DOI: 10.1002/adsc.202100141

Advanced Synthesis & Catalysis

Silver/Rhodium Relay Catalysis Enables C–H Functionalization of *In Situ* Generated Isoquinolines with Sulfoxonium Ylides: Construction of Hexahydrodibenzo[*a*,*g*]quinolizine Scaffolds

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Manuscript received: February 1, 2021; Revised manuscript received: March 6, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100141

Abstract: Employing silver/rhodium relay catalysis strategy, an intramolecular electrophilic cyclization and C–H activation followed by cascade hydrogenation and reductive amination has been developed. The acylmethylated isoquinoline derivatives could be afforded with broad substrate scope in 23–88% yields, which could be further transformed to the core skeleton of hexahydrodibenzo[*a*,*g*]quinolizine as drug-candidates. Moreover, this reaction was achieved in a gram-scale. A reasonable reaction mechanism has been proposed based on a series of control and KIE experiments.

Keywords: bimetallic relay catalysis; hexahydrodibenzo [*a*,*g*]quinolizine; sulfoxonium ylide; Silver/Rhodium,; C–H functionalization

The azapolycyclic motifs are privileged scaffolds found in many natural products and pharmaceutically active compounds.[1] Among these different types of azapolycyclic motifs, hexahydrodibenzo[*a*,*g*]quinolizine derivatives constituted core scaffolds, could be a used as drug-candidates for the treatment of neurological diseases (DC037029 or DC037081, Figure 1).[2] Moreover, tetrahydroprotoberberine alkaloids such as STY containing azapolycyclic motif can selectively bind with G-quadruplex DNA, which has been often studied as a target for *anti*-cancer drug (Figure 1).[3] In recent decades, numerous methods have been developed to construct similar structural motifs,[4] however, those methods usually suffer from complicated multistep operations. Thus, it is highly desirable to develop a creative synthetic route that enables facile preparation of a wide range of such polyheterocyclic derivatives.

Bimetallic relay catalysis involving two metal catalysts in one reaction system,[5–7] demonstrates excellent chemo-, stereo- and regio-selectivities without the isolation of unstable intermediates in a wide range of reactions, and displays unique potential in bond functioalization reactions. Jeon and co-workers[8] reported an outstanding work involving a relay of Ir-catalyzed hydrosilylation of phenyl acetates and Rh-catalyzed C–H silylation with traceless acetal directing groups in 2016 (Scheme 1, a). However, the difficulties lie in the compatibility of two metals and it is still a challenging task at the present stage. As versatile carbene precursors, sulfoxonium ylides[9] were widely ulitized because of their high flexibility, stability and

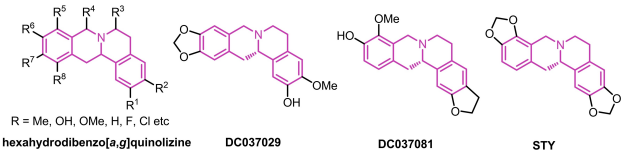
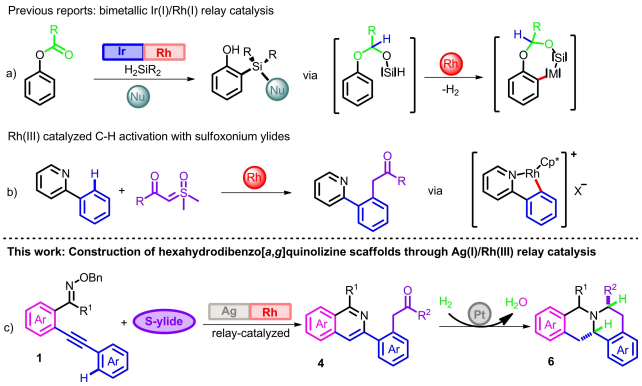


Figure 1. Representative examples of drug-candidates containing hexahydrodibenzo[*a*,*g*]quinolizine skeletons.

