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Authors: Liangliang Song, Guilong Tian, Anna Blanpain, Luc Van Meervelt, and Erik Van der Eycken

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Diversification of Peptidomimetics and Oligopeptides through Microwave-Assisted Rhodium(III)-Catalyzed Intramolecular Annulation

Liangliang Song,[a] Guilong Tian,[a]* Anna Blanpain,[a] Luc Van Meervelt[b] and Erik V. Van der Eycken[ac]*

[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven Celestijnenlaan 200F, 3001, Leuven, Belgium. guilongtian6@gmail.com; erik.vandereycken@kuleuven.be.
[b] Biomolecular Architecture, Department of Chemistry, KU Leuven Celestijnenlaan 200F, 3001, Leuven, Belgium.
[c] Peoples' Friendship University of Russia (RUDN University), Miklukho-Maklaya Street 6, Moscow, Russia.

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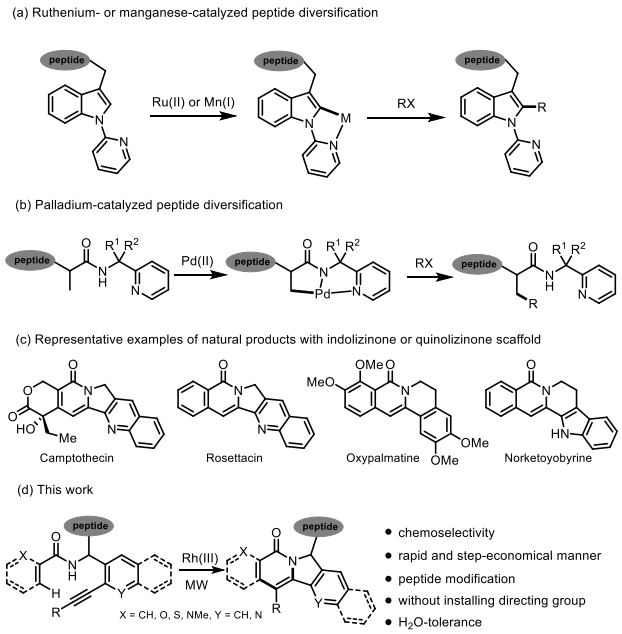
Abstract. A chemoselective rhodium(III)-catalyzed cascade annulation for the construction of the indolizinone and quinolizinone scaffolds is developed. Diversification of peptidomimetics and oligopeptides is achieved in a rapid and step-economical manner through the combination of Ugi reaction and microwave-assisted rhodium(III)-catalyzed intramolecular annulation *via* C(sp^2)-H activation without installing a directing group.

Keywords: Annulation; C-H Activation; Rhodium; Peptidomimetic; Peptide

The Ugi four-component reaction (Ugi-4CR) is regarded as one of the most attractive reactions for synthesizing multifunctional compounds,[1] especially for the generation of polymorphous peptidomimetics and peptides.[2] Moreover it also provides an opportunity for various post-transformations with diverse functional groups to synthesize pharmacologically important heterocyclic scaffolds, mostly in two operational steps.[3] Furthermore, microwave-assisted organic synthesis (MAOS) has been proven to be a powerful strategy in organic chemistry. During the past decade, researchers are investigating microwave-assisted C-H functionalizations to develop green, clean and efficient access for the construction of diverse heterocycles.[4]

Site specific modification of peptides is necessary for many biological and therapeutic applications.[5] Peptides from nonproteinogenic amino acids are required for medicinal and pharmaceutical chemistry, since they show improved pharmacokinetics and bioactivity in comparison with their natural versions.[6] For instance, peptides labeled with fluorescent groups could be used for realtime tracking of biomolecules, metabolites and cells under physiological conditions.[7] In addition, peptides labeled with drugs have been designed for selectively targeting tumor cells.[8] However, contemporary labelling strategies are mainly limited to classical reactions[9] and transition metal-catalyzed cross-coupling reactions[10], largely relying on prefunctionalizations, often leading to the formation of undesired byproducts and lengthy synthetic procedures.

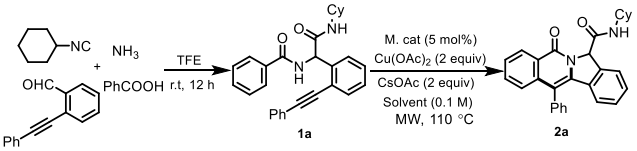


Scheme 1. Previous strategies and this approach.

