ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2018, **5**, 3263

Facile construction of hydrogenated azepino [3,2,1-*hi*]indoles by Rh(III)-catalyzed C–H activation/[5 + 2] annulation of *N*-cyanoacetylindolines with sulfoxonium ylides†

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Received 11th August 2018,
Accepted 1st October 2018

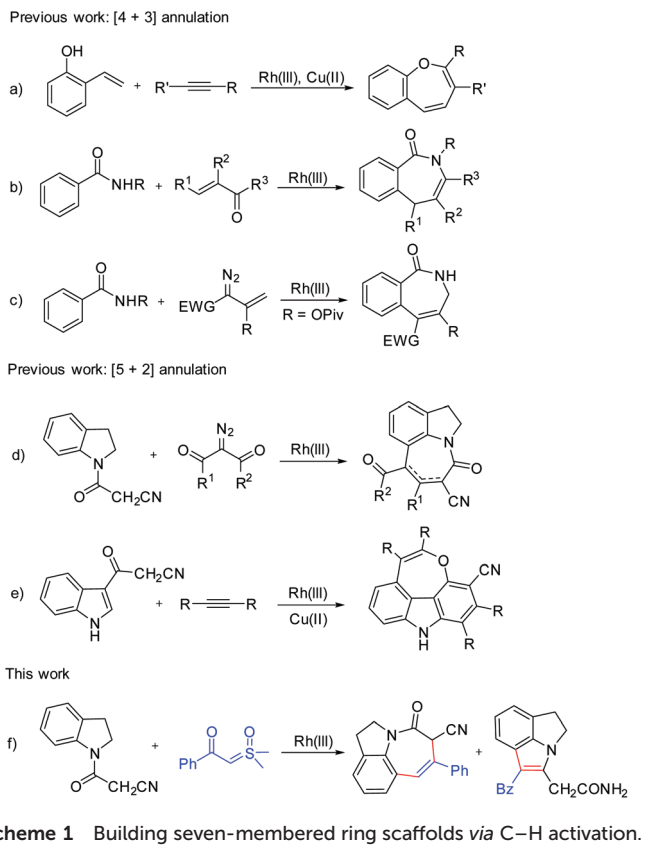
DOI: 10.1039/c8qo00861b

rsc.li/frontiers-organic

Rhodium(III)-catalyzed regio- and chemoselective [5 + 2] annulation between *N*-(cyanoacetyl)indolines and sulfoxonium ylides has been realized, leading to efficient construction of seven-membered rings under mild conditions. This reaction proceeded *via* C–H activation with sulfoxonium ylides as carbene synthons.

Metal-catalyzed C–H activation/annulation reactions have been extensively explored as an efficient and powerful means to access diverse bioactive heterocycles.[1] Among the various efficient catalysts, stable Cp*Rh(III) complexes are outstanding C–H activation catalysts for formal [3 + 2], [4 + 2] and [4 + 1] annulation reactions. These Rh(III)-catalysts are particularly useful owing to their high efficiency, good selectivity, and functional group tolerance.[2] However, Rh(III)-catalyzed synthesis of seven-membered rings *via* [4 + 3][3] annulation and especially [5 + 2][4] annulation is still rare. Gulías reported the [4 + 3] coupling of *o*-vinylphenols with alkynes leading to benzoxepines (Scheme 1a).[3a] Glorius and co-workers pioneered the synthesis of azepinones *via* Rh-catalyzed coupling of amides and acroleins (Scheme 1b).[3g] A similar skeleton was constructed by the Cui group using vinyl diazo compounds as C3 coupling reagents (Scheme 1c).[3i] Limited studies on the [5 + 2] annulation reactions by Rh(III) catalysis have been reported. The Wang group achieved two types of fused seven-membered rings by C–H activation of indoles and indolines with chelation assistance (Scheme 1d and e).[4a,c] Among these systems, the coupling partners have been mostly limited to enones, internal alkynes, and diazo compounds. Despite the progress, the efficiency and selectivity of these systems leave large room for improvement, especially given the synthetic and biological significance of various seven-membered ring skeletons.[5–8]

Seven-membered ring scaffolds widely exist in natural products and drug related molecules.[6] Among these scaffolds, hydrogenated azepino[3,2,1-*hi*]indole with a fused tricyclic structure is a skeletal compound of alkaloids such as



Scheme 1 Building seven-membered ring scaffolds *via* C–H activation.

