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Construction of Pyridazine Analogues *via* Rhodium-mediated C-H Activation

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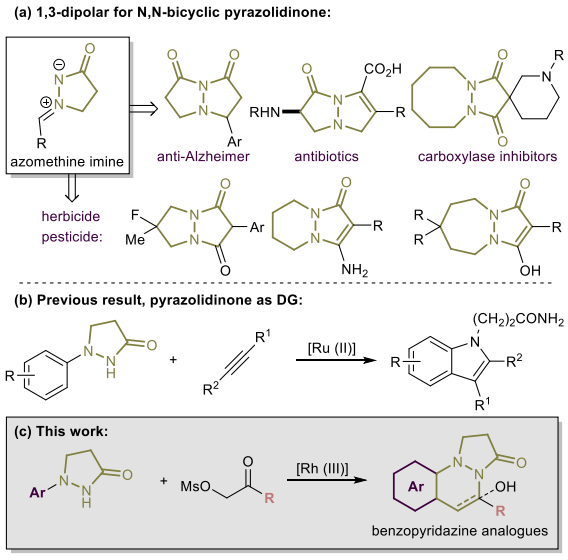
Abstract: Herein a rhodium (III)-mediated catalysis was demonstrated for approaching the structurally divergent N,N-bicyclic pyridazine analogues. The pyrazolidinone moiety was used to direct the *ortho* C-H activation and this led to a general synthesis of benzopyridazine analogues with satisfactory yields. The crucial effect of the base was illustrated in the sequential dehydration process. For mechanistic insight, control experiments were performed for illustration of the catalytic circle. Gram scale synthesis and several practical transformations were conducted for further applications.

Keywords: pyrazolidinone; rhodium catalysis; C-H activation; divergent pathways; fused heterocycle

Heterocyclic compounds are familiar as bioactive chemicals in the pharmaceutical and agrochemical industry.[1] Among which the N,N-bicyclic pyrazolidinone serves as a vital skeleton in investigations of pesticides, herbicides and inhibitors.[2] The potential of this structure has led to research into methodology development and application of derivatives. For synthetic purpose, 1,3-dipolar azomethine imine was universally regarded as a key synthon which could couple with various partners to construct the bicyclic skeletons (**Scheme 1a**). Most of the successful cases were initiated by transition metals[3] or triggered by organocatalytic systems[4] including N-heterocyclic carbenes, amines, or phosphines and led to 5- to 8-membered heterocycles. However, further fused cyclic derivatives, which are frequently used as dyestuffs, are challenging targets for these classical methods.[5] Herein we describe a C-H activation process, which involves pyrazolidinone as a directing group, for accessing fused-heterocyclic analogues straightforward.

The activation of C-H bond mediated by transition metals has dramatically aided the synthesis of complex structures. The substrate bearing directing group, which forms a chelate with metal catalysts and followed by sequential C-H activation,[6] facilitates many annulation processes especially for heterocyclic compounds.[7] In cooperation with alkynes[8], the pyrazolidinone moiety was previously designated as a directing group for ruthenium-mediated indole synthesis (**Scheme 1b**) [8f]. Herein we utilized an α-O-mesyl ketone as a partner, which acts as an oxidized alkyne equivalent[9], for construction of fused benzopyridazine analogues (**Scheme 1c**).

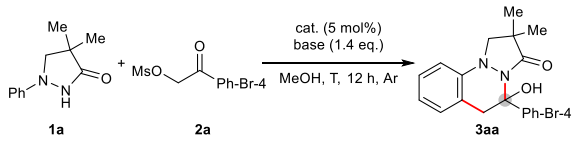


Scheme 1. Bioactive pyrazolidinone compounds.

