Rhodium^{III}/Silver^{I} Relay Catalyzed C-H Aminomethylation with Imine Equivalents and Lewis Acid Catalyzed [4+2] Cycloaddition of Indoles with Triarylhexahydrotriazine[†]

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Summary of main observation and conclusion A Rh^{III}/Ag^{I} relay-catalyzed C(sp^2)-H coupling of indoles with triarylhexahydrotriazine (THT) is reported in this context. Upon merging Rh^{III}-catalyzed C(sp^2)–H bond activation and silver promoted THT dissociation, an efficient indole's C3 aminomethylation protocol is uncovered, providing C3 aminomethyl indoles in good yields and exhibiting potential applications for the synthesis of complicated bioactive compounds. We revealed the C3-selectivity of this reaction through a detailed mechanistic investigation. Meanwhile, during the examination of the reaction conditions, we discovered another [4+2] cycloaddition pathway to afford tetrahydro-indolo[3,2-*c*]quinoline scaffold products via silver or Lewis acid catalysis.

Background and Originality Content

C-H bond activation has become one of the most powerful methods to access valuable molecules from readily available hydrocarbons.[1] Thus far, transition-metal-catalyzed direct C-H functionalization has received considerable interest in recent years as a facile and straightforward synthetic approach for the rapid construction of complex molecules without the need for pre-functionalized substrates.[2] Among these transition-metal catalysts, Cp*Rh^{III} catalysts have significantly contributed to the arsenal of heterocyclic synthesis owing to their high catalytic activity and excellent tolerance of substrate/functional group.[3]

Aminomethyl unit is a fundamental structural motif found in many biologically active substances having fused ring structures. Especially, indole derivatives having aminomethyl unit at C3 position are presented as core structural motifs in a large number of natural and unnatural compounds having important biological activities (Figure 1). For example, *Mebhydrolin* is used for symptomatic relief of allergic symptoms caused by histamine release, including nasal allergies and allergic dermatosis. *Stobadine*, a hydro delta-carboline, is an efficient antioxidant in membranous lipid environment. *Alosetron*, sold under the brand name Lotronex, is a 5-HT$_3$ antagonist used for the management of severe diarrhea-predominant irritable bowel syndrome.[4-6] Accordingly, synthetic and medicinal chemists have made significant efforts to develop creative approaches for the construction of fused ring compounds bearing an aminomethyl unit. In the synthesis of these compounds, the direct aminomethylation of heteroaromatics showed the indispensable importance.

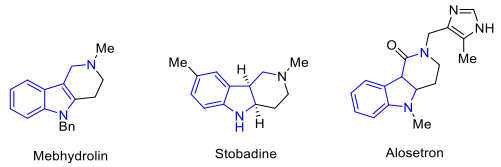
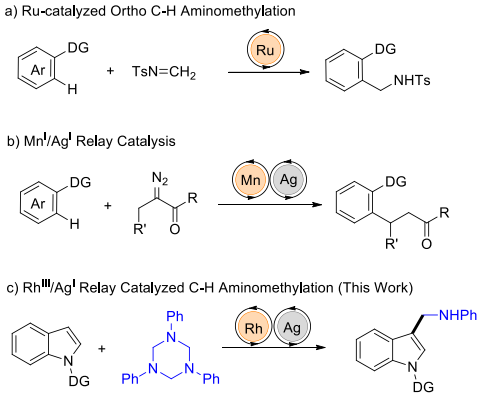


Figure 1 Representative compounds containing carboline.

In the domain of C-H activation, the catalytic addition of C–H bond to C=N bonds is particularly applicable for the preparation of diversified amino products, which are closely related to biologically active molecules and pharmaceuticals. Recently, a direct addition of C-H to C-unsubstituted imines, namely formaldimines, has been reported by Cui's group (Scheme 1a).[7] It enables a novel synthetic protocol directly from hydrocarbons to various α-substituted methylamines including benzylamine derivatives.

On the other hand, silver salts have been extensively applied in many C-H activation reactions. The role of silver salts can be divided into three categories: 1) abstracting halide from metal catalysts;[8] 2) functioning as stoichiometric co-catalysts to regenerate metal catalysts or to form highly reactive metal species;[9] 3) mediating C-H activation in certain reaction systems.[10] The former two ones are not involved with the substrate, but only functioning on the metal center. Recently, Glorius and co-workers discovered another new role of silver salt in the manganese-catalyzed C-H activation using diazo compounds as the functionalization reagents, in which Ag(I) played a role of denitrogenation/carbene rearrangement of diazo compound (Scheme 1b).[11] This is an example of silver(I) catalyzed cascade process and also an example of direct activation on the substrate.

