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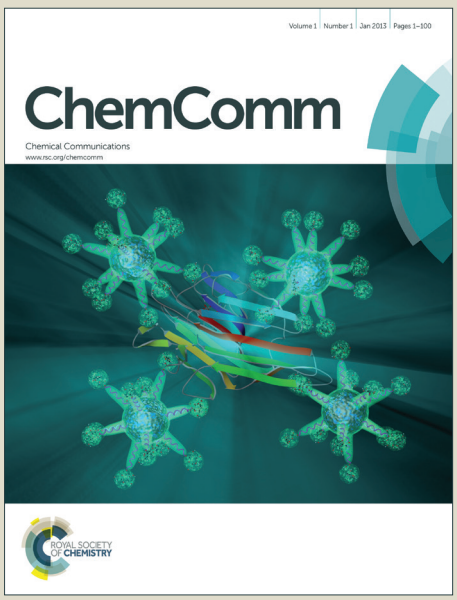

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Rhodium-catalyzed intramolecular annulation via C-H activation leading to fused tricyclic indole scaffolds

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The rhodium(III)-catalyzed intramolecular annulation of alkyne-tethered acetanilides for the synthesis of fused tricyclic indole scaffolds via C-H activation has been developed, which has the potential for the synthesis of many indole alkaloids. This reaction proceeds under mild reaction conditions and with tolerance to a variety of functional groups.

The 3,4-fused tricyclic indole nucleus are found in a number of biologically active natural products and pharmaceticals, such as lysergic acid,[1] rugulovasine A,[2] dehydrobufotenine,[3] clavicipitic acid,[4] decursivine,[5] and indolactam V (Figure 1).[6] Accordingly, the syntheses of these natural products have been the subject of intensive research, and a number of strategies are now available.[7] However, the development of conceptually different synthetic approaches is still of great interest.[8]

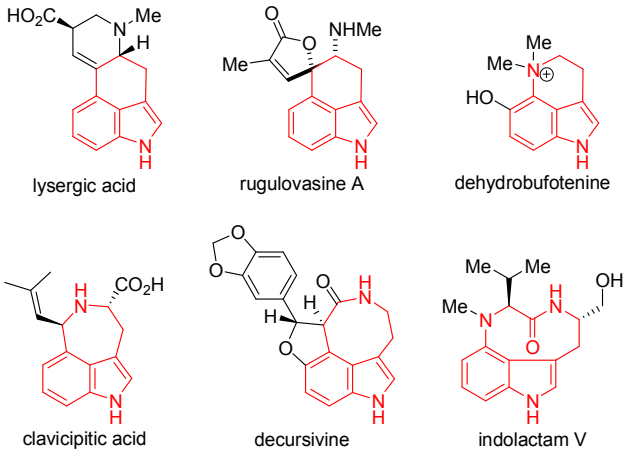
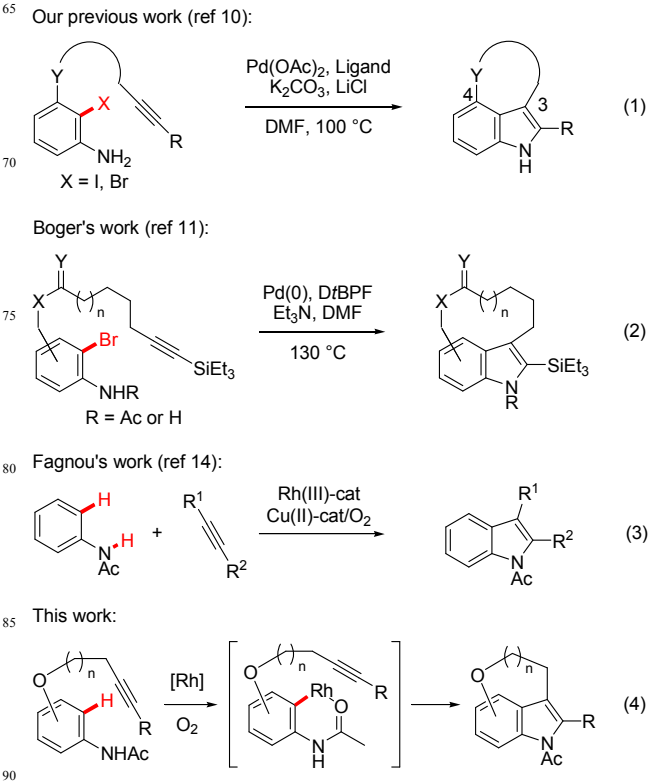


Figure 1 Selected examples of 3,4-fused indole alkaloids.