Initiating the investigation, pyrazolidinone (**1a**) and α-O-mesyl ketone (**2a**) reacted under rhodium catalytic system. Several representative bases were firstly evaluated at 60 ℃ and sodium isocyanate (NaOCN) was determined to be the best one for the annulation process. The fused heterocyclic compound **3aa** containing a tertiary alcohol center was generated efficiently (**Table 1**, entry 5). The distinct result afforded by sodium acetate indicated that an obvious anion effect might be involved in the catalytic circle, during which the isocyanate anion could activate rhodium

catalyst *via* anion exchange (entry 2). Further modulation of reaction temperature only achieved inferior conversion, and the start material decomposed rapidly under 100 °C (entry 8). Catalyst $[Cp^*RhCl_2]_2$ was specified for such annulation process, other common transition metals could only afford suboptimal result (entries 9-11). The control experiment further elucidated the essential role of transition metal, the reaction was totally inhibited w/o rhodium catalyst (entry 12).

Table 1. Optimization of Conditions.[a]



entry	catalyst	base	T [°C]	yield [%]
1	$[Cp^*RhCl_2]_2$	Cs_2CO_3	60	0
2	$[Cp^*RhCl_2]_2$	NaOAc	60	0
3	$[Cp^*RhCl_2]_2$	K_2CO_3	60	17
4	$[Cp^*RhCl_2]_2$	DMAP	60	16
5	**$[Cp^*RhCl_2]_2$**	**NaOCN**	**60**	**94**
6	$[Cp^*RhCl_2]_2$	NaOCN	40	58
7	$[Cp^*RhCl_2]_2$	NaOCN	80	76
8	$[Cp^*RhCl_2]_2$	NaOCN	100	0
9	$[Cp^*IrCl_2]_2$	NaOCN	60	35
10	[Ru(*p*-cymene)$Cl_2]_2$	NaOCN	60	59
11	$[Cp^*Co(CO)I_2]$	NaOCN	60	0
12	/	NaOCN	60	0

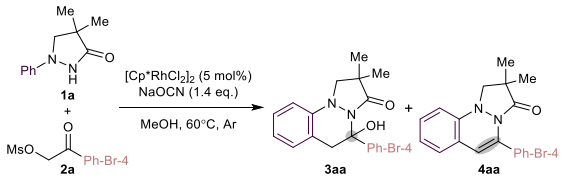
[a] Optimization of reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), catalyst (5 mol%), base (1.4 eq.), MeOH (1.0 ml), argon atmosphere. The yields were determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

With the optimized conditions in hand, we investigated the combinations of various pyrazolidinones and *α*-O-mesyl ketones (**Scheme 2**). Different substitution patterns in the phenyl ring of the pyrazolidinone are well tolerated. Substrates with electron-withdrawing groups and electron-donating groups, at different positions on the aryl moiety show universally comparable reactivity for the *ortho* C-H activation. The *orth*-methyl group causes no obvious steric difficulty for initial chelation with the metal catalyst and for the sequential C-H activation, and judging by the ready formation of product **3ga**, the reaction is seemingly unaffected by steric compression. The *meta*-substituted substrates display exclusive regiospecificity for C-H activation at the *ortho*-position with less hindrance, which emphasizes a more pronounced steric effect (products **3ha**-**3ja**). The crystal structure of compound **3pa** further confirms the structure of the product as a fused-heterocyclic skeleton containing a tertiary alcohol center.

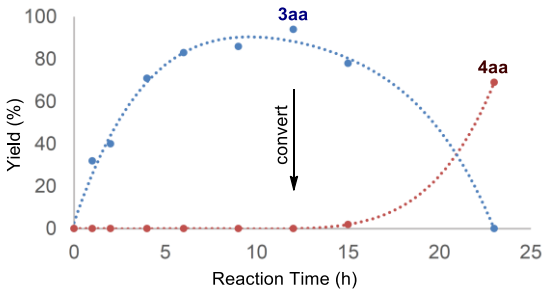
Variation of the substitution on the aryl moiety of *α*-O-mesyl ketone analogue was also evaluated. Different electronic characteristics and the substituent positions result in no attenuation in this cyclization process (products **3ab**-**3ak**). Substrates containing heterocyclic substituents, such as thienyl and furyl, are both entirely compatible and afford the desired product in satisfactory conversions (products **3al**, **3am**). A methyl ketone analogue is also a suitable substrate for the heterocycle construction and gives a moderate yield of the product **3an**.