Scheme 1 Aminomethylation catalyzed by Ru as well as transition metal-catalyzed C-H activation involving silver catalysis



As our ongoing exploration of C-H functionalization of heteroaromatics upon transition metal catalysis, herein we wish to report the development of triarylhexahydrotriazine (THT) as a highly selective and sustainable imine precursor for the catalytic indole C–H aminomethylation reactions under Rh^{III}/silver^{I} relay

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[†] Dedicated to the 30th Anniversary of State Key Laboratory of Organometallic Chemistry.

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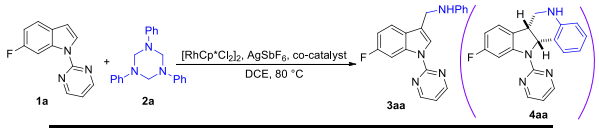
catalysis (Scheme 1c). THT, an equivalent to imine, can be easily accessed from aniline and paraformaldehyde under mild conditions. For indole derivatives with a pyrimidine directing group, the C-H activation site mainly took place at C2 position. However, with this Rh(III)/Ag(I) catalytic system, the reaction only afforded C3 aminomethylation product, in which silver salt played a crucial role to THT in the generation of active species. The plausible reaction mechanism has been also investigated by ^{1}H NMR spectroscopic tracing experiments.

Results and Discussion

Initial experiments were performed with easily prepared **1a** (1.0 equiv) and THT (0.5 equiv) as the testing substrates and AgOAc (2.0 equiv) as the co-catalyst in the presence of $[Cp^*RhCl_2]_2$ (0.05 equiv) and $AgSbF_6$ (0.20 equiv) in 1,2-dichloroethane (DCE) (1.0 mL) at 80 °C under air for 10 h, giving the desired aminomethylation product **3aa** in 52% yield without detection of any C2 position functionalization product (Table 1, entry 1).[12] We validated the necessity of AgOAc in this protocol since no aminomethylation occurred in the absence of AgOAc, indicating the requirement of a co-catalytic reagent for the formation of aminomethylated product (Table 1, entry 11). Instead, a formal [4+2] cycloaddition product **4aa** was afforded in 64% yield in this case. The examination of other different co-catalysts revealed that Ag_2CO_3, AgTFA and $Cu(OAc)_2$ are not effective co-catalysts as that of AgOAc (Table 1, entries 2-4) and the use of AgOPiv as co-catalyst failed to give the desired reaction product (Table 1, entry 5). Other co-catalysts such as CsOAc, KOAc and $Zn(OAc)_2$ failed to afford **3aa** (Table 1, entries 6-8). To improve the yield of **3aa**, some of extra additives such as inorganic bases and organic acids have been examined (Table 1, entries 9-12) and we found that adding PivOH (0.1 mmol) gave **3aa** in 87% NMR yield along with 83% isolated yield, which was the best result (Table 1, entry 12). Lowering the reaction temperature to 60 °C afforded **3aa** in the yield of 66% (Table 1, entry 13). It is noteworthy that the [4+2] cycloaddition to afford **4aa** was catalyzed by $AgSbF_6$ itself, which acted as a Lewis acid in this transformation (Table 1, entry 14).