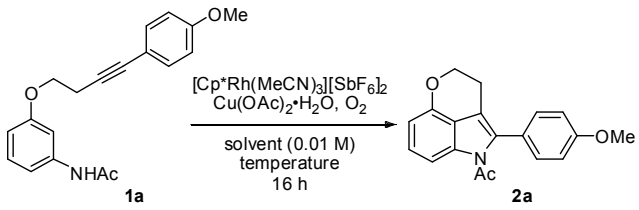
In connection with some of our work on the total synthesis of 3,4-fused indole alkaloids,[1a-b,2a,4b-c,5b-d,6a] we have recently developed a new strategy for the construction of such skeleton via intramolecular Larock indolization,[9] and achieved the total synthesis of fargesine by using this methodology (Scheme 1, eq 1).[10] Meanwhile, Boger independently reported a similar work (Scheme 1, eq 2).[11] However, these methods require *ortho*-halogenated anilines as starting materials thus adding cost[12] and limiting its further application. Recently, the rhodium-catalyzed C-H activation has received significant interest because of its high atom-economy, selectivity, and functional-group tolerance.[13] In 2008, Fagnou and co-workers reported an elegant method for the synthesis of indoles via rhodium-catalyzed oxidative annulation of acetanilides with internal alkynes. (Scheme 1, eq 3).[14] A major advance of this method is that it employs more readily available *N*-acetyl anilines as starting materials thus minimizing the substrate preactivation. Based on these observations, we became interested in the rhodium-catalyzed intramolecular reaction of alkyne-tethered acetanilides (Scheme 1, eq 4). Although the rhodium-catalyzed intramolecular C-H activation reactions have been very recently reported, to the best of our knowledge, the intramolecular reaction of alkyne-tethered acetanilides has never been reported.[15] The successful development of this reaction would lead to a more efficient and economical synthesis of 3,4- and 3,5-fused tricyclic indoles. Herein, we wish to report these results.



Scheme 1 Intramolecular annulation strategies for the synthesis of fused tricyclic indoles.

To test our hypothesis, compound **1a** was employed as a model substrate and subjected to the first-generation Fagnou's intermolecular reaction conditions. We found that treatment of **1a** with $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (210 mol%) in *t*-AmOH at 80 °C under Ar atmosphere afforded the desired 3,4-fused tricyclic indole **2a** in 31% yield (Table 1, entry 1). Increasing the reaction temperature to 100 °C gave almost the same result (Table 1, entry 2). When compound **1a** was treated with the second-generation Fagnou's intermolecular reaction conditions by using molecular oxygen as the terminal oxidant in conjunction with a catalytic amount of a $Cu(OAc)_2{\cdot}H_2O$ at 60 °C, the yield of indole **2a** was slightly increased to 37% (Table 1, entry 3). To our delight, when acetone was used as the solvent at room temperature, the desired indole **2a** could be obtained in 61% yield (Table 1, entry 4). Further optimization of the amount of catalyst showed that: when 5 mol% [Rh] was used, the yield of **2a** was remained (Table 1, entry 5); when the amount of [Rh] catalyst was decreased to 2.5 mol%, a slight decrease of the yield was observed (Table 1, entry 6). The solvent was further screened, replacement of acetone with DCE led to a 30% yield (Table 1, entry 7). When cyclohexanone was used as the solvent, the reaction did not work at all (Table 1, entry 8). It was worthy to mention that treatment of **1a** under the first-generation Fagnou's intermolecular reaction conditions by simply changing the solvent to acetone at room temperature provided the desired indole **2a** in 62% yield. Considering the use of molecular oxygen more green and economical than the use of stoichiometric amounts of a metal oxidant (2.1 equiv of $Cu(OAc)_2$), the reaction condition was optimized as $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%) under O_2 in acetone (0.01 M) at room temperature (Table 1, entry 5).