The aforementioned annulation is initiated smoothly under standard condition and affords 94% NMR yield after 12 h. However, if the reaction time is further extended, the yield of **3aa** decreases gradually, and concurrently a new product with stronger UV fluorescence is gnerated. The conversion is complete after about 23 h and the new product was identified as a dehydrated **3aa**. The control experiments (*vide infra*) support a hypothesis that the released rhodium catalyst which has promoted the annulation process plays an essential role for accelerating the dehydration of the tertiary alcohol. When NaOPiv is applied as the base additive, the reaction produces the benzopyridazine analogue (**4aa**) exclusively within 15 h (see the supporting information for more detail). The rhodium-mediated C-H activation process can lead to the formation of either of two fused heterocycle skeletons, (**3aa**, **4aa**), in ratios which can be controlled by merely selecting the base additive.

Table 2. Generation of **4aa**.[a]



entry	Time (h)	**3aa** (%)	**4aa** (%)
1	1	32	0
2	2	40	0
3	4	71	0
4	6	83	0
5	9	86	0
6	12	94	0
7	15	78	2
8	23	0	69



[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOCN (1.4 eq.), MeOH (1.0 ml), 60 °C, argon atmosphere. The yields of **3aa** and **4aa** were determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

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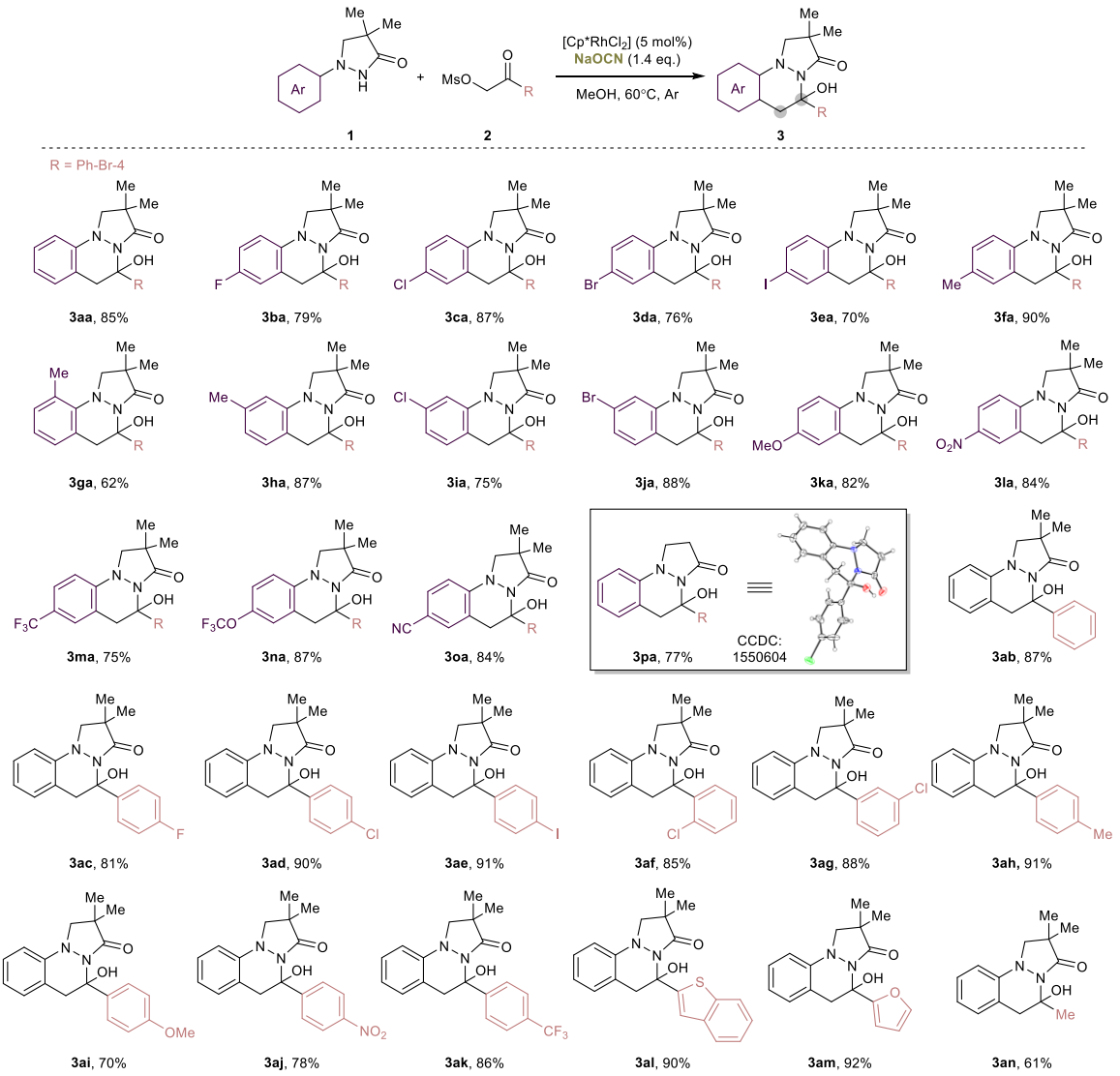

