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Fluorescent coumarin-alkynes for labeling of amino acids and peptides *via* manganese(I)-catalyzed C–H alkenylation†

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The late-stage fluorescent labeling of structurally complex peptides bears immense potential for molecular imaging. Herein, we report on a manganese(I)-catalyzed peptide C–H alkenylation under exceedingly mild conditions with natural fluorophores as coumarin- and chromone-derivatives. The robustness and efficiency of the manganese(I) catalysis regime was reflected by a broad functional group tolerance and low catalyst loading in a resource- and atom-economical fashion.

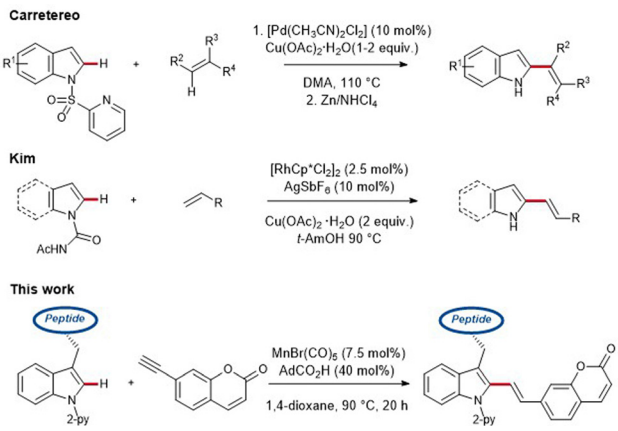
Cell-imaging, medicinal chemistry and cellular biochemistry are in high demand in selective techniques for tracking bioactive molecules, among others.[1] Traditional labeling methods based on isotope probes, photo switchers or electrochemical sensors suffer from low sensitivity in comparison to fluorescent-labeling.[1c] In recent decades, the demand for small molecule fluorophores to label proteins with minimal disruption to the natural cellular mechanism has gained considerable attention.[2] Coumarin and its constitutional isomer chromone are ideal fluorescent labels to study chemical and biochemical activities. Those second metabolites are not giving characteristics of smell and color in plants such as tonka beans or rue, but serve as defense mechanisms against predators in organisms such as bacteria, fungi and even sponges.[3] The ability to form noncovalent interactions with enzymes and receptors unlocks a wide range of biochemical applications, including their anti-inflammatory and antithrombotic activities, as exemplified by Warfarin, an oral coagulant and rodenticide.[4] Based on their outstanding biocompatibility and low toxicity, coumarins are used as fluorescent sensors to address biological systems or probes for NIR.[5] Fluorogenic molecular techniques have been recognized as potent and environmentally sensitive tools in cells.[6]

Moreover, transition-metal-catalyzed C–H activation has been established as an indispensable toolbox in molecular synthesis over the past few decades.[7] In this regard, Lavilla/Albericio,[8] Chen,[9] Yu[10] and Ackermann,[6,11] among others,[12] have developed fundamental strategies for the late-stage diversification of amino acids and peptides.

While this regime is often associated with toxic and costly palladium- and rhodium-catalysts, accompanied by undesirable metal impurities, cost-efficient, abundant 3d metal catalysis,[1e,13] such as resource-friendly and nontoxic manganese catalysis, has recently gained considerable attention (Scheme 1).[14]

As part of our research program on sustainable C–H activation, we now report on the first manganese(I)-catalyzed C–H alkenylation with easily accessible coumarin-derivatives for labeling structurally complex peptides.

We initiated our studies by probing various reaction conditions for the envisioned manganese-catalyzed labeling of tryptophan containing peptides with coumarin. The optimal



Scheme 1 Selected catalytic alkenylation examples.

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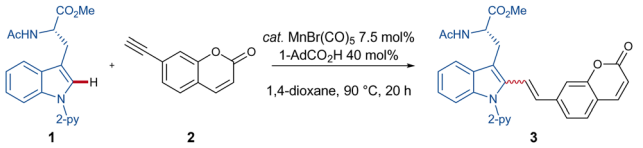
Table 1 Optimization table



