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A General Cp*Co(III)-Catalyzed Intramolecular C–H Activation Approach for the Efficient Total Syntheses of Aromathecin, Protoberberine and Tylophora Alkaloids

Andreas Lerchen[+], Tobias Knecht[+], Maximilian Koy, Constantin G. Daniliuc, and Frank Glorius*[a]

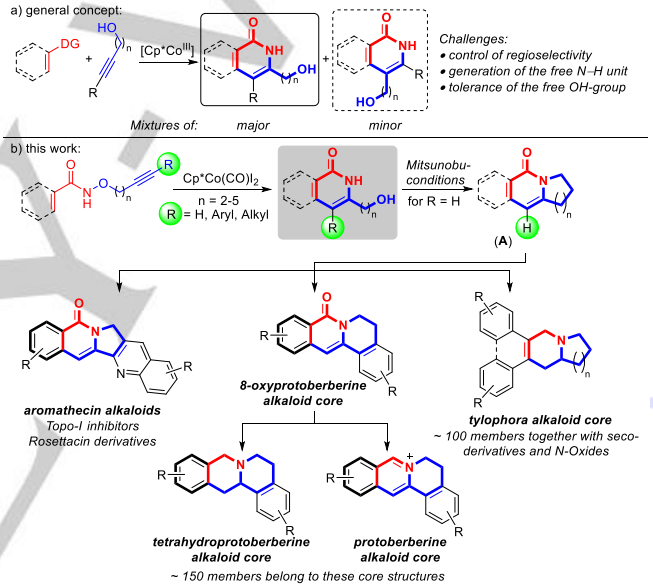
Abstract: Herein, we report a Cp*Co(III)-catalyzed C–H activation approach as key step to create highly valuable isoquinolones and pyridones as building-blocks that can readily be applied in the total syntheses of a variety of aromathecin, protoberberine and tylophora alkaloids. This particular C–H activation/annulation reaction was achieved with several terminal as well as internal alkyne coupling partners delivering a broad scope with excellent functional group tolerance. The synthetic applicability of this protocol reported herein was demonstrated in the total syntheses of two Topo-I-Inhibitors and two 8-oxyprotoberberine cores that can be further elaborated into the tetrahydroprotoberberine and the protoberberine alkaloid core. Moreover these building-blocks were also transformed to six different tylophora alkaloids in expedient fashion.

The transition metal catalyzed functionalization of C–H bonds is an attractive synthetic tool for the synthesis of several core structures in natural products and pharmaceuticals.[1] However, the incorporation of C–H activation processes in the total syntheses of natural products is still underrepresented.[2] Especially, the development of a particular C–H activation methodology with a cheap and earth-abundant Cp*Co(III)-catalyst, that can be applied in several total syntheses of natural products remains to be scarce.[3]

After the development of the Cp*Co(III)-catalyst in 2013 by Kanai and Matsunaga,[4] a variety of transformations were investigated leading to similar results compared to its Cp*Rh(III) and Cp*Ir(III) congeners in pioneering studies.[5] Subsequently, several detailed characteristic differences especially between the Cp*Rh(III)- and the Cp*Co(III)-catalysts were discovered.[6] However, within this report we wanted to develop one particular Cp*Co(III)-catalyzed C–H activation approach as a key step for the efficient total syntheses of three different classes of natural products and their analogues.

The indolizidine- and quinolizidine motifs are important core structures found in several biologically active compounds such as aromathecin,[7] protoberberine[8] as well as tylophora alkaloids.[9] Although, several syntheses of each class of those alkaloids have been reported,[10] there is still a great interest of a unified catalytic approach that streamlines the direct access to all of these alkaloid cores in high step economy.

For the development of one strategic methodology, that enables the total syntheses of the stated alkaloids, we were interested in the absolutely regioselective synthesis of isoquinolones and pyridones bearing an unsubstituted C4-position, a terminal hydroxylalkyl substituent and a free N–H unit (Scheme 1a).[11] By the incorporation of these crucial functional groups the desired core structures (A) can be obtained via a straight-forward intramolecular Mitsunobu-type cyclization (Scheme 1). These particular motifs can be further transformed into different aromathecin, 8-oxyprotoberberine, tetrahydroprotoberberine, protoberberine and tylophora alkaloids (Scheme 1b).



Scheme 1. Cp*Co(III)-catalyzed intramolecular synthesis of isoquinolones and pyridones as valuable building-blocks that give direct access to a variety of aromathecin, protoberberine and tylophora alkaloids.