diverse reactivity. In 2017, Aissa[10] and others[11] reported the Cp*Rh(III)-catalyzed C–H functionalization of arenes with sulfoxonium ylides as carbene precursors and coupling partners (Scheme 1, b). Although directing group-assisted C–H bond function-

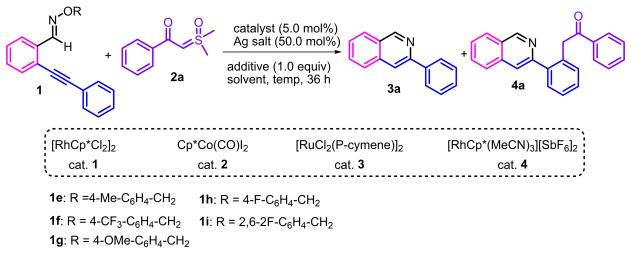


Scheme 1. Bimetallic relay catalysis strategy and construction of hexahydrodibenzo[*a*,*g*]quinolizine scaffolds with sulfoxonium ylides.

alization strategies can achieve the desired transformation with high reactivity and selectivity, the limitations of directing group strategy are that directing groups are often difficult to install and manipulate after processes are completed.[12] Inspired by the applications of sulfoxonium ylides in C–H activation and bimatellic relay catalysis, we hypothesized to design C–H bond functionalization reactions involving sulfoxonium ylides with bimetallic relay catalysis strategy. Herein, we wish to report an intramolecular electrophilic cyclization and C–H activation using bimetallic relay catalysis strategy followed by cascade hydrogenation (Scheme 1, this work). Interestingly, this protocol led to an efficient method to access hexahydrodibenzo[*a*,*g*] quinolizine derivatives, which are an integral part of drug-candidate for the treatment of neurological diseases.

We initiated our studies by exploring the coupling of *O*-alkyl benzaldoxime derivative (R=H) **1b** with ylide **2a** for this cyclization and acylmethylation. In the presence of $[RhCp^*Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (50.0 mol%) and PivOH (1.0 equiv.) in DCE at 80 °C, the alkylated product **4a** was achieved in 34% yield (Table 1, entry 1). Catalyst screening revealed that $[RhCp^*Cl_2]_2$ was the most effective one and the only use of $[RhCp^*(MeCN)_3][SbF_6]_2$ as catalyst did not give the desired product, suggesting the silver salt is essential for this transformation (Table 1, entries 2–4). Using TFE (2,2,2-trifluoroethanol) as solvent increased the yield of **4a** to 36% (Table 1, entry 5). Several substrates **1** having different protecting groups R (methyl group **1c**, pivaloyl group **1d** and benzyl group **1a**) were tested with **2a** under $[RhCp^*Cl_2]_2$, $AgSbF_6$ and PivOH in TFE at 80 °C. We noticed that employing substrate **1c** only afforded **3a**[13] in 63% yield (Table 1, entry 6); when substrate **1a** was used, the reaction was conducted by one step, one-pot method, affording **3a** in 31% yield and **4a** in 38% yield (Table 1, entry 8). The reaction went complex using **1d** as substrate

Table 1. Optimization of reaction conditions for the synthesis of **4a**.



