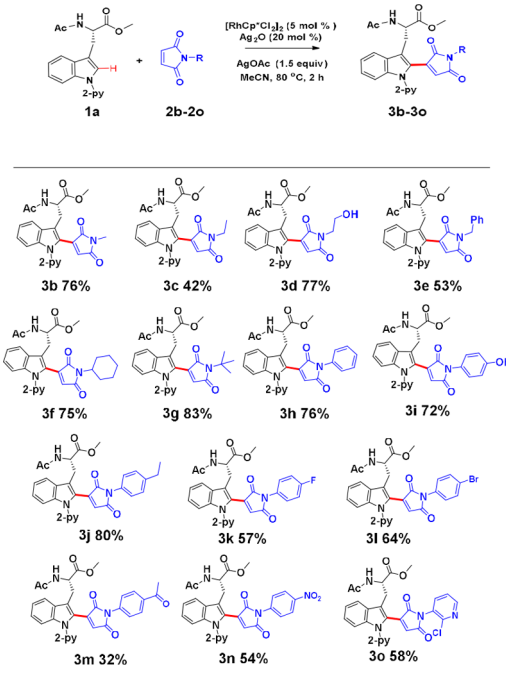



| entry | catalyst (5 mol %) | additive | solvent | yield (%) |
|---|---|---|---|---|
| 1 | $[RhCp^*Cl_2]_2$ | $Ag_2CO_3$ (30 mol %) | DCE[c] | 40 |
| 2 | $[RhCp^*Cl_2]_2$ | AgOAc (30 mol %) | DCE[c] | 49 |
| 3 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (30 mol %) | DCE[c] | 44 |
| 4 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (30 mol %) | DCE | 49 |
| 5 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (20 mol %) + AgOAc (0.9 equiv) | DCE | 55 |
| 6 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (20 mol %) + AgOAc (0.9 equiv) | NMP | 16 |
| 7 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (20 mol %) + AgOAc (0.9 equiv) | EA | 49 |
| 8 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (20 mol %) + AgOAc (0.9 equiv) | MeCN | 76 |
| 9 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (20 mol %) + AgOAc (1.5 equiv) | MeCN | 83 |
| 10 | $[RhCp^*Cl_2]_2$ | $Ag_2O$ (20 mol %) + AgOAc (1.5 equiv) | MeCN[d] | 83 |

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (5 mol %), additive, solvent (1 mL), 80 °C, 12 h, Ar. [b]Isolated yield. [c]DCE (2 mL). [d]2 h.

investigating a variety of *N*-substituted maleimide derivatives (Scheme 1). Thus, the rhodium(III) catalyst proved to be compatible with various alkyl functionalities in maleimide, including primary alkyl **2b** (76%), secondary alkyls **2c**−**2e** (42,

**Scheme 1. Scope of the Maleimide Derivatives**[a,b]




[a]Reaction conditions: **1a** (0.2 mmol), **2b**−**2o** (0.6 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $Ag_2O$ (20 mol %), AgOAc (1.5 equiv), MeCN (1 mL), 80 °C, 2 h, Ar. [b]Isolated yield.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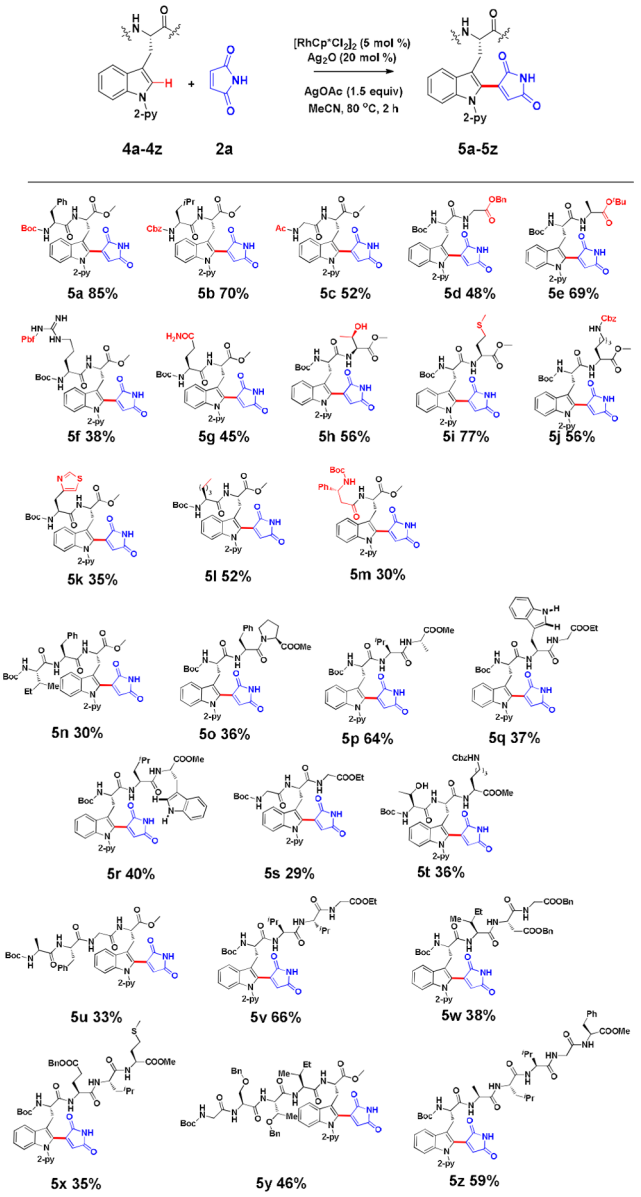
77, and 53%, respectively), tertiary alkyl **2f** (75%), and quaternary alkyl **2g** (83%), resulting in good yields of desired products. Substituted aryl groups in maleimide were also investigated. Electron-rich substitutions (**2h**, **2i**, and **2j**) provided yields (76, 72, and 80%, respectively) better than those with electron-deficient substitutions **2k**−**2n** (57, 64, 32, and 54%, respectively). In addition to alkyl and aryl groups in maleimide, heteroaromatic pyridine was also compatible with the reaction condition, leading to the formation of respective product **3o** in 58% yield. Studies of potential racemization showed that the chiral center was not racemized during the C−H alkenylation process (see Supporting Information for detailed information).

