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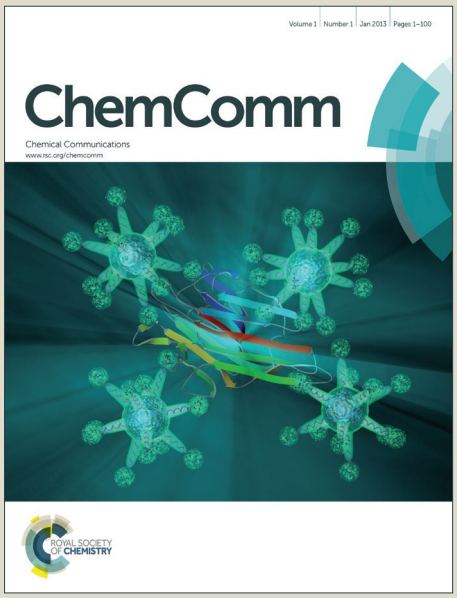

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Multi-site Cyclization via Initial C-H Activation Using Rhodium(III) Catalyst: Rapid Assembly of Frameworks Containing Indoles and Indolins†

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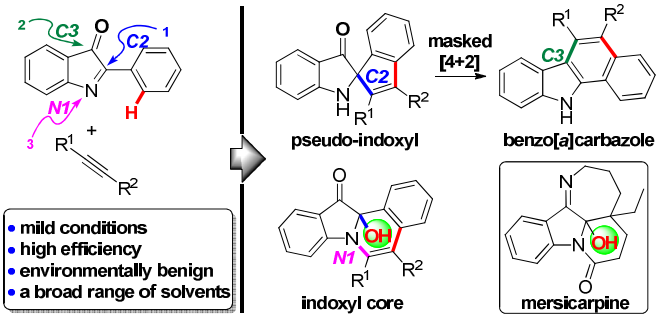
Tandem multi-site cyclization triggered by Rh(III)-catalyzed C–H activation has been achieved for highly efficient synthesis of spirocycle indolin-3-one (C2-cyclization), benzo[*a*]carbazole (C3-cyclization) and an unusual indoxyl core (N1-cyclization). In particular, the synthesis of pseudo-indoxyl is typically completed within 10 min, and the reaction tolerates air, water and a range of solvents.

Transition-metal-catalyzed C–H activation is widely used in the construction of C–C and C–heteroatom bonds.[1] Tandem cyclization following the first C–H bond cleavage has been recently described, providing efficient access to complex structures.[2,3] Studies have also been initiated to identify and exploit the possibilities of using multi-site cyclization to prepare a diverse range of complex frameworks from simple substrates.[4] Thus, continuing efforts are necessary to explore new synthetic potentials of tandem multi-site cyclization initiated by selective C–H activation.

Spiro 1,2-dihydro-3*H*-indol-3-one, commonly known as pseudo-indoxyl, is a valuable structural unit in many natural products and biologically active molecules.[5] Its derivatives have found wide applications in the fields of fluorescent dyes and solar cells.[6] The current synthetic methods typically rely on acid-mediated rearrangement and Smalley cyclization[7], which usually requires many steps, hazardous reagents and substrates that fit within a narrow scope. Therefore it remains necessary to develop more efficient and flexible protocols to access spiro pseudo-indoxyls.[8]

In this report, we describe a simplified synthesis of rigid pseudo-indoxyls through a tandem C–H activation/Grignard-like addition process involving 2-aryl-3*H*-indol-3-ones and alkynes (C2-cyclization). The pseudo-indoxyl generated in this way then undergoes facile rearrangement into the corresponding benzo[*a*]carbazole derivative through straightforward transformation of the residual carbonyl moiety (C3-cyclization).[7a-c,9] To our knowledge, this represents the first example of α-ketoimines-assisted C–H activation and also the first synthesis of NH benzo[*a*]carbazoles by direct coupling from N-unprotected indoles.[10] Even more interestingly, our studies uncovered an unusual [4+2] reaction pathway when 2-aryl-3*H*-indol-3-one reacted with certain alkynes (N1-cyclization), which afford an indoxyl core with a tertiary alcohol. Significantly, this unique framework is widespread in indole alkaloids such as mersicarpine. The C–H activation process in the approach proceeds efficiently under mild conditions in the presence of air and aqueous solvent, providing satisfactory yields in minutes with a low catalyst loading (Scheme 1).