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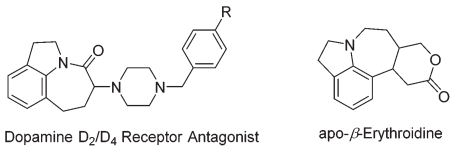
†Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical data and NMR spectra. See DOI: 10.1039/c8qo00861b



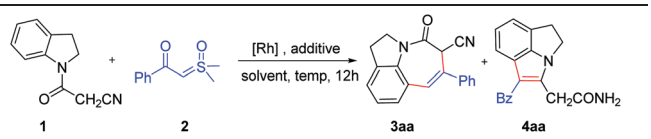
Scheme 2 Drug related molecule and a natural product containing a hydrogenated azepino[3,2,1-*hi*]indole skeleton.

β-erythroidine (Scheme 2).[5a,7] Meanwhile, it is also a skeleton of a potential dopamine D2/D4 receptor antagonist.[8]

Although it is of great significance, only very few examples for the synthesis of this skeleton by directed C–H activation/annulation reactions have been reported.[4d,9] It is noteworthy that the Wang group[4d] described a Rh(III)-catalyzed C–H activation/annulation reaction using diazo compounds as carbene precursors giving the analogous skeleton (Scheme 1d). Very recently, we and others applied sulfoxonium ylides as an attractive carbene source in Rh(III)-catalyzed C–H alkylation/annulative coupling with arenes.[10] Considering the easy accessibility and stability of sulfoxonium ylides, annulative synthesis of useful heterocycles should be explored. Herein, we wish to report the Rh(III)-catalyzed formal [5 + 2] annulation of *N*-cyanoacetylindolines with sulfoxonium ylides to deliver the fused tricyclic skeleton with the construction of seven-membered rings. Meanwhile, minor five-, five- and six-membered fused ring structures are isolated in some cases.

We started our research by treating *N*-substituted indoline **1a** (0.2 mmol) with sulfoxonium ylide **2a** (0.3 mmol) in the presence of $Cp^*Rh(OAc)_2{\cdot}H_2O$ (8 mol%) in DCE (2.0 mL) at 80 °C for 12 h (Table 1, entry 2). The corresponding fused tricyclic product **3aa** was isolated in a low yield of 24%. The *in situ* generation of the catalyst by using $[Cp^*RhCl_2]_2$ (4 mol%) and AgOAc (16 mol%) gave only a trace amount of the product (entry 1). Screening of the solvents demonstrated that *t*-AmOH was optimal (entries 3–6). The Lewis acid additives (entries 10 and 13) were found to be superior to the base additives (entries 7–9). The reaction efficiency was sensitive to the temperature, and the yield decreased at a higher or lower temperature (entries 11 and 12). It is noteworthy that a different fused tricyclic skeleton **4aa** containing five-, five- and six-membered rings was isolated with 10% yield when LiOAc was added (entry 10). It is likely that **4aa** was generated by the dehydration of methene in a sulfoxonium ylide unit with a carbonyl group in a *N*-cyanoacetylindoline unit, which is a competitive reaction to the generation of **3aa**. Changing the loading of LiOAc was not positive to increase the yield (entries 14 and 15). Finally, we chose the conditions in entry 15 as the standard reaction conditions.

Table 1 Optimization of the reaction conditions[a]