Within this work, we solved the stated challenges by the implementation of an intramolecular Cp*Co(III)-catalyzed C–H activation approach employing alkyne-tethered hydroxamic esters as a directing group (Scheme 1b).[11] This particular oxidative directing group motif enables three important objectives for the successful syntheses of these building-blocks:[12] First, the absolutely regioselective insertion of unsymmetrical alkynes can be guaranteed; second, the free hydroxylalkyl-substituent as well as the free N–H unit are delivered concomitantly by the cleavage of the redox-active N–O bond of the directing group and third, terminal alkynes which pose typically reactivity challenges could be readily addressed by the intramolecular cyclization approach leading selectively to an unsubstituted C4-position (Scheme 1b). In contrast to a recent pioneering Rh-catalyzed protocol by Park and coworkers, which was limited to the use of internal alkynes,[13] the herein developed reaction features i) broad applicability by allowing terminal and internal alkynes ii) a cheap as well as

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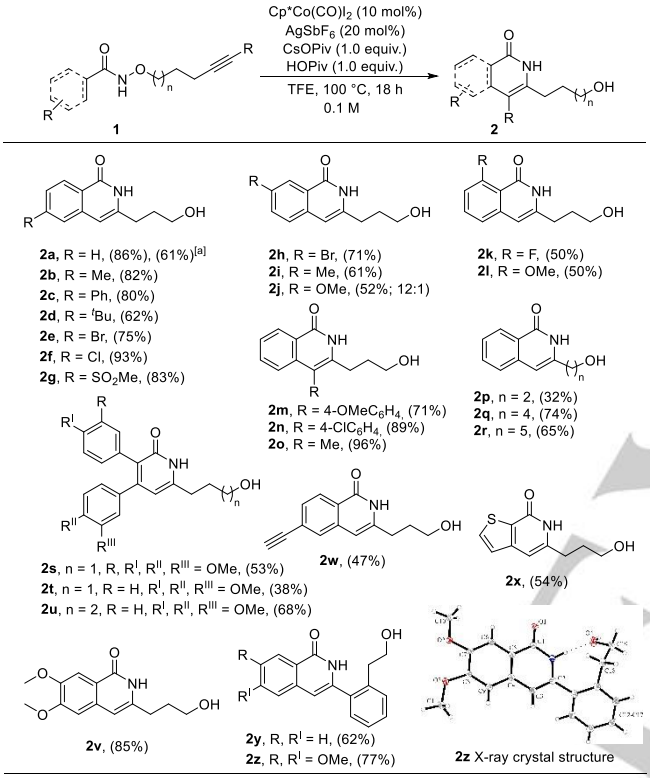
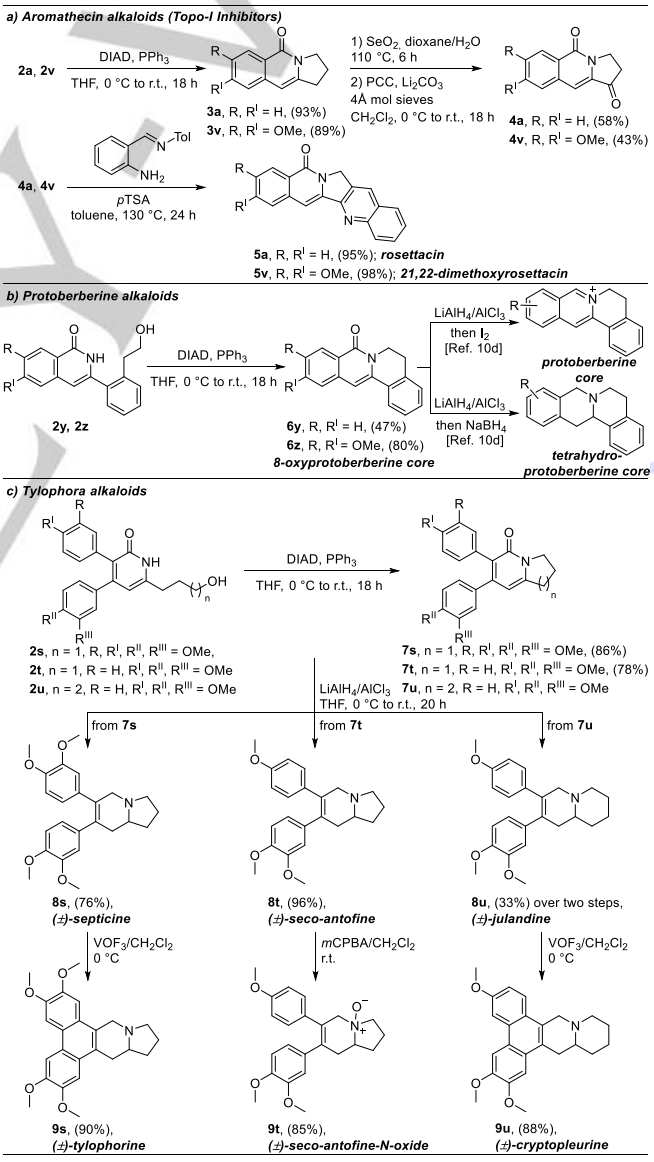
abundant metal catalyst and iii) the prevention of protecting groups that need to be installed and deinstalled.