Recently, transition metal-catalyzed C-H activation has emerged as an increasingly powerful strategy for direct peptide modification[11-17]. Despite major advances, late-stage peptide diversification frequently focuses on the synthesis of non-natural peptides or fluorescence peptide labelling through one-step coupling, and mostly requires external monodentate (Scheme 1a) or bidentate auxiliary assistance (Scheme 1b), causing the need to introduce and remove a directing group. Based on our previous studies on the

functionalization of amino acids and the construction of polyheterocyclic frameworks,[4a, 18] we herein report the chemoselective rhodium(III)-catalyzed cascade annulation for the synthesis of the indolizinone and quinolizinone scaffolds, which forms the core of many natural products with pharmacological relevance, such as rosettacin, oxypalmatime, camptothecin and norketoyobyrine [19-20] (Scheme 1c and 1d). Remarkable features of our approach include 1) the development of a versatile rhodium(III)-catalyzed intramolecular cascade annulation of peptidomimetics and peptides, 2) post-translational peptidomimetic and peptide modification in a rapid and step-economical manner through the combination of Ugi reaction and microwave-assisted C-H activation, 3) the utilization of an internal amide group as directing group to build up the indolizinone or quinolizinone scaffolds, and 4) the synthesis of complex fused ring system in a twofold and threefold manner.

Table 1. Optimization of the reaction conditions.[a)]