Subsequently, the universality of the rhodium(III)-catalyzed C−H alkenylation strategy was investigated for the diversification of dipeptides, which provided an efficient route to synthesize a broad range of maleimide-decorated dipeptides (Scheme 2).

Classical amine protecting group protected peptides, such as Boc-Phe-Trp(2-py)-OMe (**4a**), Cbz-Leu-Trp(2-py)-OMe (**4b**), and Ac-Gly-Trp(2-py)-OMe (**4c**), and acid protecting group protected peptides, such as Boc-Trp(2-py)-Gly-OBn (**4d**) and Boc-Trp(2-py)-Ala-O$^t$Bu (**4e**), were all tolerant of the C−H alkenylation process in good yields ranging from 48 to 85%. However, the 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) group for arginine Boc-Arg(Pbf)-Trp(2-py)-OMe (**4f**) could only afford product in moderate yield (38%). Notably, free carboxamide Boc-Gln-Trp(2-py)-OMe (**4g**), OH-free Thr peptide Boc-Trp(2-py)-Thr-OMe (**4h**), and sulfur-containing peptide Boc-Trp(2-py)-Met-OMe (**4i**) were obtained with medium to good levels of yields (range from 45 to 77%), indicating the compatibility with protic functional groups via the rhodium(III)-catalyzed C−H activation reaction. On the other hand, peptides containing unnatural amino acids and $\beta$-amino acids were explored to identify the versatility of rhodium(III) catalyst in the C−H activation reaction. We were pleased to observe the chemoselective C−H alkenylation of dipeptides containing unnatural amino acids (**4k** and **4l**) and $\beta$-amino acid (**4m**) with yields ranging from 30 to 52%, even though dipeptides contained thiazole.

Encouraged by the efficacy of C−H alkenylation in dipeptides, we explored the rhodium(III)-catalyzed C−H activation strategy toward the late-stage modification of tryptophan-containing complex peptides (Scheme 2). Indeed, a broad range of tripeptides delivered the desired products with moderate levels of yields (29−64%) when tryptophan was at the C-terminal of peptide chain **5n** (30%), at the N-terminal of peptide chains **5o**−**5r** (36, 64, 37, and 40%, respectively), or in the middle of peptide chains **5s** and **5t** (29 and 36%). Notably, NH-free tryptophan-containing peptides (**5q** and **5r**) were also tolerated by the rhodium(III)-catalyzed C−H activation, indicating the outstanding chemoselectivity ensured by the directing-group-induced chelation assistance. Tryptophan-containing tetrapeptides Boc-Ala-Phe-Gly-Trp(2-py)-OMe (**4u**), Boc-Trp(2-py)-Val-Val-Gly-OEt (**4v**), Boc-Trp(2-py)-Ile-Asp(OBn)-Gly-OBn (**4w**), and Boc-Trp(2-py)-Glu(OBn)-Leu-Met-OMe (**4x**) could also be transformed into desired products (33, 66, 38, and 35%, respectively), whereas more complicated pentapeptide Boc-Gly-Ser(OBn)-Thr(OBn)-Ile-Trp(2-py)-OMe (**4y**) and hexapeptide Boc-Trp(2-py)-Ala-Leu-Val-Gly-Phe-OMe (**4z**) were compatible with this transformative C−H alkenylation reaction, with 46 and 59% corresponding products obtained. The chemoselectivity of the C−H transformation was