Scheme 2. Scope for pyrazolidinone containing fused rings. Conditions: pyrazolidinone **1** (0.30 mmol), *α*-O-mesyl ketones **2** (0.45 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOCN (1.4 eq.), MeOH (3.0 ml), 60 °C, argon atmosphere. Yields are for the isolated products.

The efficiency of annulation-dehydration cascade was further evaluated under the standard condition and utilizing NaOPiv as the optimal base (**Scheme 3**). Different *α*-O-mesyl ketone analogues, including (hetero)aryl and alkyl ketone, perform well under the modified condition, affording the desired products in moderate to good yields (products **4ab**-**4an**). The electronic properties of both aryl moiety of pyrazolidinone and *α*-O-mesyl ketone show no obvious suppression for the reaction conversion. Reactions for different substrate combinations proceed smoothly and afford comparable results (products **4ba**-**4ka**). The absence of *gem*-dimethyl substituents at the *α*-position of amide tends to lower the yield and this phenomenon may be ascribed to the instability of the pyrazolidinone moiety under the reaction condition (products **4pa**-**4pb**).

For mechanistic insight, a series of control experiments were performed to illustrate the catalytic circle. In the absence of *α*-O-mesyl ketone, pyrazolidinone **1a** proceeds complete deuterium incorporation at both *ortho*-positions of aryl moiety in CD_3OD (**Scheme 4a**). This result indicates that the C-H activation mediated by rhodium catalyst might be a reversible process. When deuterated solvent is utilized instead in the standard condition, partial deuterium incorporation is observed at the benzyl methylene (55%) of the annulation product. Meanwhile, *α*-O-mesyl ketone is recovered with 70% deuterium incorporation in the *α*-position. This performance might originate from the tautomerization of ketone moiety in substrate or reaction intermediate, which is prone to exist as enol form for rapid H/D exchange. Partially dueterated *ortho*-position (60%) of product