Table 1 Optimization of the reaction conditions

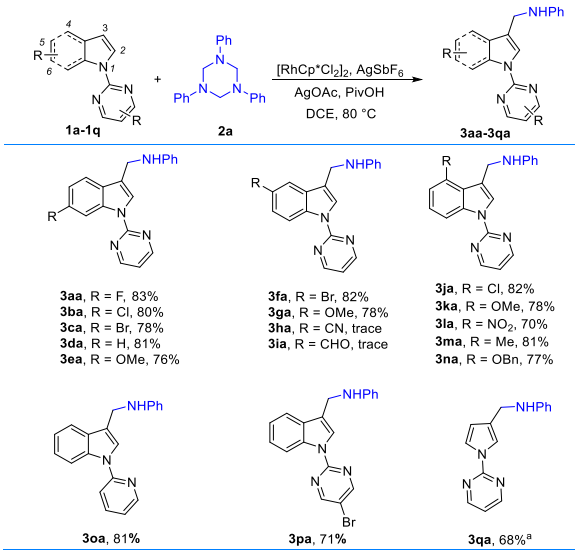


entry[a]	co-catalyst	additive	yield (%)[b] 3aa
1	AgOAc	-	52
2	Ag_2CO_3	-	37
3	AgTFA	-	31
4	$Cu(OAc)_2$	-	27
5	AgOPiv	-	n.d.
6	CsOAc	-	n.d.
7	KOAc	-	n.d.
8	$Zn(OAc)_2$	-	n.d.
9	AgOAc	KOAc	47
10	AgOAc	K_2CO_3	trace
11	AgOAc	MesCOOH	74
12	AgOAc	PivOH	87 (83)[c]
13[d]	AgOAc	PivOH	66
14[e]	-	PivOH	n.d. (**4aa**)

[a] All the reactions were carried out with **1a** (0.1 mmol), **2a** (0.05 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol) and co-catalyst (0.2 mmol) additive (0.1 mmol) in DCE (1.0 mL) at 80 °C for 10 h unless otherwise specified. [b] Yield of the product is determined by ^{19}F NMR spectroscopy using 1-fluoronaphthalene as an internal standard. [c] Isolate yield. [d] at 60 °C. [e] only afforded **4aa** in 64% yield.

After THT/AgOAc has been identified as a highly effective reagent combination that enables the C-H aminomethylation reaction at indole's C3 position, the substrate scope was then explored and the results are shown in Scheme 2. A series of substituents and functional groups were tested in this transformation. This aminomethylation exhibited a good functional group compatibility with a variety of substituents having different electronic property to furnish the desired products **3aa**-**3ea** in good yields ranging from 76% to 83%, as exemplified by substrates **1a**-**1e** with halide and methoxy at C6 position. We also tested substituent and functional group at the C5 position. Bromine atom and methoxy group still tolerated, giving the desired products **3fa** and **3ga** in 82% and 78% yields, respectively. However, substrates **1h** and **1i** bearing a cyano group and an aldehyde group at C5 position only gave the corresponding products **3ha** and **3ia** in trace. The substituent at the C4 position was also examined and we identified that chlorine atom, methoxy group, nitro group, methyl group and OBn group were all compatible, affording the desired products **3ja**-**3na** in 70%-82% yields. The substrate scope of this protocol could be further extended to other directing group such as pyridine and 5-bromo pyrimidine, furnishing the corresponding aminomethylation products **3oa** and **3pa** in 81% and 71% yields, respectively. Pyrrole scaffold was also tolerated, giving the desired product **3pa** in 68% yield.

Scheme 2 Substrate scope of indoles[a,b]

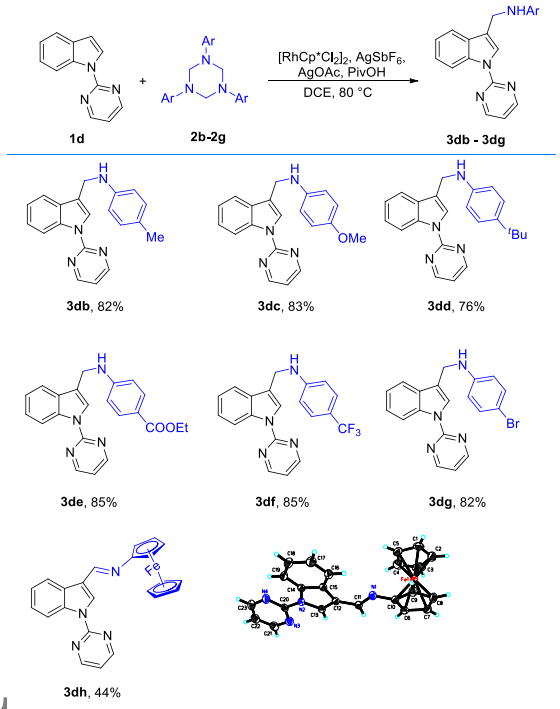


[a] All the reactions were carried out with **1** (0.1 mmol), **2a** (0.05 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol) and AgOAc (0.2 mmol) PivOH (0.1 mmol) in DCE (1.0 mL) at 80 °C for 10 h unless otherwise specified. [b] Isolated yield.