Entry[a]	1	Catalyst	Ag salt	Solvent	Temp/ [°C]	Yield/ %[b] **3a**	Yield/ %[b] **4a**
1	**1b**	cat.1	$AgSbF_6$	DCE	80	–	34
2	**1b**	cat.2	$AgSbF_6$	DCE	80	–	–
3	**1b**	cat.3	$AgSbF_6$	DCE	80	–	–
4	**1b**	cat.4[e]	–	DCE	80	–	–
5	**1b**	cat.1	$AgSbF_6$	TFE	80	–	36
6	**1c**	cat.1	$AgSbF_6$	TFE	80	63	–
7	**1d**	cat.1	$AgSbF_6$	TFE	80	–	–
8[c]	**1a**	cat.1	$AgSbF_6$	TFE	80	31	38
9[d]	**1a**	cat.1	$AgSbF_6$	TFE	80	–	61
10[d]	**1e**	cat.1	$AgSbF_6$	TFE	80	–	63
11[d]	**1f**	cat.1	$AgSbF_6$	TFE	80	–	59
12[d]	**1g**	cat.1	$AgSbF_6$	TFE	80	–	55
13[d]	**1h**	cat.1	$AgSbF_6$	TFE	80	–	61
14[d]	**1i**	cat.1	$AgSbF_6$	TFE	80	–	63
15[d]	**1a**	**cat.1**	**$AgSbF_6$**	**TFE: DCE (1:1)**	**80**	–	**65 (65)**[f]
16[d]	**1a**	cat.1	$AgSbF_6$	TFE:DCE (1:1)	70	–	55
17[d]	**1a**	cat.1	$AgSbF_6$	TFE:DCE (1:1)	100	–	40

[a] Reaction conditions: **1** (0.2 mmol), **2a** (1.5 equiv.), $[RhCp^*Cl_2]_2$ (5.0 mol%), silver salt (50.0 mol%) and silver salt (1.0 equiv.) were added in solvent (2.0 mL), under an Ar atmosphere for 36 h, in a sealed tube.
[b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard.
[c] One step, one-pot method.
[d] Reaction conditions: **1** (0.2 mmol), silver salt (5.0 mol%) in solvent (1.0 mL) under an Ar atmosphere for 6 h, and then followed by **2a** (1.5 equiv.), $[RhCp^*Cl_2]_2$ (5.0 mol%), silver salt (45.0 mol%), additive (1.0 equiv.) and solvent (1.0 mL) for another 30 h, in a sealed tube.
[e] Purified by a column chromatography on silica gel (DCM/MeOH = 100/1) to remove trace amount of silver salt (see Supporting Information).
[f] Isolated yield.

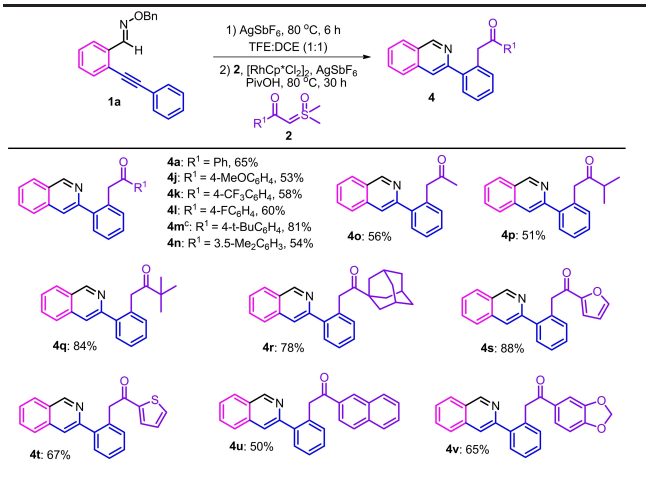
(Table 1, entry 7). To further improve the yield, **1a** was added with $AgSbF_6$ (5.0 mol%) in TFE at 80 °C for 6 hours followed by **2a**, $[RhCp^*Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (45.0 mol%) and PivOH (1.0 equiv.). Fortunately, the desired product **4a** was obtained in 61% yield (Table 1, entry 9). The electronic property of the

protecting group R in substrates **1e–1i** did not affect the product yield significantly (Table 1, entries 10–14). Considering that it is a two-step process, the mixed solvent was also tested; the combination of TFE:DCE afforded a better result, providing **4a** in 65% yield (Table 1, entry 15) with the 73% yield of benzaldehyde detected (for details see the Supporting Information at page S15). The examination of reaction temperature revealed that the reaction carried out at 80 °C gave the best result (Table 1, entries 16–17).