We began our studies using *N*-(pent-4-yn-1-yloxy)benzamide **1a** as model substrate for the intramolecular annulation reaction (Scheme 2). After judicious optimization of the reaction parameters, we were able to isolate the desired isoquinolone product (**2a**) in 86% yield with excellent selectivity. A control experiment in the absence of the cobalt catalyst led to no product formation according to HPLC-MS. With these results in hand, we investigated the scope of the developed intramolecular annulation reaction (Scheme 2).



Scheme 2. Reaction conditions: **1** (0.2 mmol), [Cp*Co(CO)I_2] (10 mol%), $AgSbF_6$ (20 mol%), CsOPiv (1.0 equiv.), HOPiv (1.0 equiv.), in TFE (2 mL) at 100 °C for 18 h; [a] 2.0 mmol scale.

Both electron-donating (EDG, **2b**–**2d**) and electron-withdrawing (EWG, **2e**–**2g**) groups in the para-position on the substrate were tolerated. Meta-substitution (EWG or EDG) on the aromatic ring did not influence the reactivity and the desired products could be isolated as single regioisomers (**2h**, **2i**). For the meta-methoxy substituted substrate (**1j**) the desired product (**2j**) was isolated in moderate yield and two regioisomers were obtained in a ratio of 12:1. Moreover, the ortho-substitution pattern with EWG (**1k**) and EDG (**1l**) were tolerated under the reaction conditions and the corresponding products (**2k**, **2l**) were isolated in reasonable yields. The disubstituted substrate **1v** afforded the desired isoquinolone (**2v**) in an excellent yield of 85%. Additionally, the reaction was not restricted to a specific length of the alkyne tether. Thus, the butyne-, hexyne- and heptyne tether delivered the corresponding products (**2p**–**2r**) in moderate to good yields. Moreover, aryl-substituted alkynes with EDG (**1m**) and EWG (**1n**) as well as the methyl substituted alkyne-tether (**1o**) led also to product formation in excellent yields (**2m**–**2o**). To our delight, heteroarenes were also tolerated and the desired isoquinolone product **2x** was isolated in a synthetically useful yield of 54%. Also a terminal alkyne on the substrate **1w** was successfully applied, highlighting the broad functional group tolerance of the developed methodology, and the product **2w** could be isolated in moderate yield. Moreover, the substrates **1y** and **1z** bearing an additional aryl-ring in the tether led to the desired products in good yields (**2y**, **2z**). The absolute structure of **2z** was confirmed by X-ray diffraction.[14] In addition to the arene C–H bond functionalization, we investigated the olefinic C–H bond functionalization. The optimized reaction conditions delivered a variety of pyridones (**2s**–**2u**) in moderate up to good yields and several methoxy substituents as well as different alkyne tethers were tolerated. We further performed a large scale reaction (2.0 mmol) of **1a** which afforded **2a** in reasonable 61% yield.



Scheme 3. Elaboration of the building-blocks. For detailed reaction conditions, see the Supporting Information.

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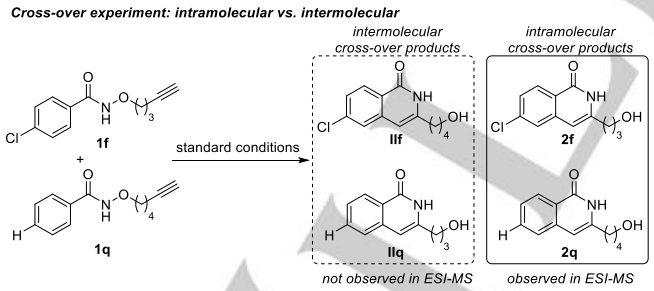
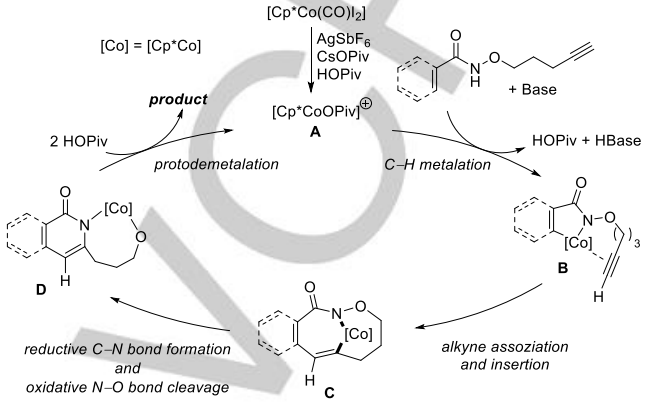
The synthetic applicability of this protocol reported herein, could be shown in the total syntheses of several alkaloids. First, two different aromathecin alkaloids that show biological activities as Topo-I-inhibitors were synthesized in three high yielding steps from isoquinolone compounds **2a** and **2v** (Scheme 3a). After the Mitsunobu reaction (**3a**, **3v**) and sequential oxidation using SeO_2/PCC (**4a**, **4v**), the desired aromathecin alkaloids (**5a**, **5v**) could be obtained in high overall efficiency.[10b,13a] Additionally, the isoquinolones **2y** and **2z** were converted to the 8-oxyprotoberberine core (**6y**, **6z**) under Mitsunobu conditions in good up to high yields (Scheme 3b). These compounds can either be reduced to the quarternary protoberberine salts or to the tetrahydroprotoberberine cores by literature protocols.[10d] Moreover, after the Mitsunobu reaction, the pyridones (**2s**–**2u**) could be transformed to the corresponding phenanthroindolizidine as well as the phenanthroquinolizidine cores in excellent yields (**7s**–**7u**) (Scheme 3c).[13a] After reduction of **7s** we could isolate (±)-septicine (**8s**) in 76% yield which could then be further transformed via an oxidative coupling to (±)-tylophorine (**9s**) in 90% yield. After reduction of **7t** under identical conditions, we were able to obtain (±)-seco-antofine (**8t**) in 96% yield that could further be oxidized in high yield (85%) to (±)-seco-antofine-*N*-oxide (**9t**) using *m*CPBA.[15] (±)-Julandine (**8u**) could be synthesized after reduction of **7u** and after an additional oxidative coupling, we were able to isolate (±)-cryptopleurine (**9u**) in 80% yield.

