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Ruthenium-catalysed one-pot regio- and diastereoselective synthesis of pyrrolo[1,2-*a*]indoles *via* cascade C-H functionalization/annulation

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A cascade approach has been developed towards dual C-C bond formation *via* consecutive C-H functionalization /cyclization giving access to pyrrolo[1,2-*a*]indoles in a highly regio- and diastereoselective manner using catalytic [*Ru(p-cymene)Cl*$_2$]$_2$. The methodology was further expanded to attain pentacyclic structures involving manifold C-C bond creation.

The concept of direct C-H bond functionalization plays an important role in cascade syntheses to architect complex structures, as it removes the barrier of prefunctionalization to activate substrates towards C-C/C-X bond formation.[1] In this perspective, the decoration of indole nucleus has always been an attractive choice for chemists due to its frequent appearance and essential role in many alkaloids as well as in medicinally important building blocks.[2]

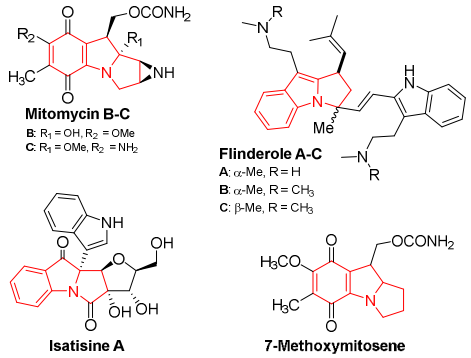

Figure 1. Biologically active pyrrolo[1,2-a]indole skeleton.

The triclyclic pyrrolo[1,2-*a*]indole core is of great significance due to its valuable contribution to biological and pharmacological activities as in the Mitomycins and Mitosenes (antitumor/antibiotic)[3], Flinderol A-C (antimalarial)[4] and Isatisine A (antiviral)[5] (Figure 1). A literature survey revealed that the available synthetic methodologies for the pyrrolo[1,2-*a*]indole ring system require sequential multi-step processes.[6] Despite extensive knowledge has already been explored in past decades to furnish such type of polycyclic skeleton, one-pot method for the synthesis of pyrrolo[1,2-*a*]indoles is rather scarce.[7] Consequently, it is highly challenging for synthetic chemists to develop a reliable methodology to furnish the pyrrolo[1,2-*a*]indole in a single operation.

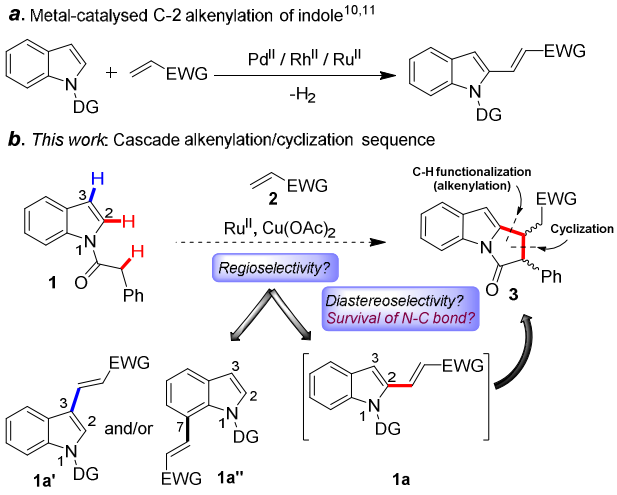

Figure 2. **a**. Transition metal-catalysed C-2 alkenylation of indole. **b**. Cascade C-2 alkenylation of indole and cyclization sequence.

Over the past decades, the direct C-H functionalization, especially arylation[8] and alkenylation,[9] of indoles at the more electrophilic C-2 center with unactivated partners (such as aryl/alkyl halides, acrylates, alkenes/alkynes) has been

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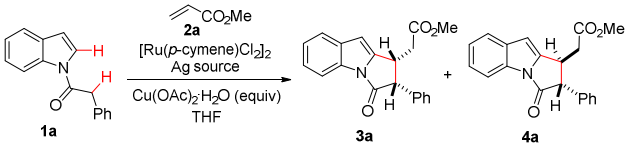
achieved using Pd(II), Rh(III) and Ru(II) metal complexes *via* oxidative Heck transformation[10] assisted by various directing groups[11] (Figure 2, **a**). On the other hand, the work from M. Greaney and co-workers proved the supremacy of ruthenium catalysts for multiple C-H bond functionalization, describing the formation of carbocycles in a single operation, without prefunctionalization of substrates.[12] Inspired by this finding regarding the multitasking role of the ruthenium catalyst,[13] we describe here a methodology for the regio- and diastereoselective synthesis of pyrrolo[1,2-*a*]indoles **3** from readily accessible *N*-acylindole **1** and acrylate **2** in a cascade C-C coupling/cyclization fashion (Figure 2, **b**). The pyrrolo[1,2-*a*]indole **3** consists of a fused tricyclic architecture with a diversely substituted pyrrolidinone subunit featuring two distinct stereocenters. We envisaged that substrate **1** would undergo selective ruthenation at the C-2 position of the indole, employing $[Ru(p\text{-cymene})Cl_2]_2$ as a pre-catalyst, followed by reaction with alkene **2** to afford *in-situ* generation of a 2-alkenyl indole. Subsequent cyclization provides pyrrolo[1,2-*a*]indole **3** in the final step. The two important questions here to deal with: 1) regioselectivity of the alkenylation at the C-2 position, over C-3/C-7 alkenylation, and 2) the fate of cyclization sequence, which lead to the generation of two stereocenters in product **3** (diastereoselectivity).