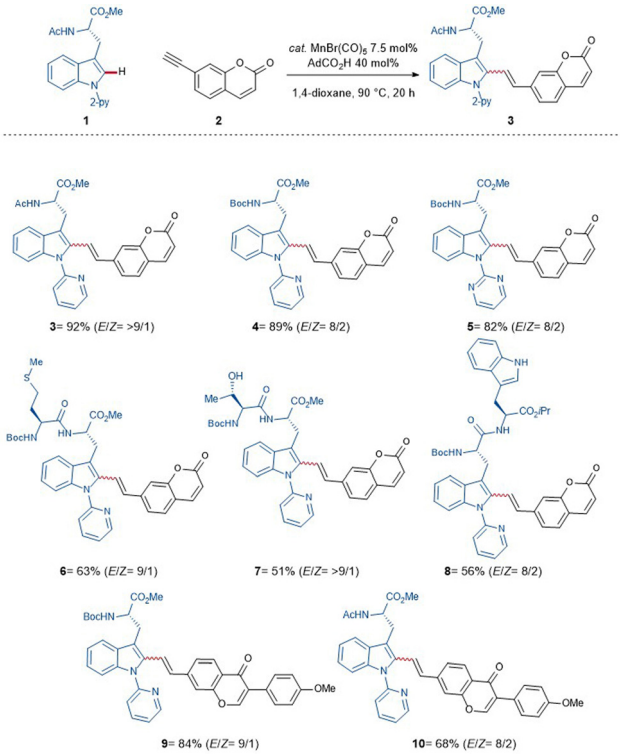
Entry	Deviation from standard conditions	Yield[ab] [%]
1[b]	—	92
2	12 h	53
3	16 h	66
4	120 °C	91
5	55 °C, 71 h	79
6	NaOAc instead of $AdCO_2H$	42
7	KOAc instead of $AdCO_2H$	33
8	5 mol% $MnBr(CO)_5$	82
9	2.5 mol% $MnBr(CO)_5$	68
10	Without $MnBr(CO)_5$	nd
11	DCE	69

General reaction conditions: **1** (0.10 mmol), **2** (0.11 mmol), [Mn] (7.5 mol%), 1-$AdCO_2H$ (40 mol%), 1,4-dioxane (1.0 mL), 90 °C, 20 h, under N_2-atmosphere. [a] Of isolated products. [b] E/Z ratio = >9/1 determined with ^{1}H-NMR. DCE: 1,2-dichloroethane.

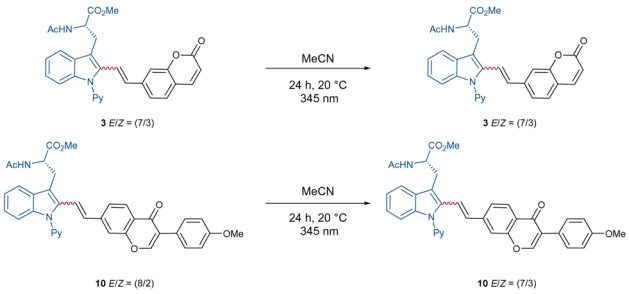
reaction conditions for the C–H alkenylation are 40 mol% of $AdCO_2H$ in 1,4-dioxane with 7.5 mol% $MnBr(CO)_5$ (Table 1, entry 1). It was shown that the reaction time has a considerable impact on the reaction outcome (entries 2 and 3). Increasing the reaction temperature to 120 °C did not have an influence on the efficiency (entry 4). However, reducing the temperature to a mild 55 °C, albeit with an increased reaction time, yielded the product in 79% yield (entry 5).

Altering the additives from $AdCO_2H$ to NaOAc (entry 6) or KOAc (entry 7) led to a diminished performance. Importantly, the efficiency of the manganese catalyst was demonstrated by reducing the loading to 5 mol% (entry 8) and 2.5 mol% (entry 9), with product formation in 82% and 68% yield. Control experiments verified the need for the catalyst for the reaction to proceed (entry 10). Additionally, the use of DCE has shown no impact on the E/Z ratio (entry 11).

With these optimized reaction conditions in hand, the compatibility of the coumarin-alkyne **2** was probed (Scheme 2). Here, it was shown that the ratio of E/Z was influenced by the properties of the corresponding peptide backbone. The threonine containing dipeptide **7** has shown the highest E/Z ratio of over >9/1. The chromone-labeled compounds **9** and **10** gave E/Z ratios of 9/1 and 8/2, and a linear correlation of alkyne-length to the E/Z ratio was not observed. Isomerization studies were conducted with compounds **3** and **10** to evaluate the influence of UV-light on the E/Z ratio (see Scheme 3, for more information see ESI†). To better understand the catalyst mode of action, DFT calculations were carried out at the PW6B95-D4/def2-TZVP+SMD(1,4-dioxane)//TPSS-D3(BJ)/def2-SVP level of theory[11f] between C–H activation and the proto-demetalation steps (see ESI† for further information). With this knowledge in hand, we tried to overcome the obstacle by exploiting a coumarin-alkyne **11** with a small linker, in this case a CH_2-group. Under the



Scheme 2 Alkenylation substrate scope of coumarins and chromones.