Under the optimized reaction conditions, we first investigated the scope of various decorated sulfoxonium ylides **2** (Table 2). The substrates **2** having either electron-withdrawing or -donating groups present on the benzene ring were all compatible in this reaction, providing the desired products (**4a–n**) in 54–81% yields, indicating that the electronic property of R^1 and steric hindrance of the phenyl rings did not have a significant impact on the product yield. Notably, the sulfoxonium ylides were not limited to those having aryl substituents; alkyl and heteroaryl sulfoxonium ylides were also suitable for this reaction, affording the desired products (**4o–4t**) in 51–88% yields. For the naphthalene-containing substrate **2u** afforded **4u** with a slightly decreased yield in 50%. In the case of substrate **2v**, in which 1,3-benzodioxole is contained, the corresponding product **4v** was also produced in 65% yield.

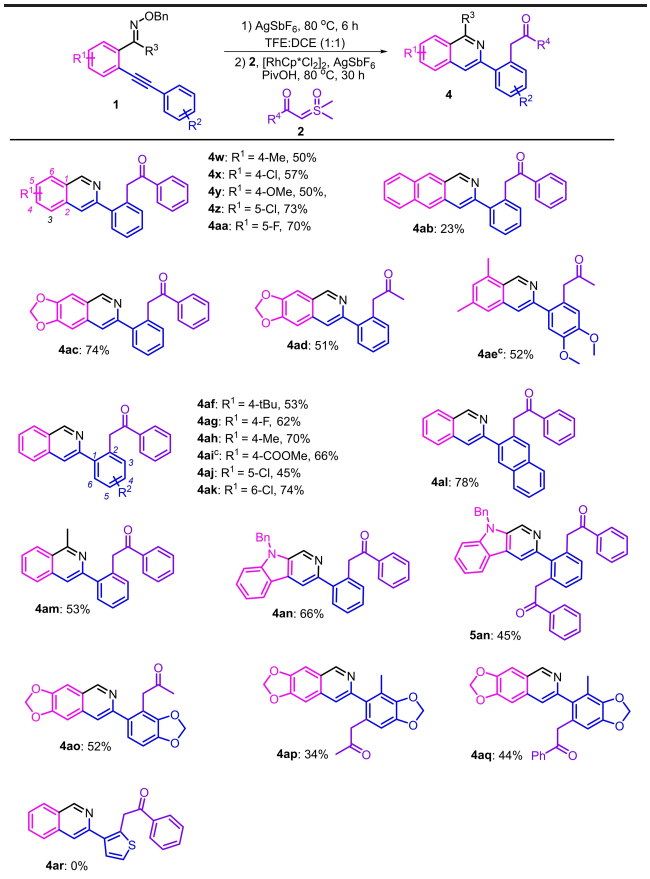
Under the optimal conditions, a wide range of substrates **1** successfully underwent these reactions, providing the desired products in good yields (Table 3).

Table 2. Reaction scope of sulfoxonium ylides **2**.[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), silver salt (5.0 mol%) in solvent (1.0 mL) under an Ar atmosphere for 6 h, and then followed by **2** (1.5 equiv.), $[RhCp^*Cl_2]_2$ (5.0 mol%), silver salt (45.0 mol%), additive (1.0 equiv.) and solvent (1.0 mL) for another 30 h, in a sealed tube.
[b] Isolated yield.
[c] **2** (0.4 mmol) was used.

Table 3. Substrate scope of **1**.[a,b]



[a] Reaction conditions: **1** (0.2 mmol), silver salt (5.0 mol%) in solvent (1.0 mL) under an Ar atmosphere for 6 h, and then followed by **2a** (1.5 equiv.), $[RhCp^*Cl_2]_2$ (5.0 mol%), silver salt (45.0 mol%), additive (1.0 equiv.) and solvent (1.0 mL) for another 30 h, in a sealed tube.
[b] Isolated yield.
[c] **2** (0.36 mmol) was used.