Scheme 1 Synthesis of different frameworks via initial C–H activation.

We began our investigation on the coupling of 2-phenyl-3*H*-indol-3-one **1a** with alkyne **2a** (Table 1). The catalytic conditions comprising of $[RhCp^*Cl_2]_2$ and $AgSbF_6$ afforded C2-cyclization product **3aa** in moderate yield, while the catalytic system of $RhCp^*(MeCN)_3(SbF_6)_2$ led to a higher yield (entries 1–2).[11] Additive screening showed that AcOH and pivalic acid dramatically increased reaction rate as well as yield, such that good yields were obtained after only 5 min (entries 3–8). Solvent screening identified several

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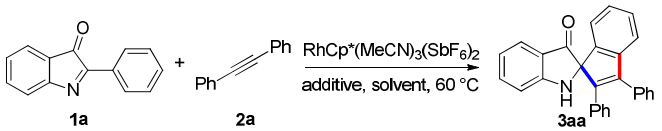
Table 1 Optimization of C2-cyclization reaction conditions.[a]



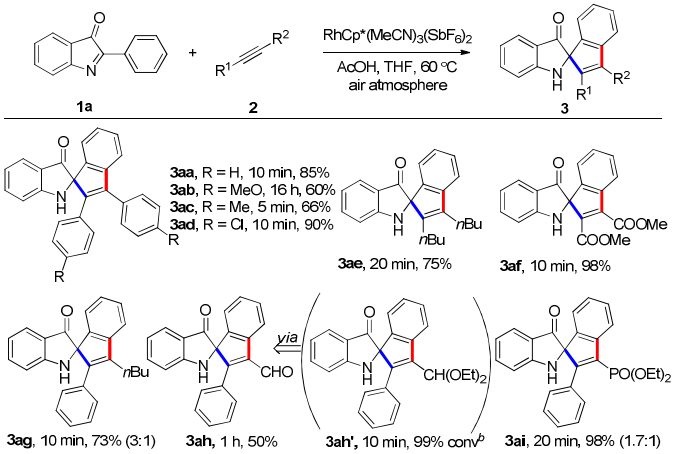
1a 2a 3aa

entry	additive	solvent	time	yield (%)[b]
1[c]	–	DCE	8 h	48
2	–	DCE	3 h	68
3	AcOH	DCE	5 min	83
4	PivOH	DCE	5 min	83
5	CF_3CO_2H	DCE	24 h	42
6	NaOAc	DCE	20 min	83
7	Cs_2CO_3	DCE	24 h	65
8	$Cu(OAc)_2$	DCE	10 min	79
9	AcOH	THF	5 min	85
10	AcOH	MeCN	2 h	82
11[d]	AcOH	THF	5 min	84
12[d,e]	AcOH	THF	20 min	85
13[d,f]	AcOH	THF	40 min	86
14[d,g]	AcOH	THF	10 min	85
15[d,g,h]	AcOH	THF	1 h	84
16[d,g,i]	**AcOH**	**THF**	**10 min**	**85**
17[d,g,i,j]	AcOH	THF	10 min	86

[a]Reaction conditions unless otherwise specified: 0.1 mmol of **1a**, 0.2 mmol of **2a**, 5 mol % of $RhCp^*(MeCN)_3(SbF_6)_2$, 1.0 equiv of additive, 2.0 mL of solvent, 60 °C, Ar atmosphere. [b]Isolated yield. [c]5mol % of $[Cp^*RhCl_2]_2$. [d]0.12 mmol of **2a**. [e]40 °C. [f]Room temperature. [g]2 mol % of $RhCp^*(MeCN)_3(SbF_6)_2$. [h]Under 1 atm of oxygen. [i]Air atmosphere. [j]2.0 equiv of H_2O was added.