**Scheme 2. Scope of the Tryptophan-Containing Peptides**[a,b]




[a]Reaction conditions: **4a**−**4z** (0.2 mmol), **2a** (0.6 mmol), [RhCp*Cl$_2$]$_2$ (5 mol %), Ag$_2$O (20 mol %), AgOAc (1.5 equiv), MeCN (1−2 mL), 80 °C, 2 h, Ar. [b]Isolated yield.

reflected by complete tolerance of complex peptides containing protected lysine, aspartate, glutamic acid, threonine, serine, and methionine.

It should be mentioned that gram-scale reactions of **1a** and **2a** proceeded smoothly to give **3a** without negative effects on the reaction efficiency (Scheme 3a). The synthetic application of the C−H alkenylation reaction was demonstrated by removal of the pyridyl motif without reduction of the double bond in maleimide in the presence of Pd(OH)$_2$/C and ammonium formate (Scheme 3b). To expand our application, dipeptide derivative **5e** was chosen for complete deprotection. After sequential removal of the directing group and protecting group, the maleimide-decorated dipeptide **7b** can be obtained in good yield (Scheme 3c).

After establishing a robust method for the C−H alkenylation on peptides, we focused on complexity-increasing trans-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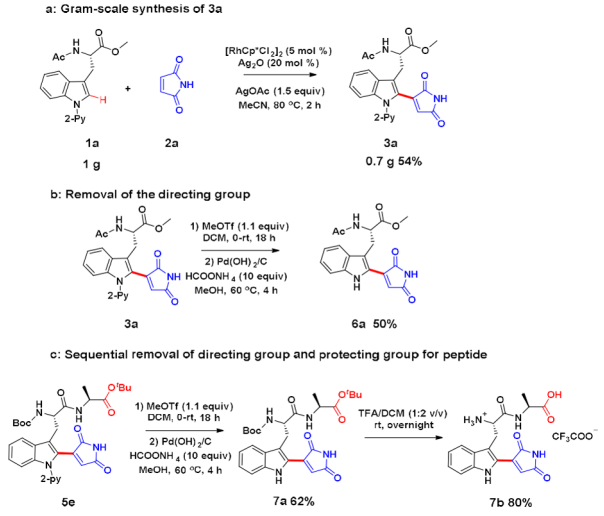
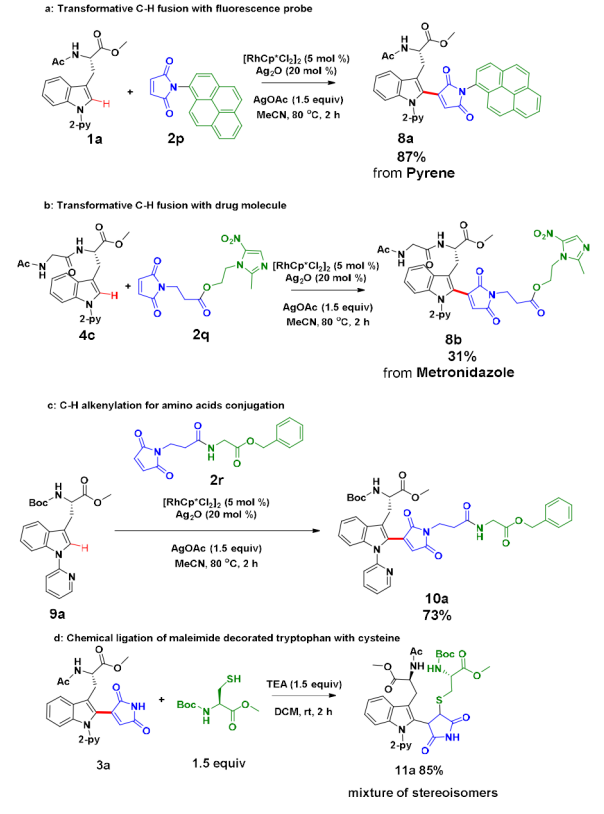
**Scheme 3. Gram-Scale Synthesis and Removal of the Directing Group and Protecting Groups**




formations with different molecular architectures. The rhodium(III) catalyst proved to be effective for conjugating peptides through C−H activation with fluorescence probes (Scheme 4a)