Table 1 Optimization of reaction conditions[a]

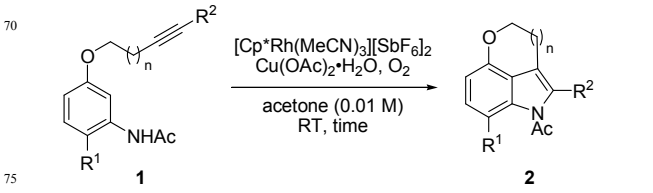


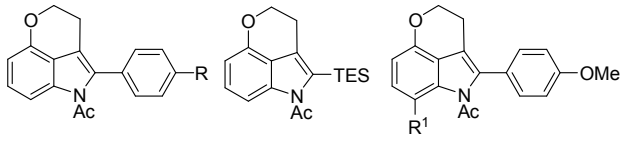
Entry	Equiv. of [Rh]	Equiv. of [Cu]	Solvent	Temp.	Yield (%)
1 [b]	0.10	2.10	*t*-AmOH	80 °C	31
2 [b]	0.10	2.10	*t*-AmOH	100 °C	33
3	0.10	0.50	*t*-AmOH	60 °C	37
4	0.10	0.50	Acetone	RT	61
5	**0.05**	**0.20**	**Acetone**	**RT**	**63**
6	0.025	0.20	Acetone	RT	53
7	0.05	0.20	DCE	RT	30
8	0.05	0.20	Cyclohexanone	RT	0
9 [b]	0.05	2.10	Acetone	RT	62

[a] Reaction conditions: **1a** (0.1 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$, $Cu(OAc)_2{\cdot}H_2O$, under O_2, acetone (10 mL), room temperature. Isolated products are given. [b] Reaction performed under Ar atmosphere.

With the optimized reaction in hand, we next examined the substrate scope of the reaction. Under our optimized reaction conditions, the reaction proceeded smoothly to give a series of 3,4-fused tricyclic indoles in moderate to excellent yield (Table 2). Firstly, the electronic effects of aryl groups attached to the terminal alkyne were first examined (Table 2, **2a-e**). Compounds **1a** and **1b** with electron-donating groups gave the desired products **2a** and **2b** in 63% and 60% yield, respectively. Compounds **1c** with electron-neutral group provided the corresponding product **2c** in 55% yield. Compounds **1d** with electron-withdrawing group provided the corresponding product **2d** in 48% yield. These results indicated that electronic factors of the phenyl moiety indeed affected the reactivity of this transformation. The triethylsilyl-group substrate also tolerated the reaction condition and produced the desired indole in 55% yield (Table 2, **2e**).

Table 2 Substrate scope for the formation of 3,4-fused indoles[a]

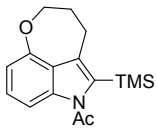




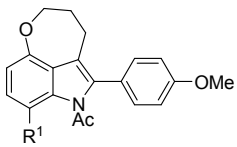
2a, R = OMe, 16 h, 63%
2b, R = Me, 16 h, 60%
2c, R = H, 16 h, 55%
2d, R = Cl, 16 h, 48%

2e, 16 h, 55%

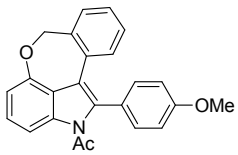
2f, R^1 = OMe, 16 h, 99%
2g, R^1 = Me, 16 h, 92%
2h, R^1 = Cl, 16 h, 29% (99%)[b]



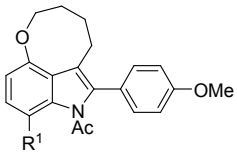
2i, 48 h, 63%



2j, R^1 = H, 16 h, 72%
2k, R^1 = Me, 16 h, 98%
2l, R^1 = OMe, 16 h, 99%



2m, 72 h, 38% (93%)[b]