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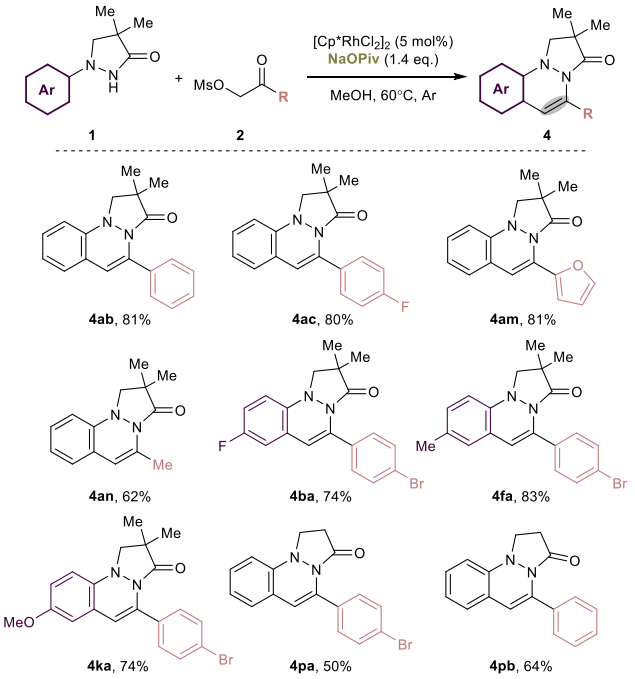
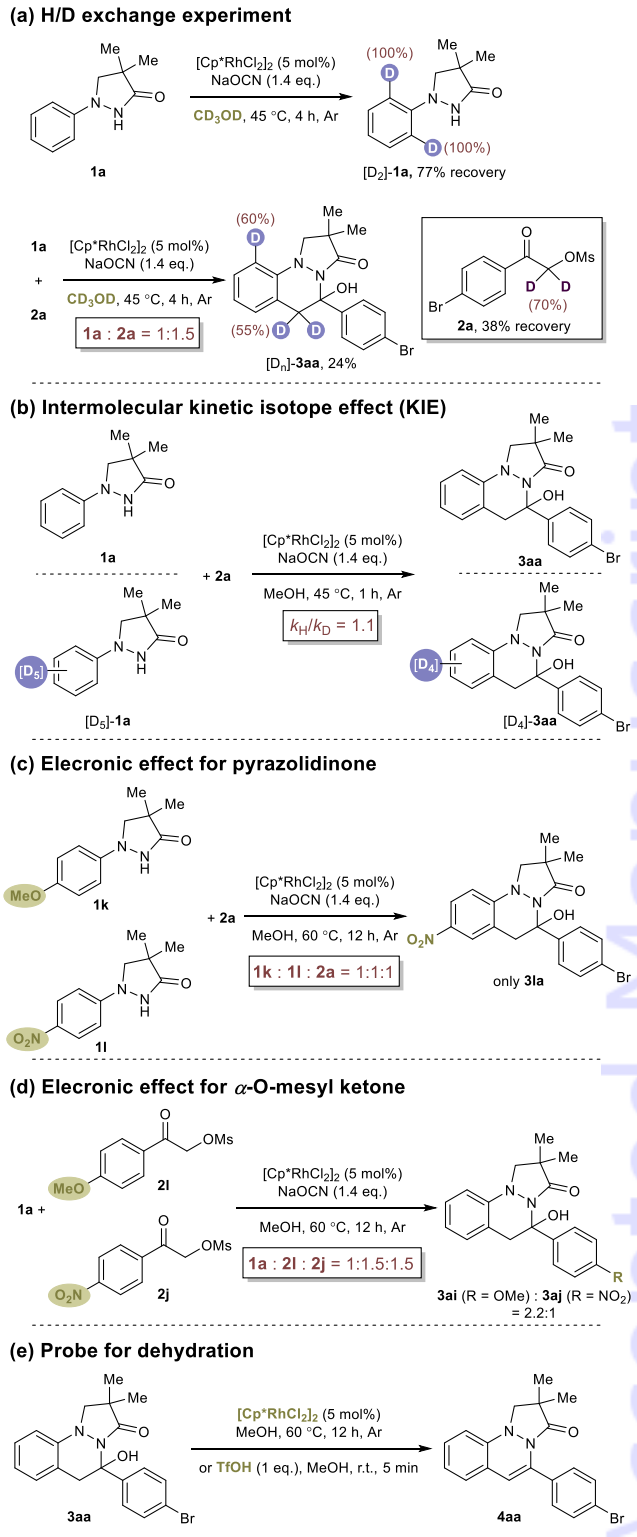


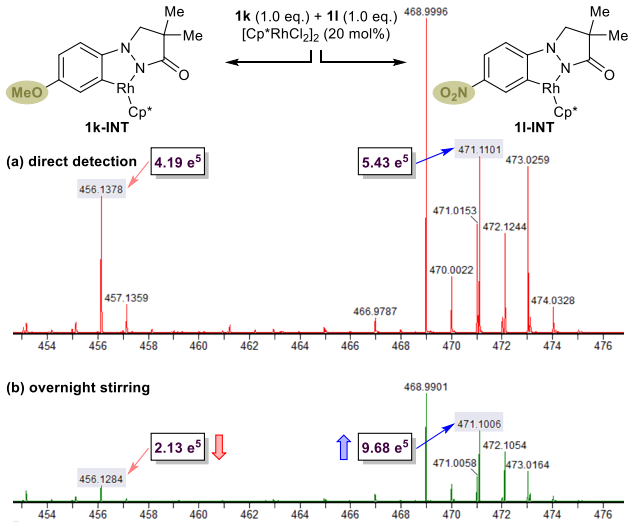
Scheme 3. Scope for benzopyridazine analogues. Conditions: pyrazolidinone **1** (0.30 mmol), α-OMs ketones **2** (0.45 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOPiv (1.4 eq.), MeOH (3.0 ml), 60 ºC, argon atmosphere. Yields are for the isolated products.