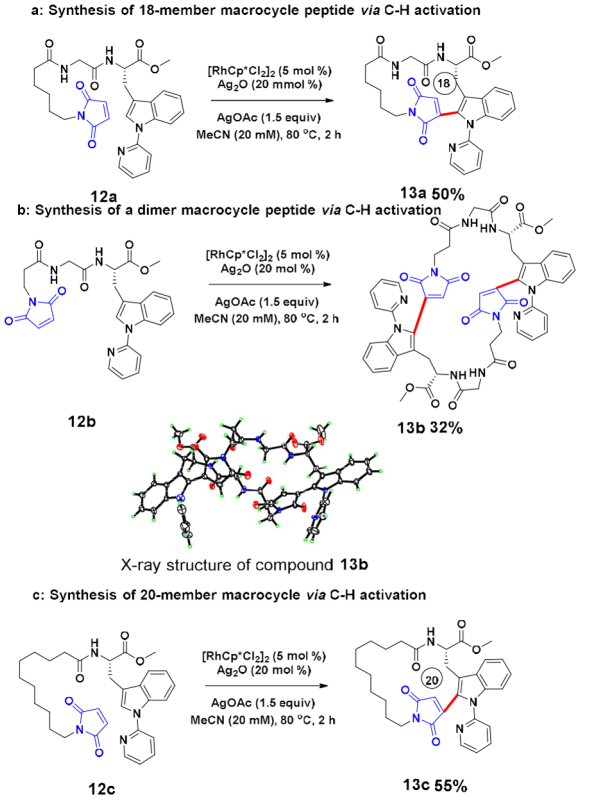
**Scheme 4. Transformative C−H Fusion with Different Molecules**




and drug molecules (Scheme 4b). The fluorescence probe could be linked to tryptophan via a maleimide linker, which was a potential way to label the amino acid. The labeled tryptophan derivative **8a** could be obtained in 87% yield. The C−H transformation with **2q** was mirrored by the tolerance of a *N*-containing heteroring, thus providing a synthetic route for conjugating peptides with small molecular drugs. Dipeptide **4c** can be linked with metronidazole via maleimide in 31% yield. In addition, the rhodium(III) catalysis method was shown to be tolerant of a maleimide-linked amino acid such as Gly-OBn, which was an efficient synthetic route for delivering amino acid conjugation product with good levels of site-selectivity (Scheme 4c). Tryptophan **9a** and maleimide-linked Gly-OBn **2r** can be conjugated in 73% yield. Maleimide-decorated tryptophan can potentially react with thiols such as cysteine. So it may be interesting if maleimide-decorated tryptophan and cysteine can be linked together via Michael addition. We indeed obtained the addition product **11a** with a desirable yield (Scheme 4d).

Cyclic peptides have been widely used in medicinal chemistry due to their unique stability against enzymatic degradation. Thus, an efficient synthetic route to these key structural motifs is still in high demand.[23] Encouraged by the unique robustness of our method, we explored the utility of the intramolecular and intermolecular C−H activation toward tryptophan-based macrocycles. Thus, unbiased amino acid derivative **12a** was successfully cyclized to provide the 18-membered macrocycle **13a** in 50% yield (Scheme 5a); while cutting the length of the

**Scheme 5. Synthesis of Macrocycles via C−H Activation**




maleimide linker of substrate, we cannot obtain the desired 15-membered macrocycle; however, a dimer macrocycle **13b** can be obtained in 32% yield (Scheme 5b). The structure of **13b** is determined by X-ray. In addition, the larger 20-membered macrocycle **13c** is also tolerated in our method (Scheme 5c), indicating it a useful route for macrocycle synthesis.

In summary, we developed a new rhodium(III)-catalyzed C−H alkenylation strategy toward maleimide-decorated peptides. Maleimide-decorated peptides can be obtained under mild and epimerization-free reaction condition. Classical protecting groups and heteroatom-containing functional groups were fully tolerated, thus indicating the robustness of the C−H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activation reaction. Our findings further highlight the unique practical application of rhodium(III)-catalyzed C−H activation for peptide conjugation with a fluorescence probe, drug molecule, and amino acid derivative as well as the synthesis of macrocyclic peptides.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00086.

Detailed experimental procedures, reaction development, studies on potential racemization, and characterization data for all compounds (PDF)

### Accession Codes

CCDC 1961640 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Jiang Wang** − *State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China;* orcid.org/0000-0003-1705-4905; Email: jwang@simm.ac.cn

**Hong Liu** − *State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China;* orcid.org/0000-0002-0863-7853; Email: hliu@simm.ac.cn

### Authors

**Jingjing Peng** − *State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China*

**Chunpu Li** − *State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China*

**Mirzadavlat Khamrakulov** − *State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00086


### Notes

The authors declare no competing financial interest.

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