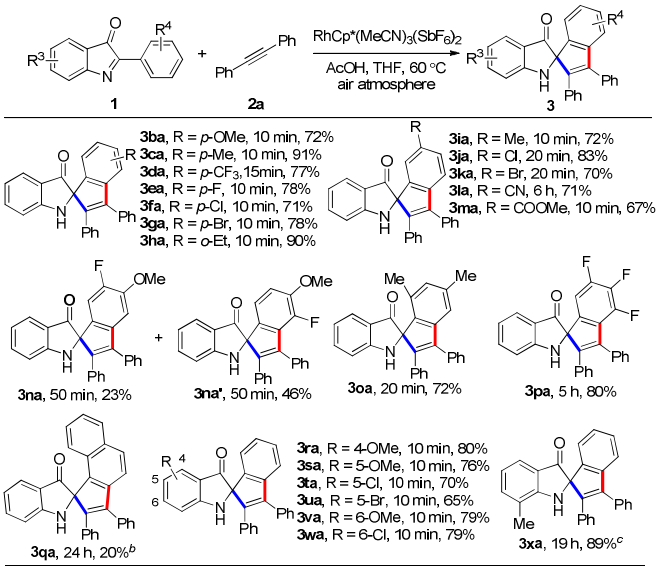
solvents compatible with this reaction (entries 9–10; Table S3). Good yield was obtained when less **2a** or catalyst was used, as well as when the reaction was conducted at room temperature (entries 11–14). The reaction proceeded to completion in 1 h under an oxygen atmosphere (entry 15). The reaction also proceeded smoothly in air and in the presence of water (entries 16–17).

Table 2 Reaction of 2-phenyl-3*H*-indol-3-one **1a** with alkynes **2**.[a]



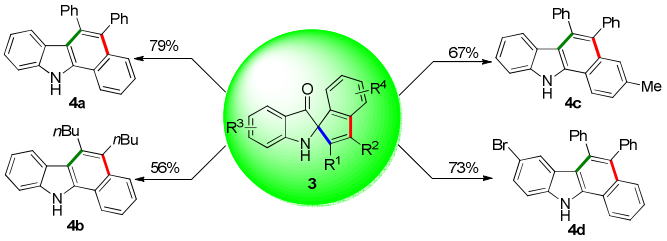
[a]Reaction conditions unless otherwise specified: 0.1 mmol of **1a**, 0.12 mmol of **2**, 2 mol % of $RhCp^*(MeCN)_3(SbF_6)_2$, 0.1 mmol of AcOH, 2.0 mL of THF, 60 °C, air atmosphere. Yields are reported for the isolated products. Ratios of regioisomers are given within parentheses and were determined by ^1H NMR analysis. Major isomers are shown. [b]The yield and regioselectivity of **3ah'** were verified by *in situ* conversion to **3ah** by extending the reaction time to 1 h.

Table 3 Substrate scope and limitations of 2-aryl-3*H*-indol-3-ones.[a]



[a]Reaction conditions unless otherwise specified: 0.1 mmol of **1**, 0.12 mmol of **2a**, 2 mol % of $RhCp^*(MeCN)_3(SbF_6)_2$, 0.1 mmol of AcOH, 2.0 mL of THF, 60 °C, air atmosphere. Yields are reported for the isolated products. [b]**1q** was recovered and an unidentified product was also detected. [c]2.0 mL of DCE, Ar atmosphere.

Using optimized conditions, we tested representative symmetrical and asymmetrical alkynes in our reaction (Table 2). Reactions with symmetrical alkynes revealed that electron-donating substituents appeared to slow the reaction and lower the yield (**3aa–3af**). Non-symmetrical alkyne **2g** reacted smoothly with **1a** to produce **3ag** in good yield with moderate regioselectivity. The corresponding hydrolyzed product **3ah** was constructed *in situ* after formation of **3ah'**. Electron-deficient alkyne **2i** showed excellent reactivity, giving a mixture of regioisomers in 98% yield.



Scheme 2 C3-cyclization for the synthesis of benzo[*a*]carbazole derivatives **4**. Reagents and conditions: To 0.1 mmol of **3** in 6.0 mL of dioxane was added 0.4 mmol of LiBr, and then 2.1 mmol of $NaBH_4$ was added partially to the reaction mixture at room temperature. HCl (conc., 0.35 mL) was added to the reaction mixture after **3** was consumed, and then the reaction was stirred at 50 °C for another 5 minutes.