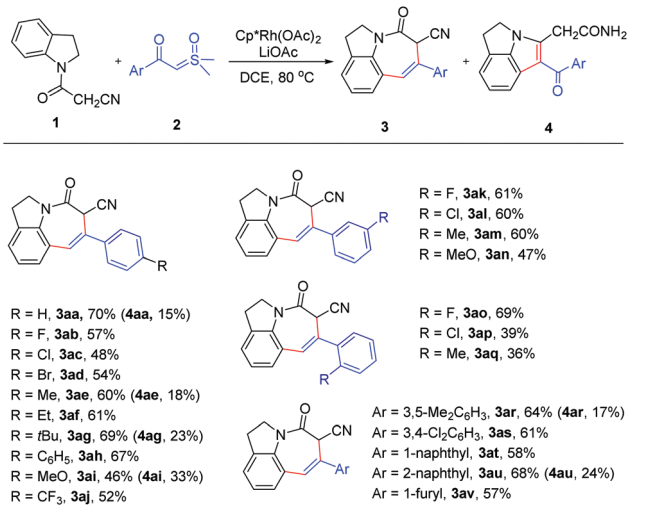


Entry	Additive (mol%)	Solvent (mL)	Temp (°C)	Yield of **3aa** (%)
1[b]	AgOAc (16)	DCE (2)	80	Trace
2	NO	DCE (2)	80	24
3	NO	Dioxane (2)	80	37
4	NO	TFE (2)	80	nd
5	NO	Toluene (2)	80	21
6	NO	*t*-AmOH (2)	80	51
7	CsOAc (50)	*t*-AmOH (2)	80	37
8	K_2CO_3 (50)	*t*-AmOH (2)	80	20
9	KOAc (50)	*t*-AmOH (2)	80	40
10	$Mg(OAc)_2$ (50)	*t*-AmOH (2)	80	56
11	$Mg(OAc)_2$ (50)	*t*-AmOH (2)	60	24
12	$Mg(OAc)_2$ (50)	*t*-AmOH (2)	100	47
13	LiOAc (50)	*t*-AmOH (2)	80	69 (10)
14	LiOAc (100)	*t*-AmOH (2)	80	68 (10)
15	**LiOAc (25)**	***t*-AmOH (2)**	**80**	**70 (15)**

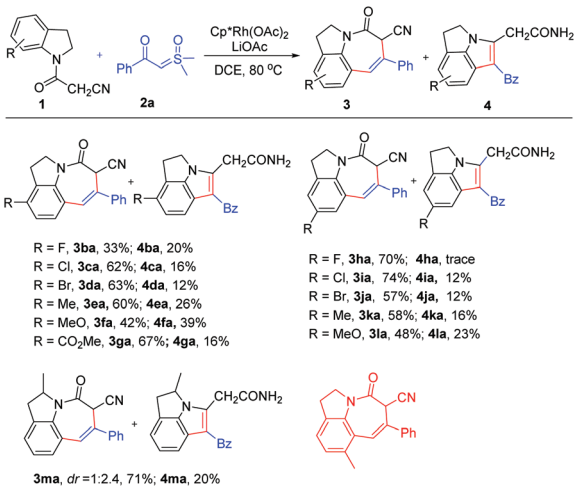
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Cp^*Rh(OAc)_2{\cdot}H_2O$ (8 mol%), additive, solvent (2 mL), 12 h, under an Ar atmosphere at 80 °C, isolated yield of **3aa**, isolated yield of **4aa** in parentheses. [b] $[Cp^*RhCl_2]_2$ (4 mol%) instead of $Cp^*Rh(OAc)_2{\cdot}H_2O$ (8 mol%).

A broad scope of sulfoxonium ylides has been established for the [5 + 2] annulation reaction system under the standard conditions (Scheme 3). Benzoyl-substituted sulfoxonium ylides bearing electron-donating or -withdrawing groups at 2-, 3-, and 4-positions of the phenyl ring all coupled with **1a** affording the fused products in moderate to good yields (**3aa–3aq**). Sulfoxonium ylides with multi-substituted phenyl groups (**2r** and **2s**) were also applicative in this catalytic system. In the cases of **2e**, **2g**, **2i** and **2r** with the introduction of electron-donating groups (Me, *t*Bu, OMe and di-Me), a minor five-membered fused product was isolated in a relatively low yield, indicative of the sensitivity to the electronic effect. Besides, the substrates of 1-naphthoyl, 2-naphthoyl and 1-furoyl substituted sulfoxonium ylides also provided the corresponding products (**3at–3av**, 57%–68%).

Next, the scope of the *N*-substituted indolines was investigated (Scheme 4). *N*-Cyanoacetylindolines bearing methyl,



Scheme 3 Substrate scope of sulfoxonium. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $Cp^*Rh(OAc)_2{\cdot}H_2O$ (8 mol%), LiOAc (25 mol%), *t*-AmOH (2 mL), 80 °C, 12 h, isolated yield.

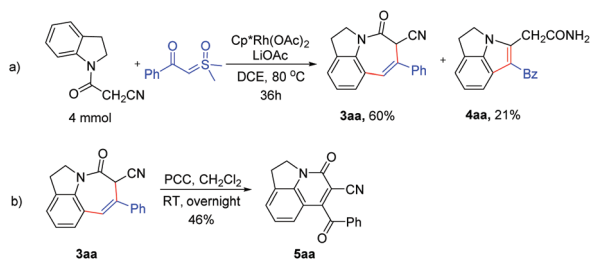


Scheme 4 Substrate scope of indolines. Reaction conditions: 1 (0.2 mmol), **2a** (0.3 mmol), Cp*Rh(OAc)$_2$·H$_2$O (8 mol%), LiOAc (25 mol%), *t*-AmOH (2 mL), 80 °C, 12 h, isolated yield.