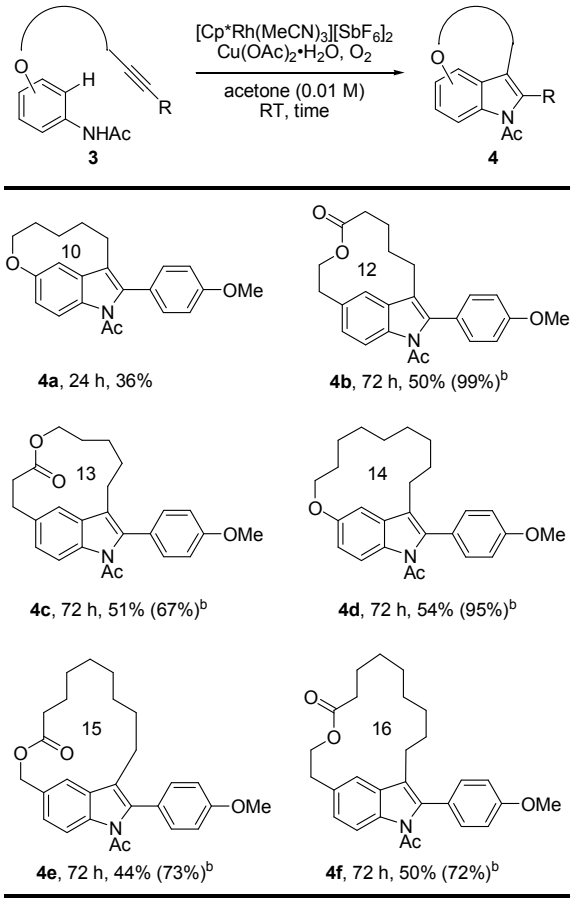


2n, R^1 = H, 16 h, 18%
2o, R^1 = Me, 48 h, 62% (99%)[b]
2p, R^1 = OMe, 48 h, 64% (97%)[b]

[a] Reaction conditions: **1a** (0.1 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), under O_2, acetone (10 mL), room temperature. Isolated products are given. [b] Yield based on recovered starting material in parentheses.

The electronic effects of acetanilides were next examined (Table 2, **2f-h**). Surprisingly, substrates **1f** and **1g** with electron-rich R^1 groups gave the desired products in excellent yield under the optimized reaction conditions (Table 2, **2f** and **2g**). However, substrate with election-deficient R^1 group resulted in only moderate yield (Table 2, **2h**). These results imply that the acetanilide metalation step was extremely sensitive to electronic effects. Most likely, the election-withdrawing effect of R^1 group had a strong influence on the C-H activation process. The reaction was then extended to prepare 3,4-medium ring (7- and 8-membered rings). We were pleased to find that the desired indole products were still obtained in good to excellent yield (Table 2, **2i-p**), although the yield of substrate leading to 8-membered ring **2n** was relatively low. As mentioned above, substrates with electron-rich R^1 groups gave the desired 3,4-fused tricyclic indoles in better yield (Table 2, **2k**, **2l**, **2o** and **2p**).

Table 3 Substrate scope for the formation of 3,5-fused indoles[a]



[a] Reaction conditions: **1a** (0.1 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2 \cdot H_2O$ (20 mol%), under O_2, acetone (10 mL), room temperature. Isolated products are given. [b] Yield based on recovered starting material in parentheses.

Encouraged by the results for the 3,4-fused tricyclic indoles, without individual optimization, the scope of the intramolecular reaction was examined for the preparation of 3,5-fused tricyclic indoles from the corresponding acetanilides (Table 3). The reaction was found to be very general and compatible with a variety of ring sizes. Although the 10-membered tricyclic products **4a** was formed in moderate yield, the 3,5-macrocycle (≥ 12-membered ring) indole products **4b-f** could be obtained in good to excellent yield.

In summary, we have developed the first rhodium-catalyzed intramolecular annulation of alkyne-tethered acetanilides for the synthesis of fused tricyclic indoles via C−H bond activation. This reaction proceeds under mild reaction conditions (room temperature) and with tolerance to a variety of functional groups, and employs molecular oxygen as the stoichiometric terminal oxidant. We expect that this intramolecular protocol will find widespread use in chemical synthesis.

Acknowledgements

We gratefully acknowledge the support of the National Natural Science Foundation of China (Nos. 21372017, 21290183), the National Basic Research Program of China (973 Program, NO. 2010CB833200), and the Ph.D. Programs Foundation of Ministry of Education of China (No. 20120001110100).

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic characterization. See DOI: 10.1039/b000000x/

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