Table 1. *Reaction optimization*



Entry[a]	Ru dimer (mol%)	Ag source (mol%)	Oxidant (equiv)	(**3a**+**4a**)[b] (% yield)[c]
1	10	$AgSbF_6$ (40)	2	22[d]
2	10	$AgSbF_6$ (40)	2	40[e]
3	10	AgOTf (40)	2	38[e]
4	10	$AgBF_4$ (40)	2	30[e]
5	10	$AgNTf_2$ (40)	2	32[e]
6	10	AgOAc (40)	2	30[e]
7	5	$AgSbF_6$ (20)	2	47[f]
8	5	$AgSbF_6$ (20)	2	61[f,g]
9	**5**	**$AgSbF_6$ (20)**	**2**	**65**[f,g]
10	5	$AgSbF_6$ (20)	1.5	50[f,g,h]
11	5	-	2	nd
12	-	$AgSbF_6$ (20)	2	nd
13	5	$AgSbF_6$ (20)	-	nd

[a] Reaction conditions: 0.2 mmol of **1a**, 0.6 mmol of **2a**, Ru dimer, Ag source, $Cu(OAc)_2{\cdot}H_2O$, 1.5 mL of THF, T = 100 °C, 24 h. [b] Diastereomeric ratio **3a**:**4a** was determined by NMR analysis of the crude reaction mixture and indicated a ratio of ~ 4:1 in all cases. [c] Yields of isolated products are given. [d] DCE was used as a solvent. [e] Reaction stirred at T = 120 °C for 48 h. [f] Reaction stirred at T = 100 °C for 48 h. [g] 5 equiv of AcOH was added. [h] 0.4 mmol of **2a** was used. (nd = not detected)

In order to validate the proposed hypothesis (Figure 2, b) for our dual C-C bond formation concept, compound **1a** was chosen as model substrate and subjected to reaction with methyl acrylate **2a** using $[Ru(p\text{-cymene})Cl_2]_2$ (10 mol%) as catalyst, $AgSbF_6$ (40 mol%) as co-catalyst and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv) as an oxidant in DCE at 100 °C for 24 h. To our delight, the intended pyrrolo[1,2-*a*]indole was obtained as an inseparable mixture of *cis* (**3a**) and *trans* (**4a**) having a diasteromeric ratio of 4.3:1 and a combined yield of 22% (Table 1, entry 1). The reaction was found to be selective and formation of other regioisomeric C-3/C-7 alkenylated products was not observed. The structure and stereochemistry of the major diastereomer **3a** was confirmed by NMR- and X-Ray analysis (See ESI file).

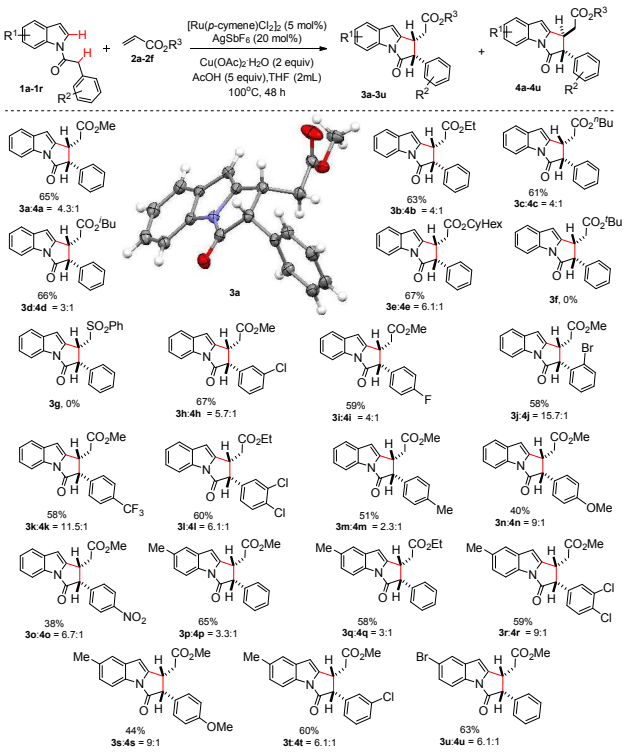


Figure 3. Substrate scope of pyrrolo[1,2-a]indoles **3**. All yields are combined yields of both diastereomers after purification by column chromatography. Diastereomeric ratios were determined by NMR analyses of the crude reaction mixture.