indicates that both of the reversible C-H activations at *ortho*-positions proceed preferentially than the C-C bond formation, or the second C-H activation occurs prior to the final annulation process (**Scheme 5**). The intermolecular kinetic isotopic effect (KIE) was also evaluated. The ratio for rate constants of **1a** *vs* **[D$_5$]-1a** suggestes that the C-H cleavage mediated by rhodium catalyst is not the essential rate-determining step (**Scheme 4b**). The electronic effects for both pyrazolidinone and α-O-mesyl ketone were further demonstrated by competing experiments. When equivalent substrates with divergent electronic properties, **1k** & **1l**, were incorporated into same catalytic system, only product **3la** could be generated specifically (**Scheme 4c**). It seems that the aryl moiety with lower electron density exhibits more tendency for interception of C-H bond, also superior chelation with the rhodium catalyst. In sharp contrast, the aryl moiety containing electron donating group provided a superior reactivity for the ketone substrate in a ratio of 2.2:1 (**Scheme 4d**, **3ai** *vs* **3aj**). It is speculated that **2j** performs a more stable enol tautomer which in turn compresses the reactivity towards nucleophilc attack (both the C-C bond formation and the annulation steps). When the fused heterocycle containing tertiary alcohol was treated with catalytic amount of $[Cp^*RhCl_2]_2$, the dehydration product **4aa** was generated smoothly (**Scheme 4e**). The rhodium catalyst may meanwhile act as a Lewis acid for chelating with the hydroxyl group, promotes this condensation process which can also be accelerated by Brønsted acid such as triflic acid.



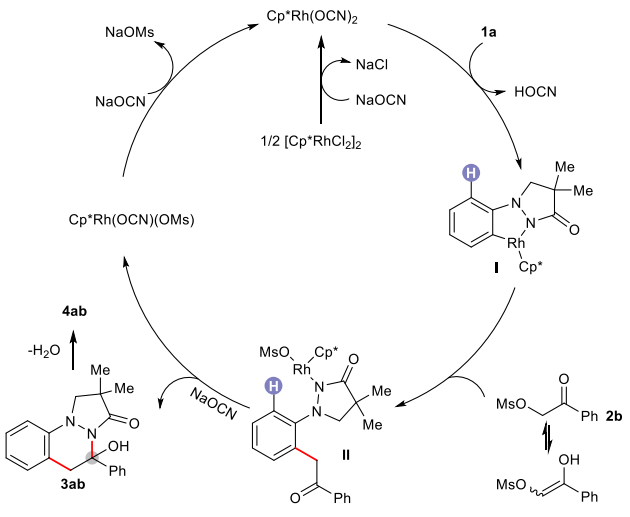
Scheme 4. Mechanistic studies.

ESI mass spectrum was generated for further demonstration of the competing experiment (**Scheme 5**). When two start materials being stirred with $[Cp^*RhCl_2]_2$ overnight, opposite variation tendencies of ion enrichment were observed for the corresponding intermediates (**1l-INT** *vs* **1k-INT**). The electron deficient aryl moiety indeed preferentially chelates with catalyst.