Scheme 3 Isomerization studies.

optimized conditions (Table 1), similar good to excellent yields have been isolated (Scheme 4). Different protecting groups of the C- and N-termini as well as a different directing group were tolerated, and the various functional groups of the peptide-backbone like the free indole of the tryptophan did not compromise the yield.

Indeed, with this procedure, excellent E/Z ratios for all compounds (Scheme 4) of >20:1 were accomplished.

Due to the sensitive nature of the push–pull alkyne motif, previously established protocols have thus far proven ineffective for the removal of the pyridine directing group (for further information, see the ESI†). Furthermore, fluorescent studies showed emission wavelengths of $\lambda_{em.}$ = 426 nm, $\lambda_{em.}$ = 396 nm and $\lambda_{em.}$ = 443 nm for products **3**, **10** and **11**, respectively, within an excitation wavelength of $\lambda_{exc.}$ = 330 nm (see Fig. 1).

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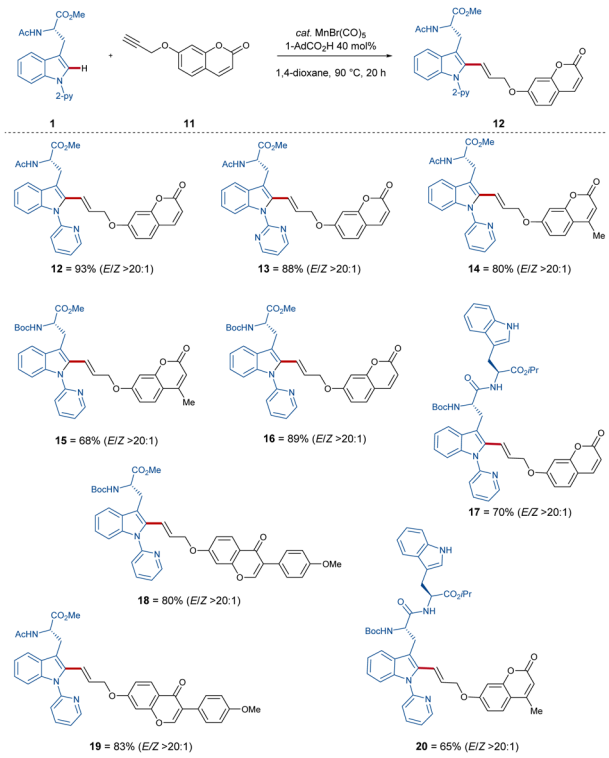

Scheme 4 Expanded substrate scope of coumarins and chromones.

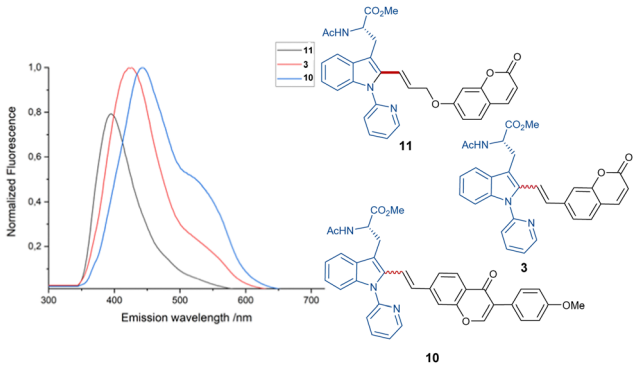

Fig. 1 Fluorescence studies of compounds **3**, **10**, and **11**.

Based on the simplicity of the core-structure and the easy tunability, plenty of opportunities regarding dye characteristics in the case of stoke fluorescence become available.

In summary, we have developed an efficient, site selective manganese(I) catalyzed C–H alkenylation, which enabled labeling of tryptophan-containing-peptides with coumarin and chromone probes, thus expanding the toolbox of fluorescent probes to image living cells in real-time.

A. K., and L. A. conceived the project and wrote the manuscript. A. K. performed the synthetic experiments. T. O. performed the DFT calculations.

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Conflicts of interest

There are no conflicts to declare.

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