With the intention to improve the efficiency of the reaction, various parameters such as solvent, metal-catalyst, silver salt and oxidant were optimized (see ESI for complete details). Changing the solvent (from DCE to THF) and increasing the reaction temperature (from 100 °C to 120 °C) significantly enhanced the yield to 40% (Table 1, entry 2). Alteration of the silver source (^-OTf, $^-BF_4$, $^-NTf_2$, ^-OAc) worked equally well having slight variation in the yield (Table 1, entry 3-6). Further, lowering the catalyst (5 mol%) and co-catalyst (20%) loading gave favourable results (Table 1, entry 7, 47%). The outcome of the reaction was still not satisfactory and we decided to introduce an additive in the reaction media having the concept of Concerted Metallation-Deprotonation (CMD) in mind.[14] As expected, addition of acetic acid to the reaction mixture shifts the pendulum and increased the yield to 61% (Table 1, entry 8). A cleaner reaction profile was obtained with a slight change

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in temperature (100 °C) and quantity of acrylate (2 equiv) (Table 1, entry 9, 65%). A remarkable reduction of the yield was observed upon lowering the oxidant amount to 1.5 equiv (Table 1, entry 10). Control experiments were done to demonstrate the necessity for the combination of [Ru], [Ag] and [Cu] in a single reaction medium (Table 1, entry 11-13). The silver source [Ag^+] was found to be essential for the formation of cationic ruthenium [Ru^{II}] through halide ion abstraction from the ruthenium pre-catalyst and copper was used to oxidize eliminated ruthenium [Ru^0] to activated [Ru^{II}] species in the ruthenocycle. However, palladium and other ruthenium catalysts were unsuccessful for this cascade coupling/cyclization (see ESI file). Having the optimized reaction conditions in hand, we next explored the substrate scope for the synthesis of pyrrolo[1,2-*a*]indoles (Figure 3). The protocol proved efficient for the cascade reaction with considerable yields 61-67% (**3a-3e**) using various acrylates (**2a-2f**). The use of *t*-butyl acrylate was found to be abortive in this system, most probably due to steric reasons (**3f**). In case of phenyl vinyl sulfone as an alkene substituent, after analysing all the products appeared on HPLC, we were disappointed not to observe the formation of **3g** possibly due to the strong electron withdrawing power of the sulfone functionality, or degradation of the materials because of the acidic media of the reaction. Substituents on the arene ring were well tolerated. Arene containing halogen units (Cl, F, Br, CF_3, dichloro) undergo facile ruthenation leading to viable yields (**3h-3l**); *p*-tolyl and *p*-methoxy aryl functionalities avail moderate yields (**3m,3n**), while a *p*-nitro aryl entity also sustained in this process, albeit with a lower yield of 38% (**3o**). Indole containing methyl or bromine at its aryl part also formed products even with variation of acrylate and aryl portions (**3p-3u**).

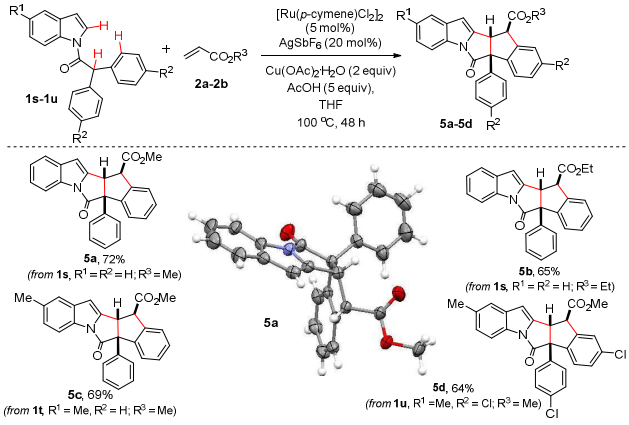

Figure 4. Indeno[2',1':3,4]pyrrolo[1,2-a]indole synthesis.

The strategy of dual C-H functionalization/cyclization was further expanded to achieve double cyclized products having three consecutive stereocenters (one quaternary carbon and two tertiary carbons) through a multiple C-H activation sequence to realize complex fused pentacycles that would offer a series of indeno[2',1':3,4]pyrrolo[1,2-*a*]indoles **5** (Figure 4). To our delight, positive response was observed on applying the previously optimized reaction conditions on substrate **1s**. The reaction furnished fused pentacyclic core **5a** in 72% yield as a single diastereomer. The relative configuration of the three stereocenters was confirmed by X-ray analysis. Similarly, compounds **5b**-**5d** were obtained in good yields from different substrates **1s**-**1u**, with variation of the acrylate.