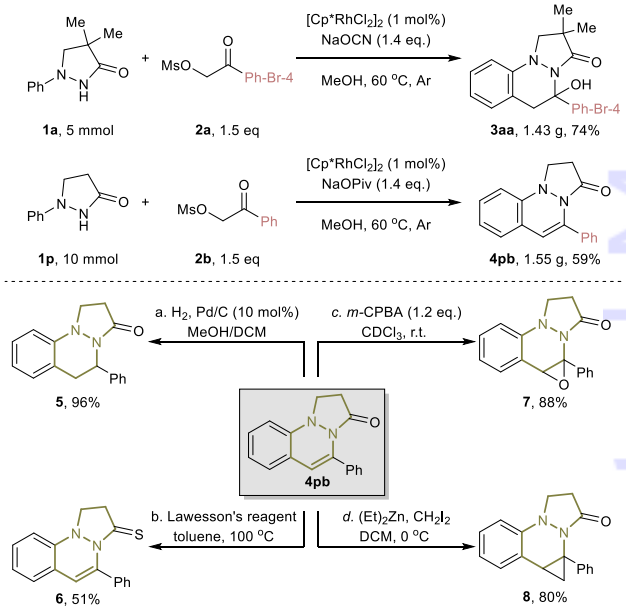
Scheme 5. ESI mass spectrum of competing experiment

Based on the mechanistic insight, a presumable catalytic circle for the annulation-dehydration cascade was sequentially envisaged (**Scheme 6**).[9a] The active rhodium species is firstly generated *via* anion exchange, the pyrazolidinone moiety directs the chelation and the sequential C-H activation for generating cyclic-rhodium intermediate **I**. This C(sp^2)-Rh species nucleophilic attacks the *α*-O-mesyl ketone (rapid equilibrium with enol form) affording Rh(III)-amido intermediate **II** which could also conduct the second C-H activation (responsible for the *ortho*-dueterated product [D_n]-**3aa** in **Scheme 4a**). Due to the steric hinder of the newly constructed *ortho*-alkyl group, however, inducing the second C-C bond formation is forbidden. Instead, anion exchange and the intramolecular nucleophic additon of nitrogen anion to the carbonyl group are triggered. The final annulation process affords the fused heterocycle **3ab** and the further dehydration leads to another useful derivative **4ab**.



Scheme 6. Proposed catalytic circle.

The synthetic utility of this methodology was further evaluated by scaleup version and chemical derivatization. Both the annulation or dehydration cascade proceed efficiently in gram scale and afford consistent isolated yields with lower catalyst loading (**Scheme 7**). Several representative conversions have been investigated and provide initial information for potential applications of such skeletons. The fused heterocycle involving a benzopyridazine skeleton, can serve as versatile synthon for sequential chemical transformations. With Pd/C and under a hydrogen atmosphere, the pyridazine moiety can be reduced efficiently, affording compound **5** with excellent yield. Using Lawesson's reagent under 100 °C, the amide group was converted to the thioamide (**6**) in moderate yield. The double bond in **4pb** is oxidized efficiently by 3-chloroperoxybenzoic acid affording a fused cyclic skeleton containing an oxacyclopropane moiety (**7**). The cyclo-propanation can be achieved by introducing diiodomethane and diethylzinc, giving compound **8**. Further transformations and applications of such fused heterocycles are also under study to provide more information concerning structural derivatization.



Scheme 7. Application and derivatization.

In summary, divergent synthetic pathways for fused heterocyclic compounds mediated by rhodium catalyst have been described. The annulation and the annulation-dehydration cascade can be achieved by simply adjusting the base additive. A series of control experiments for the mechanistic insight were also involved, a presumable catalytic circle was sequentially hypothesized to demonstrate the reaction pathway. The potential applications of such fused ring structures were preliminarily evaluated by scaleup reactions and several practical conversions. Further structural information for the pharmaceutical and agricultural applications is under investigation.

Experimental Section

General procedure for constructing fused heterocycles: pyrazolidinone (**1a**) (0.3 mmol), α-O-mesyl ketone (**2a**) (0.45 mmol), $[Cp^*RhCl_2]_2$ (5 mol%) and the corresponding base (NaOCN or NaOPiv respectively, 1.4 eq.) were mixed in an oven-dried tube which was equipped with rubber plug. The tube was degassed and back-filled with argon, anhydrous MeOH (3 mL) was injected sequentially. The reaction mixture in the sealed tube was stirred at 60 °C for a specific time. Upon complete consumption of **1a**, the mixture was cooled down and concentrated. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 10:1) to afford the desired products.

CCDC-1550604 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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