A mechanistic experiment was conducted to probe whether the reaction is operating through an intramolecular or an intermolecular reaction pathway. By the analysis of a cross-over experiment, no intermolecular cross-over products (**IIf**, **IIq**) could be obtained, whereas exclusively the intramolecular cross-over products (**2f**, **2q**) were detected in the ESI-MS of the crude reaction mixture (Scheme 4 and see the Supporting Information). Based on these results, we propose that the intramolecular reaction pathway is active in the present reaction, leading to the observed selective alkyne insertion.



Scheme 4. Mechanistic cross-over experiment.

A plausible reaction mechanism based on the above mentioned experiments is proposed in Scheme 5.[13a] The active catalyst **A** is generated by the dehalogenation with the corresponding silver salt. After the C–H activation/metalation process, a 5-membered cobaltacycle **B** is proposed to be formed. This species **B** can coordinate intramolecularly to the tethered alkyne leading to an insertion of the terminal alkyne to generate a 7-membered cobaltacycle **C**. Subsequently, this species can undergo the reductive C–N bond formation followed by an oxidative O–N bond cleavage (species **D**). After protodemetalation of **D**, the desired isoquinolone or pyridone product can be released and the active catalyst species **A** is regenerated. An alternative reaction pathway, according to a report of Gulías and coworkers cannot be excluded and is described in the Supporting Information.[13b]



Scheme 5. Proposed catalytic cycle.

In summary, we have developed an efficient and highly regioselective synthesis of isoquinolones and pyridones enabled by a Cp*Co(III)-catalyzed intramolecular C–H activation approach Furthermore, an excellent scope with a high functional group tolerance of the developed methodology could be shown. The value and versatility of the herein developed reaction protocol were demonstrated in the total syntheses of two Topo-I-Inhibitors that belong to the class of aromathecin alkaloids. Additionally, two different 8-oxyprotoberberine cores which can be further elaborated to the protoberberine- and tetrahydroprotoberberine alkaloid core as well as six structurally diverse tylophora alkaloids were synthesized.

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Keywords: alkaloids • C–H activation • Cobalt(III) • pyridones • isoquinolones

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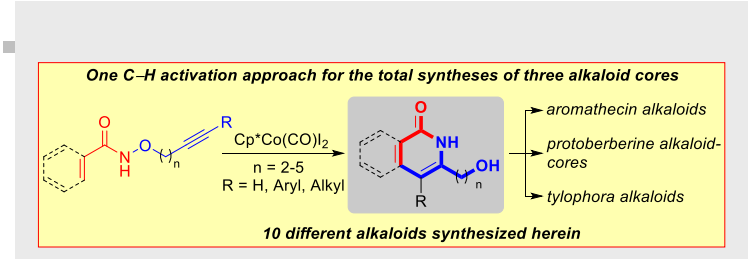

Con't get enough: Herein, we report a general intramolecular Cp*Co(III)-catalyzed C–H activation approach for the regioselective synthesis of isoquinolone- and pyridone derivatives as highly valuable and versatile building-blocks. The synthetic applicability of these building-blocks was further utilized in the total syntheses of two aromathecin alkaloids, two 8-oxyprotoberberine cores and six different tylophora alkaloids.

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