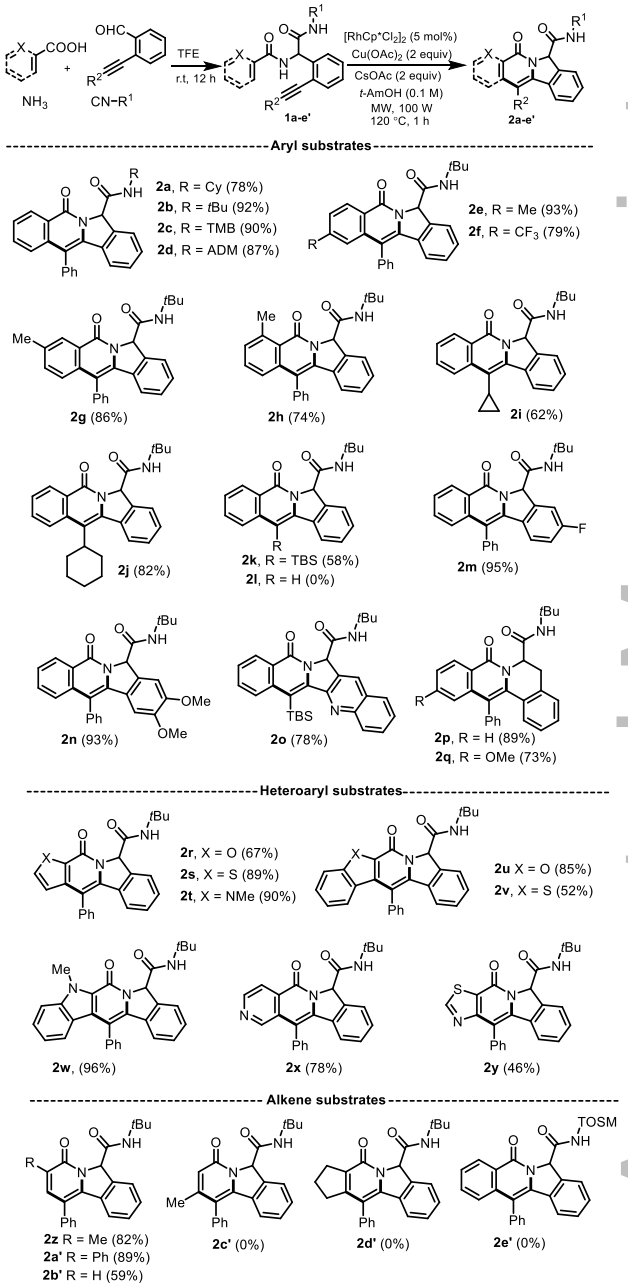


Entry	Solvent	M. cat	Power (W)	t (h)	Yield[b)] (%)
1	*t*-AmOH	$[RhCp^*Cl_2]_2$	300	1	90
2	1,4-Dioxane	$[RhCp^*Cl_2]_2$	300	1	79
3	Toluene	$[RhCp^*Cl_2]_2$	300	1	67
4	DMF	$[RhCp^*Cl_2]_2$	300	1	22
5	CH_3CN	$[RhCp^*Cl_2]_2$	300	1	46
6	THF	$[RhCp^*Cl_2]_2$	300	1	78
7	DCE	$[RhCp^*Cl_2]_2$	300	1	73
8	*t*-AmOH	$[Ru(p\text{-cymene})Cl_2]_2$	300	1	39
9	*t*-AmOH	$[RhCp^*Cl_2]_2$	300	2	99
10	*t*-AmOH	$[RhCp^*Cl_2]_2$	100	1	92
11[c)]	***t*-AmOH**	**$[RhCp^*Cl_2]_2$**	**100**	**1**	**99 (78)[d)]**
12[e)]	*t*-AmOH	$[RhCp^*Cl_2]_2$	—	1	36
13[c)]	*t*-AmOH	$[Cp^*IrCl_2]_2$	100	1	0
14[c)]	*t*-AmOH	$Cp^*Co(CO)I_2$	100	1	0

[a)] Conditions: **1a** (0.3 mmol), catalyst (0.015 mmol), $Cu(OAc)_2$ (0.6 mmol), CsOAc (0.6 mmol), solvent (3.0 mL). [b)] Determined by ^1H NMR analysis of the crude reaction mixture. [c)] 120 °C. [d)] Isolated yield. [e)] Reaction was performed conventionally at 120 °C in *t*-AmOH.

We commenced our exploration with the optimization studies on the annulation of peptidomimetic **1a**, which was readily constructed through Ugi-4CR. When the reaction was performed with $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv) and CsOAc (2 equiv) in *t*-AmOH at 110 °C for 1 h with 300 W maximum power, the indolizinone **2a** was obtained in 90% yield (Table 1, entry 1). Then various solvents were screened, showing that *t*-AmOH was the best one (Table 1, entries 2-7). When $[Ru(p\text{-cymene})Cl_2]_2$ was used, a lower conversion was observed (Table 1, entry 8). Extension of the reaction time to 2 h resulted in the formation of **2a** in 99% yield (Table 1, entry 9). Decreasing the maximum power to 100 W for 1 h, yielded **2a** in 92% (Table 1, entry 10). A higher temperature of 120 °C for 1 h (100 W), delivered **2a** in 99% yield (Table 1, entry 11). Only 36% yield of **2a** was 1observed when the reaction was performed under conventional heating for 1h at 120 °C in *t*-AmOH (Table 1, entry 12). We also tried other catalysts, such as $[Cp^*IrCl_2]_2$ and $Cp^*Co(CO)I_2$, but both of them did not work under the standard conditions (Table 1, entries 13-14).

Table 2. Rhodium(III)-catalyzed annulation of peptidomimetics.[a)b)]



[a)] Conditions: **1** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), $Cu(OAc)_2$ (0.6 mmol), CsOAc (0.6 mmol), *t*-AmOH (3.0 mL). [b)] Isolated yield. Cy = cyclohexyl, TMB = 1,1,3,3-tetramethylbutyl, ADM = adamantyl, TOSM = *p*-toluenesulfonylmethyl.

With the optimal conditions in hand, we next evaluated the scope of the protocol (Table 2).