On the basis of previous literature reports and our observations during the development, a plausible mechanism for the Ru(II) catalysed cascade C-H funcationalization/cyclization has been depicted in Figure 5. The first step is the formation of alkenylated compound **6** through selective ruthenation at the C-2 position of the indole (rate determining step) directed by the carbonyl group. This is followed by rapid cyclization in a *5-exo-trig* fashion (intermediate **7**, R = H) through a radical mechanism (the possibility of Michael addition *via* copper enolate cannot be ruled out)[12] catalysed by $Cu(OAc)_2$ furnishing major product **3a**. In case, when intermediate **7** has a diphenyl system (R = Ph), pentacyclic product **5a** could be obtained *via* two consecutive cyclization through intermediate **8**. The formation of the C-2 alkenylated intermediate **6**, however, was not detected by NMR analysis of the reaction mixture, though we were able to observe the formation of the final product. In an effort to stimulate the formation of intermediate **6**, a decrease of the quantity of $Cu(OAc)_2$ to one equivalent did not help and the reaction led to a poor conversion (<10%) of starting material **1a** with minor amount of product **3a**. A possible explanation might be the high reactivity of the C-2 alkylated product under oxidising conditions, which might rapidly be led to product **3a** as soon as it is formed.

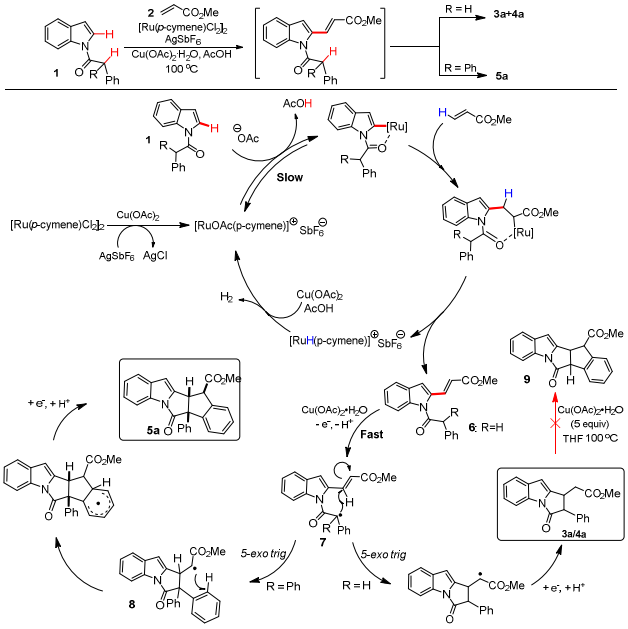

Figure 5. Proposed mechanism for sequential C-H functionalization/cyclization.

The formation of the *cis*-geometry as major diastereomer **3a** over *trans* product **4a** might be understood through a more favourable pseudo-chair conformation **I** of the radical

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intermediate as proposed in Figure 6.[15] Both conformations **I** and **II** are shown in their most stable state as aryl and ester groups are at pseudo-equatorial positions. However, chair-like conformation **I** is more favourable which led to *cis*-geometry as a major isomer (Figure 6). Further, we expected that dual cyclization could also be possible if product **3a** would be treated with excess of $Cu(OAc)_2$. However, the formation of product **9** was not detected under these conditions showing that the presence of an extra phenyl group is necessary to push double cyclization (Figure 5).

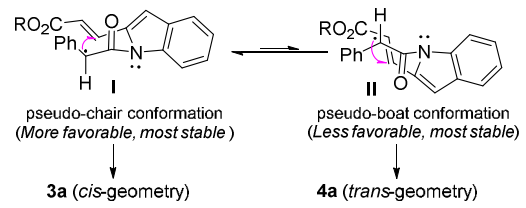

Figure 6. Proposed mechanism for radical cyclization.

In conclusion, a highly versatile and efficient Ru(II)-catalysed cascade C-H functionalization/cyclization approach has been described for the dual formation of C-C bonds resulting in an expedient access to pyrrolo[1,2-*a*]indole **3** by the utilization of very simple starting materials with moderate to good yields, sustainable substrate choice and controlled regio- and diastereoselectivity. Moreover, the method can be expanded to three successive C-H activations to furnish indeno[2',1':3,4]pyrrolo[1,2-*a*]indole skeletons **5**. The method reported here underscores the importance of Ru(II)-catalysis.

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Graphical Abstract:

Catalytic, regioselective and diastereoselective synthesis of pyrrolo[1,2-a]indoles through a cascade C-H activation and cyclization process