Subsequently, we investigated the scope of 2-aryl-3*H*-indol-3-ones in reactions with **2a** (Table 3). Substrates bearing electron-donating or -withdrawing groups at the *para*- and *ortho*- positions of the 2-phenyl moiety led to 71%–91% yields in less than 15 min (**3ba**–**3ha**). Reactions with various *meta*-substituted 2-phenyl-indolin-3-ones showed that steric interactions largely controlled the yields of the corresponding products **3ia**–**3ma**. Among these substrates, **1l** with a *meta*-nitrile substitution reacted more slowly, probably due to inhibition by nitrile coordination. Subtle steric effects of **1n** carrying a meta-F atom has been observed, leading to isomers **3na** and **3na'** with moderate regioselectivity. Di- or tri-

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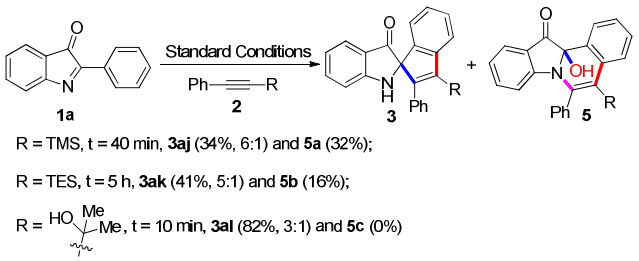
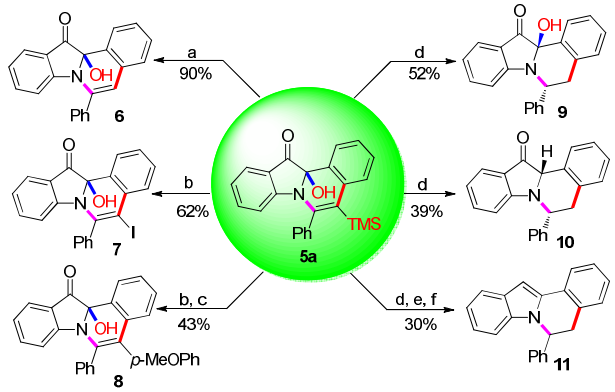
substituted 2-phenyl-indolin-3-ones **1o** and **1p** also reacted smoothly. However, 1-naphthyl-substituted **1q** gave lower reactivity, likely due to strong steric effects during formation of the rhodacyclic intermediate. In addition, we explored the reactions of various indolin-3-ones bearing 2-phenyl substitutions with **2a** to further probe the generality of the transformation (**3ra**–**3xa**).

To demonstrate the synthetic usefulness of our approach, we converted the carbonyl of C2-cyclization products **3** into the corresponding alcohol intermediates by reduction in dioxane. These intermediates then underwent acid-promoted selective vinyl migration to produce benzo[*a*]carbazole derivatives **4** in moderate to good yields over two steps (Scheme 2).[12]



Scheme 3 N1-cyclization for the synthesis of special indoxyl cores **5**. Major isomers are shown.

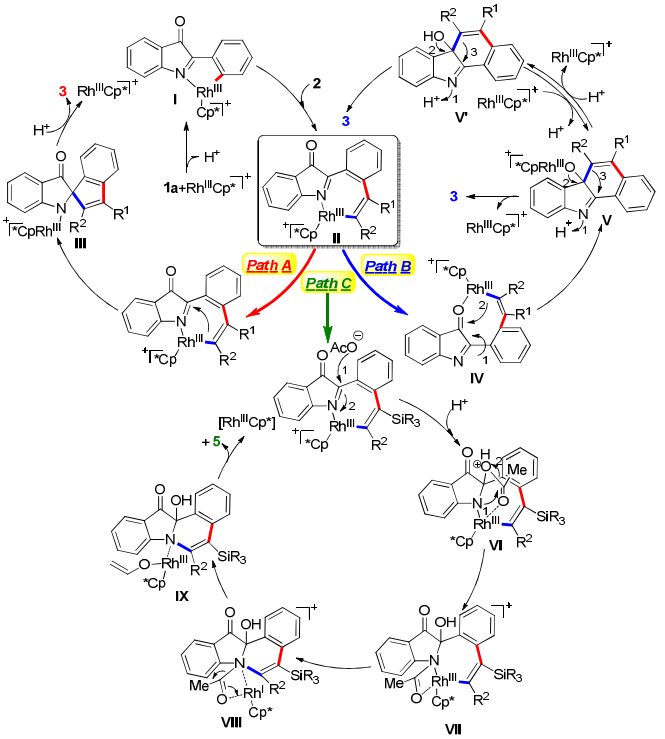
Terminal alkynes failed to react under our standard conditions, alternatively, the terminal alkyne precursor trimethylsilyl-substituted alkyne **2j** reacted smoothly, affording isomers **3aj** and **3aj'** in 34% yield. We were surprised to isolate compound **5a** bearing an indoxyl skeleton with a tertiary alcohol, which is structurally similar to that of many indole alkaloids (Scheme 3). Further screening of reaction conditions did not improve the yield of **5a** (Table S4).[13] Triethyl(phenylethynyl)silane **2k** also provided the isomers **3ak** and **3ak'** in 41% yield. Despite the similar steric effects as **2j**, **2l** gave only the C2-cyclization products.