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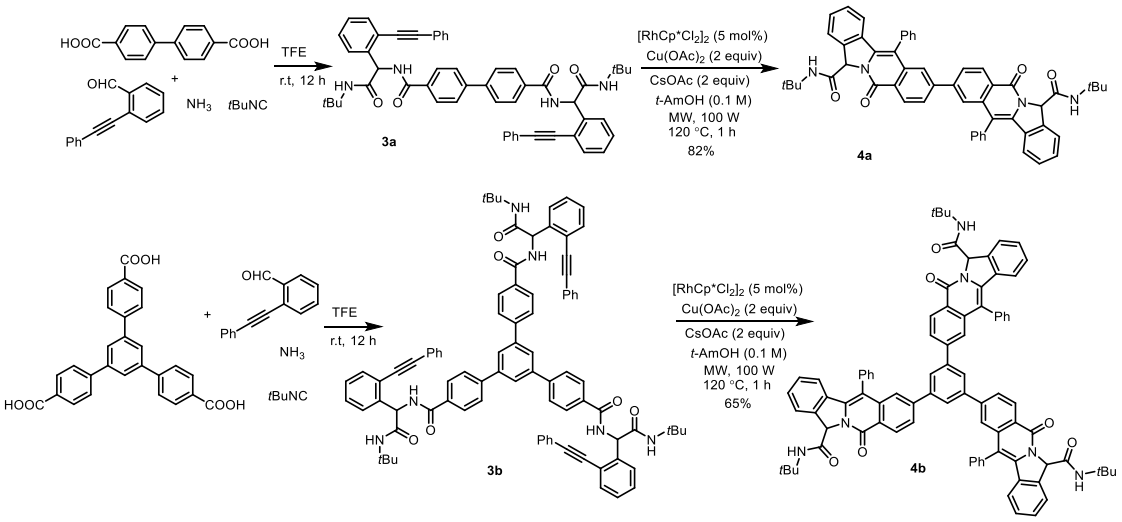
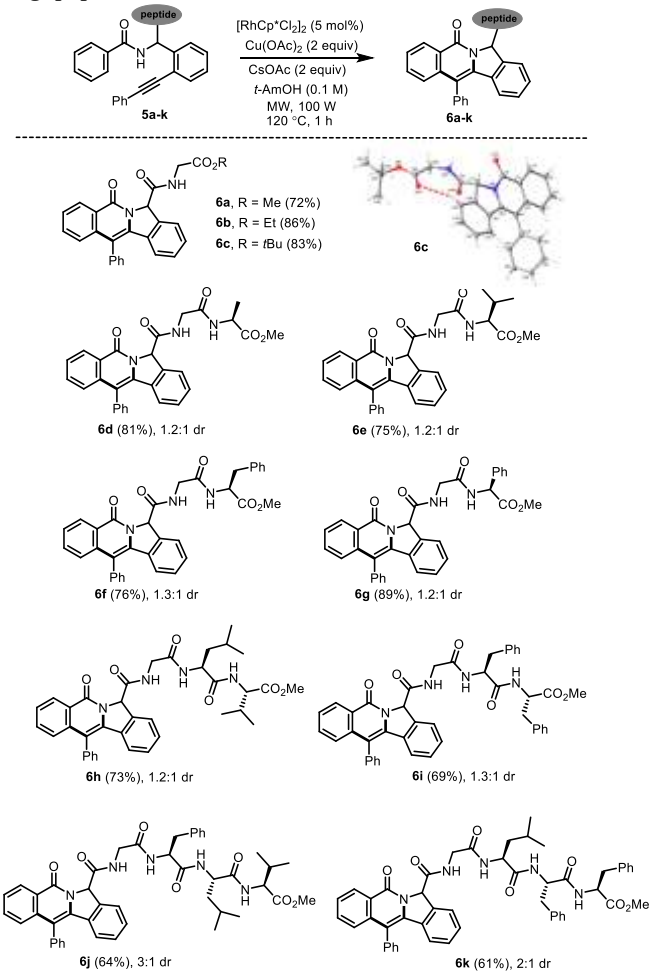


Scheme 2. Twofold and threefold rhodium(III)-catalyzed annulation.

Table 3. Rhodium(III)-catalyzed annulation of oligopeptides.[a)b)]



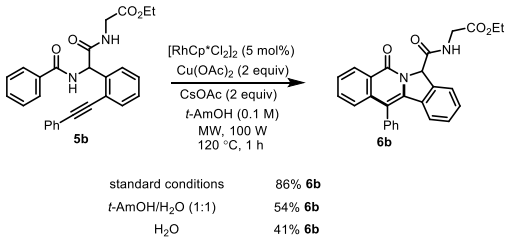
[a)] Conditions: **5** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), $Cu(OAc)_2$ (0.6 mmol), CsOAc (0.6 mmol), *t*-AmOH (3.0 mL). [b)] Isolated yield.

Peptidomimetics bearing various secondary amide groups derived from the corresponding isocyanides, yielded the corresponding indolizinones **2b-d** in 87-92%. However, the peptidomimetic **1e'** did not undergo the reaction. Thereaction was also applicable to *para*-Me and -CF_3 substrates, giving the indolizinones **2e** (93%) and **2f** (79%). The reactions with *meta*- or *ortho*-Me substrates smoothly afforded the corresponding indolizinones in 86% (**2g**) and 74% (**2h**) yield respectively. The phenyl substituent of the alkyne could be replaced by a cyclopropyl, cyclohexyl or TBS group, yielding the indolizinones **2i-k** in 58-82%. However, the terminal alkyne substrate failed to give the corresponding indolizinone **2l**. The substrate with a fluoro or dimethoxy group in the phenyl substituent derived from the benzaldehyde, turned out to be compatible, offering the indolizinones **2m** (95%) and **2n** (93%). The 2-ethynylquinoline substrate smoothly reacted to yield the corresponding indolizinone **2o** (78%), which has the same skeleton as the natural product rosettacin. The annulation worked well with substrates bearing a longer carbon chain between the benzamide and the phenylalkyne, leading to the corresponding quinolizinones **2p** (89%) and **2q** (73%), having the same scaffold as the natural product oxypalmatime.