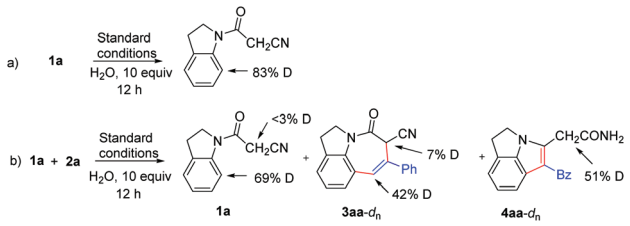
methoxy, halo and methoxycarbonyl groups at different positions afforded both the corresponding major seven-membered fused products in moderate yields and the minor five-membered fused products in low yields (**3ba–3la**, 33%–74%; **4ba–4la**, 12%–39%). Among these, the 4-methoxy indoline substrate **1f** gave equipotent yields of the two kinds of products owing to the electron-donating effect of the methoxy group. Besides, diastereomeric products were isolated when 2-methyl-substituted indoline **3m** was treated with **2a**. Unfortunately, the 6-substituted indoline was not applicative in this catalytic system which may be attributed to the steric hindrance.

To demonstrate the synthetic utility of the [5 + 2] annulation reaction, the gram-scale synthesis (4 mmol scale) of **3aa** and **4aa** was performed. The seven-membered fused ring product **3aa** was obtained in 60% yield and the five-membered fused ring product **4aa** was obtained in 21% yield (Scheme 5a). Moreover, the derivatization of **3aa** with PCC was conducted and a five-, six-, and six-membered fused ring product 6-benzoyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carbonitrile was obtained in 46% yield (Scheme 5b).

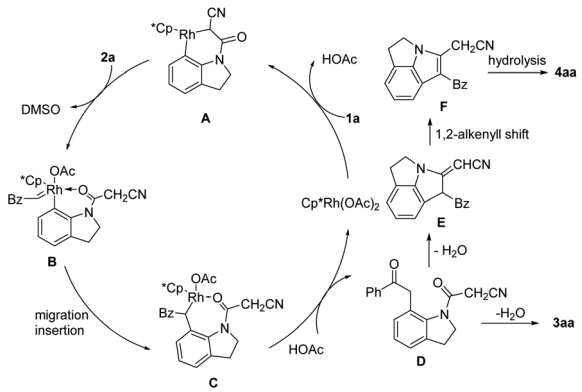
To gain some insight into the mechanism of this annulation reaction, H/D exchange reactions were performed. 83% Deuteration at the C7-position of recovered **1a** was detected in



Scheme 5 Gram-scale synthesis and synthetic applications.



Scheme 6 Mechanistic studies.



Scheme 7 Proposed reaction pathway.

the presence of **2a** and D_2O (Scheme 6a). H/D exchange was also observed in the presence of D_2O and the absence of **2a** (Scheme 6b). These results indicate the reversibility of C–H bond cleavage at the indoline C7-position. Deuteration of the olefin C–H bond of the product **3aa**-d_n revealed that a hydrolysis process may occur before the intramolecular condensation annulations. And there may be a 1,2-alkenyl shift process according to the result of deuteration of CH_2 in the product **4aa**-d_n.

On the basis of previous reports[4a,10a,11] and the experimental results, a plausible catalytic cycle is proposed (Scheme 7). The first step is likely to be C-coordination assisted cleavage of the C–H bond of the C7-position to give a rhodacyclic intermediate **A**, which then reacts with **2a** to afford the carbene species **B** with the elimination of DMSO. Migratory insertion of the carbene into the Rh–C bond followed by a protonolysis process generates the intermediate **D**. Selective condensation of CH_2CN with the carbonyl group of the ylide unit gives the major product **3aa**. The condensation of CH_2 of the ylide unit with the carbonyl group of the indoline unit gives an intermediate **F** followed by a 1,2-alkenyl shift process and a hydrolysis process leading to the minor product **4aa**.

Conclusions

In summary, we have demonstrated Rh(III)-catalyzed construction of seven-membered rings by regioselective C–H activation of the C7 position of indolines. The formal [5 + 2] annulation

reactions proceeded efficiently under mild and redox-neutral conditions. The scopes of indolines and sulfoxonium ylides were investigated and found to be quite decent. Given the rapid assembly of the fused tricyclic skeletons otherwise hard-to-access, broad substrate scope, and mild and redox-neutral conditions, this C–H activation/annulation reaction may find applications in the synthesis of related structures.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The NSFC (No. 21525208 and 21472186), research fund from Henan Normal University (5101034011009), and start-up fund from Henan Normal University (qd16111, for B. L.) are gratefully acknowledged.

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