Scheme 4 Derivatization of special indoxyl core **5a**. Reagents and conditions: (a) TBAF (1.5 equiv), THF, rt, 3 h, 90%; (b) N-iodosuccinimide (0.9 equiv), MeCN, rt, 2 h, 62%; (c) 4-methoxy-phenylboronic acid (3.0 equiv), $CsCO_3$ (10.0 equiv), $(Ph_3P)_4PdCl_2$ (0.05 equiv), 1,4-dioxane/H_2O (4:1), 50 °C, 1.5 h, 70%; (d) 10 wt. Pd/C (30%), H_2 (1 atm), DCM, rt, 5 h, **9** (52%), **10** (39%); (e) LiBr (4.0 equiv), $NaBH_4$ (24.0 equiv), 1,4-dioxane, 12 h; (f) $BF_3{\cdot}Et_2O$ (2.0 equiv), Et_3SiH (2.2 equiv), 0.3 h, 78% over two steps.

Further conversion of **5a** into other useful synthetic building blocks was investigated. Firstly, the TMS group could be easily removed to give corresponding terminal alkyne coupling product **6**. Iodination of **5a** afforded **7**, which was then transformed into the formal non-symmetrical internal alkyne coupling product **8**. By hydrogenation (palladium/C), **5a** was reduced to **9** and **10** in respective yields of 52% and 39%. Further conversion of **10** produced indole derivative **11** (Scheme 4).

A plausible catalytic cycle is proposed in Scheme 5. First, the imine **1a** directs *ortho* C–H activation to form a five-membered rhodacycle intermediate **I**, which undergoes regioselective alkyne insertion to yield seven-membered ring **II**. In path A, Grignard-like addition of the organometallic species **II** to the imine group generates a rhodium intermediate **III**. Final protonolysis of **III** provides the desired product **3** and regenerates the catalyst. Based on a report that the carbonyl group of **1a** can be attacked prior to Grignard-like addition,[14] we propose the alternative path B, in which intermediate **II** is converted to **IV** via a "roll-over" process. Intermediate **IV** subsequently undergoes Grignard-like addition to produce **V**. Intermediate **V** or its hydrolytic form **V'** affords **3** through acid-mediated rearrangement.[15] In path C, an acetate ion undergoes intermolecular nucleophilic addition to intermediate **II,** forming a C–O bond and generating **VI**. Subsequent intramolecular aminolysis produces **VII**. Then a process of reductive elimination/oxidative addition (**VIII**/**IX**) gives the N1-cyclization product **5** and releases the rhodium catalyst.



Scheme 5 Possible mechanism for the reaction of **1a** with internal alkynes.

Conclusions

In conclusion, we have developed a highly efficient synthesis of pseudo-indoxyl via C2-cyclization under mild conditions. The synthesis is complete within several minutes in most cases. In addition, we provided an alternative synthetic strategy of masked [4+2] annulation via a [3+2] process. Simple transformation allowed the construction of benzo[*a*]carbazole derivative, another valuable heterocyclic scaffold, via formal C3-cyclization. Most importantly, N1-cyclization was observed when TMS- or TES-modified internal alkynes were employed as coupling partners, affording a series of indoxyl cores of indole alkaloids. Further studies of catalytic mechanism and synthetic applications are under investigation in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/Address here.

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11 For more studies employing $[RhCp^*Cl_2]_2$ catalyst, see Tables S1 and S2 in the Supporting Information. For single crystal X-ray analysis of **3a** (CCDC 982769), see the Supporting Information.

12 The structure of rearrangement product **4a** was further confirmed by comparison with previous reports after methylation (ref 10c).

13 For single crystal X-ray analysis of **5a** (CCDC 1003133) and further mechanistic studies, see the Supporting Information.

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15 Regardless of whether the reaction occurs by path A or B, the carbonyl moiety of **1** is essential, probably because of its strong electron-withdrawing properties. Imines in which the ketone was replaced with alkane or lactone, such as **1y** and **1z**, did not react in this catalytic system.