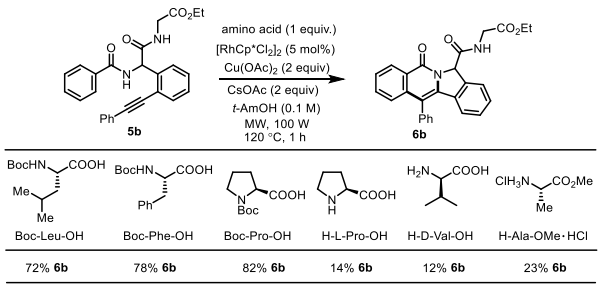
Considering the fact that the strong coordination activity of medicinally important heterocycles continues to constitute major challenges to transition metal catalysts, often resulting in poisoning of the catalyst or undesired C-H bond activation, [21] we extended the reaction scope to heteroaryl peptidomimetics, containing a furan, a thiophene, a pyrrole, a benzofuran, a benzothiophene or an indole moiety. They all smoothly afforded the corresponding indolizinones **2r-w** in 52-96% yield. Even isonicotinamide and thiazole-5-carboxamide substrates delivered the corresponding indolizinones **2x** (78%) and **2y** (46%). It was also observed that the benzamide substrates could be replaced by α-substituted acrylamide substrates, resulting in the corresponding indolizinones **2z-b'** in 59-89% yield. However, β-substituted and α, β-disubstituted acrylamide substrates **1c'** and **1d'** did not undergo the

reaction. Maybe the β-substitution or α, β-disubstitution of acrylamides sterically prevented the cyclometalation. Interestingly, the robustness of the Rh^{III}-catalyzed C-H activation approach enabled twofold and threefold annulation to deliver the di- and trimers **4** in high yields (Scheme 2).

Subsequently, we evaluated our procedure for oligopeptides (Table 3). Dipeptides **5a-c** were well tolerated, affording the corresponding indolizinones **6a-c** in 72-86%. Compound **6c** was unambiguously characterized by X-ray crystallography.[22] Diverse tri-, tetra- and pentapeptides were compatible with this approach, delivering the corresponding indolizinones **6d-k** with excellent levels of chemoselectivity. LC-MS analysis showed that there was no detectable racemization of indolizinone **6h** (see SI).



Scheme 3. Rhodium(III)-catalyzed annulation with H_2O.



Scheme 4. Chemoselectivity screen with amino acids.

The compatibility on Rh^{III}-catalyzed intramolecular annulation protocol for diversification of peptides was evaluated by using water as solvent (Scheme 3). Employing *t*-AmOH/H_2O (1:1) could not give complete conversion, delivering **6b** in 54% yield. Using solely H_2O gave **6b** in 41% yield. In addition, the excellent robustness of the Rh^{III}-catalyzed intramolecular annulation was proven by a chemoselectivity screen in the presence of specifically added *O*-unprotected amino acids (Scheme 4). *N*-unprotected amino acids seem to have a detrimental effect on the reaction. Maybe the free amine (NH_2 group) coordinated with the metal.

In conclusion, we have developed a chemoselective rhodium(III)-catalyzed cascade annulation protocol for the construction of indolizinone and quinolizinone scaffolds. Ugi reaction and microwave-assisted C(sp^2)-H activation set the stage for the diversification of various peptidomimetics and oligopeptides in a rapid and step-economical manner employing the internal amide group as the directing group. A twofold and threefold cascade annulation is carried out to produce complex fused ring system.

Experimental Section

To a 10 mL glass tube equipped with a stir bar were added **1**, **3** or **5** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), CsOAc (0.6 mmol), $Cu(OAc)_2$ (0.6 mmpl) and *t*-AmOH (3 mL) without any particular precautions to extrude oxygen or moisture. The reaction mixture was irradiated under MW at 120 °C with maximum power of 100 W for 1 h, then cooled to room temperature. The solvent was removed in *vacuo* and the remaining residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate) to afford the product **2**, **4** or **6**.

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[22] CCDC-1885561 (**6c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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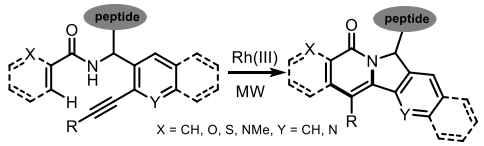
Liangliang Song,[a] Guilong Tian,[a]* Anna Blanpain,[a] Luc Van Meervelt[b] and Erik V. Van der Eycken[ac]*



● chemoselectivity ● rapid and step-economical manner ● peptide modification
● without installing directing group ● H_2O-tolerance