Substrate **1** with electron-donating and -withdrawing substituents (including methyl, halides and methoxy substituents) at the 4-position and 5-position of the benzene ring all reacted with excellent efficiencies, affording products **4w–4aa** in 50–73% yields. The X-ray diffraction pattern of **4aa**, whose structure had been unambiguously determined, is shown in Supporting Information. Replacing the benzene ring by naphthalene ring, the reaction was less facile, and the product **4ab** was isolated in 23% yield. For substrate **1ac** containing 1,3-benzodioxole, **4ac** and **4ad** were obtained in 74% and 51% yields, respectively, when benzoyl sulfoxonium ylide and methyl sulfoxonium ylide were used. Sterically hindered substrate **1ae** could also undergo this process, delivering the corresponding product **4ae** in 52% yield under a slightly modified reaction condition. The electronic properties and steric hindrance performances were also tested on

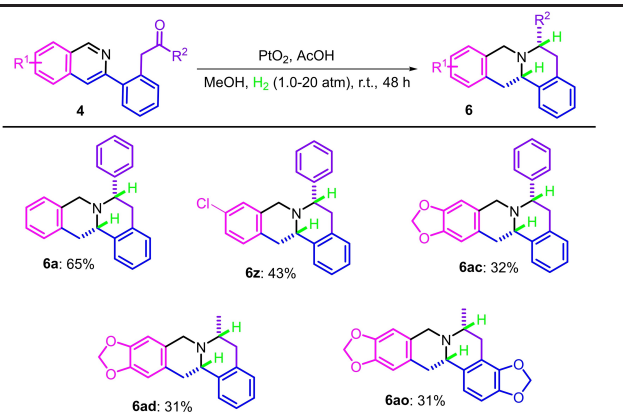
R^2 position in substrate **1**. Substrate **1** bearing electron-withdrawing and -donating substituents, such as, methyl, *tert*-butyl, halide, and ester at the 4-, 5-, and 6-positions of the benzene ring turned out to be applicable under optimal reaction conditions, producing the desired annulated products **4af**–**4ak** in yields of 45%–74%. For substrate **1aj**, C–H bond activation occurred on the less bulky site to obtain **4aj** in 45% yield. For the substrate **1al** containing naphthalene moiety, the desired product **4al** was accessed with an increased yield in 78%. Fortunately, using (*E*)-**1am** as substrate, the desired product **4am** could also be obtained in 53% while (*Z*)-**1am** could not undergo this reaction.[13] Employing substrate **1an** containing indole moiety, the corresponding products **4an** and **5an** could be obtained using 1.2 and 2.0 equiv. of the sulfoxonium ylide in 66% and 45% yields, respectively. It is worth noting that substrate **1ao** having 1,3-benzodioxole moiety underwent the reaction to afford single regioselective product **4ao** in 52%; the high regioselectivity probably roots in the electronic property of 1,3-benzodioxole moiety. For substrate **1ap** containing 1,3-benzodioxole and methyl groups, the corresponding products **4ap** and **4aq** were obtained in 34% and 44% yields, respectively, when benzoyl sulfoxonium ylide and methyl sulfoxonium ylide were used. Unfortunately, we failed to get the desired product **4ar** after several attempts under different reaction conditions.

To further demonstrate the synthetic utility of this method, the obtained product **4** was used as substrate for the synthesis of hexahydrodibenzo[*a*,*g*]quinolizine compound. As summarized in Table 4, the desired product **6a** was isolated in 65% yield in the presence of PtO_2 and AcOH under hydrogen atmosphere (1.0 atm)[14] at room temperature for 48 hours. The product **6z** could also be afforded in 43% under the standard condition. As for the substrates with electron-rich 1,3-benzodioxole **4ac**, **4ad** and **4ao**, higher pressure of hydrogen (20.0 atm) was needed with AcOH replaced by TFA, affording **6ac**, **6ad** and **6ao** in 32%, 31% and 31% yields, respectively. The X-ray data of **6ac** are indicated in the Supporting Information.

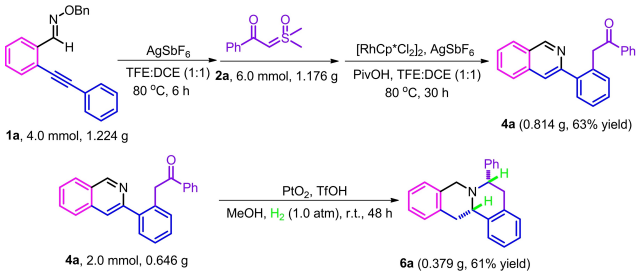
The scale-up experiments of **4a** and **6a** were also carried out as shown in Scheme 2. For a 4.0 mmol scale reaction, the product **4a** (0.814 g) could be achieved in 63% yield by prolonging the reaction time to 48 hours. The systhesis of hexahydrodibenzo[*a*,*g*]quinolizine **6a** was also successful without decreasing product yield when 2.0 mmol of **4a** was employed.

As shown in Scheme 3, the deuterium labeled kinetic experiment and several control experiments were conducted to gain some insights into the reaction mechanism. The kinetic isotope effect of this reaction was measured on the basis of parallel experiments, and a k_H/k_D value of 5.7 was obtained (Scheme 3, a), which suggests that the C–H activation might be involved in the turnover-limiting process. Upon treatment of **3a**

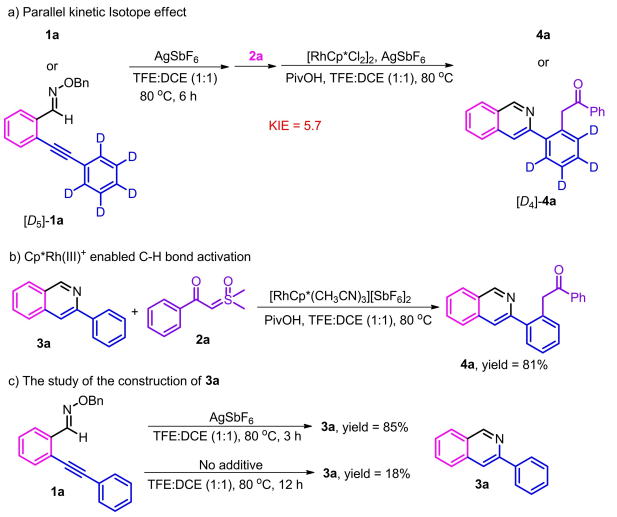
Table 4. The synthesis of hexahydrodibenzo[*a*,*g*]quinolizine **6**.[a,b]



[a] Reaction conditions: **4** (0.2 mmol), acid (0.6 mmol), PtO_2 (5.0 mol%) in MeOH (2.0 mL) under H_2 (1.0 atm–20.0 atm) for 48 h.
[b] Isolated yield.



Scheme 2. Large-scale synthesis of **4a** and **6a**.

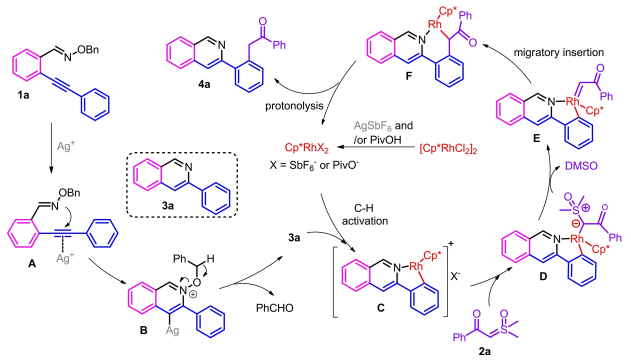


Scheme 3. Control experiments.

with **2a** in the presence of treated [RhCp*-(MeCN)$_3$][SbF$_6$]$_2$ (silver content was measured by ICP-OES,[15] see Supporting Information at page S8) and PivOH in TFE:DCE (1:1) at 80 °C, the product **4a** could be accessed in 81% yield, indicating that Cp*RhX$_2$ complex[16] is the active catalyst (Scheme 3, b). Treatment of **1a** with AgSbF$_6$ in TFE:DCE (1:1) for 3 hours produced **3a** in 85% yield; heating compound **1a** without AgSbF$_6$ for 12 hours afforded **3a** only in 18% yield after 12 h. These results suggested that Ag(I) played an important role in the formation of cyliczed isoquinoline product **3a** and the active Cp*RhX$_2$ complex (Scheme 3, c).

On the basis of the results of above control experiments and previous work,[10,13] a mechanism for Ag/Rh relay catalysis reaction is suggested as shown in Scheme 4. Coordination of Ag(I) with the alkyne moiety of **1a** generates an intermediate **A**, which initiates an intramolecular electrophilic cyclization, producing a cyclized intermediate **B**. Subsequent bimolecular E$_2$-type elimination[13] and protonation afford isoquinoline derivative **3a** containing new directing group with the release of benzaldehyde, which can be detected in the experiment (see Supporting Information at page S5 and S15 for the details). The pre-catalyst [RhCp*Cl$_2$]$_2$, AgSbF$_6$ and/or PivOH would generate active Cp*RhX$_2$ complex via ligand exchange which coordinates to the *in situ* generated **3a** to afford a five-membered rhodacyclic intermediate **C**. Then, sulfoxonium ylide **2a** attacks the metal center of intermediate **C** to deliver intermediate **D**, which undergoes α-elimination of DMSO to afford the carbenoid species **E**. The migratory insertion of complex **E** leads to an intermediate **F**. Finally, the protonolysis of **F** delivers the final product **4a** and regenerates the Rh(III) catalyst.

In conclusion, we have developed a synthesis of the core skeleton of hexahydrodibenzo[*a*,*g*]quinolizine through intramolecular electrophilic cyclization and C–H activation followed by cascade hydrogenation and reductive amination using silver/rhodium relay catalysis strategy. A wide range of substrates could be tolerant in this reaction, affording acylmethylated isoquinoline derivatives in 23–88% yields. The products could be further transformed to interesting compounds applied in the synthesis of potential drug-candidate molecule for the treatment of neurological diseases. More importantly, this work discovered new reaction model about the synthesis of azapolycyclic compound, which will help organic chemists to design new reaction model in the synthesis of alkaloids.



Scheme 4. Proposed Reaction Mechanism.

Experimental Section

General Procedure for Synthesis of 4a

To a stirred solution of **1a** (0.2 mmol) was added AgSbF$_6$ (5.0 mol%) in TFE:DCE = 1:1 (1.0 mL) under argon atmosphere. The resulted mixture was stirred at 80 °C for 6 h. Then, sulfoxonium ylide **2a** (0.3 mmol), AgSbF$_6$ (45.0 mol%), [RhCp*Cl$_2$]$_2$ (5.0 mol%), PivOH (0.2 mmol) and TFE:DCE = 1:1 (1.0 mL) were added for another 30 h. After the filtration and the removal of solvent under reduced pressure, the residue was purified by a column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to afford the corresponding compounds **4a** in 65% yield.

General Procedure for Synthesis of 6a

To a solution of **4a** (0.2 mmol) in 2.0 mL of freshly distilled anhydrous MeOH was added PtO$_2$ (0.1 equiv.) and AcOH (3.0 equiv.) at room temperature under H$_2$ (1.0 atm) atmosphere for 48 hours. After the reaction completion monitored by TLC analysis, the residue was purified by a silica gel flash chromatography on silica gel (eluent: petroleum ether/EtOAc = 50/1) to afford compound **6a** in 65% yield.

Supporting Information Available

Detailed descriptions of experimental procedures and their spectroscopic data as well as the crystal structures are presented in the Supporting Information. CCDC 2006002 (**4aa**) and CCDC 2031004 (**6ac**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We are grateful for the financial support from the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), the National Natural Science Foundation of China (21372250, 21121062, 21302203, 20732008, 21772037, 21772226, 21861132014 and 91956115).

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