To further explore the substrate scope of this novel transformation, we subjected a range of THTs having different aromatic groups to the reaction with indole **1d** under the standard conditions and the results are indicated in Scheme 3. A variety of substituents such as methyl group, methoxyl group,

^{t}Bu group, ester group, CF_3 group and bromine atom could be introduced at the benzene ring of THTs afforded the desired products **3db**-**3dg** in good yields ranging from 76% to 85%. No significant impact on the electronic property of THTs was realized in this process, suggesting a good functional group tolerance for THTs. Moreover, the use of ferrocene derived THT in this protocol afforded an imine product **3dh** in 44% yield rather than a regular aminomethylation product perhaps due to the stability of this imine compound under oxidative reaction conditions. Its structure has been determined by a X-ray diffraction. The ORTEP drawing is shown in Scheme 3 and the corresponding CIF data are summarized in Supporting Information.

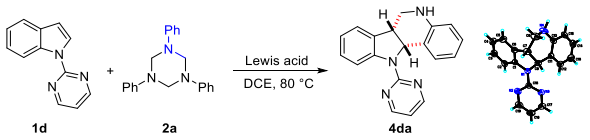
Scheme 3 Substrate scope of THTs[a,b]



[a] All the reactions were carried out with **1d** (0.1 mmol), **2** (0.05 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol) and AgOAc (0.2 mmol) PivOH (0.1 mmol) in DCE (1.0 mL) at 80 °C for 10 h unless otherwise specified. [b] Isolated yield.

The formation of product **4aa** was found accidentally in the absence of AgOAc. We next examined the [4+2] cycloaddition of **1d** with **2a** under the standard conditions without addition of AgOAc.[13] The corresponding product **4da** was formed and its structure was determined by a X-ray diffraction. The ORTEP drawing of **4da** is shown in Table 2 and its CIF data are presented in the Supporting Information. We speculated that rhodium(III) catalyst was not involved in the formation of **4da** and $AgSbF_6$ actually took the responsibility for this formal [4+2] cycloaddition reaction acting as a Lewis acid. Using $AgSbF_6$ as a sole Lewis acid, we found that this [4+2] cycloaddition reaction indeed took place to give **4da** in 71% yield (Table 2, entry 1). Hence, we screened several Lewis acids and Brønsted acids in this reaction and the results are shown in Table 2. The use of AgOTf gave **4da** in 58% yield and AgOAc did not catalyze this reaction (Table 2, entries 2 and 3). Using $Zn(OAc)_2$ or $Zn(OTf)_2$ as the catalyst also could afford **4da** in moderate yields ranging from 29 to 38%, presumably due to the partial decomposition of THTs with these Lewis acids during the reaction (Table 2, entries 4 and 5). Brønsted acid PivOH itself did not promote this reaction, but the stronger Brønsted acid HBF_4 could catalyze this reaction as well, affording **4da** in 55% yield (Table 2, entry 7). Next, we found that $[Ph_3C]BF_4$ was a suitable Lewis acid for this reaction, giving **4da** in 77% yield in DCE at 80 °C (Table 2, entry 8).[14]

Table 2 Optimization of the reaction conditions for **4da**

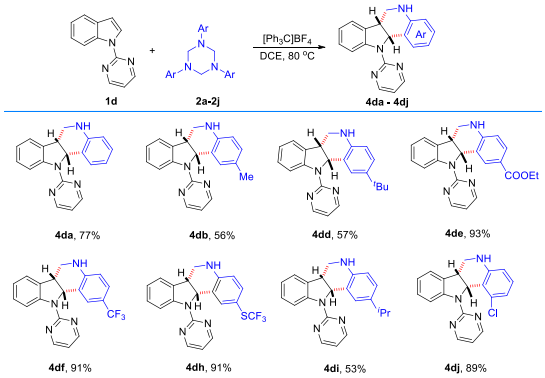


Entry[a]	Lewis acid	Yield[b] (%)
1	$AgSbF_6$	71
2	AgOTf	58
3	AgOAc	trace
4	$Zn(OAc)_2$	38
5	$Zn(OTf)_2$	29
6	PivOH	trace
7	HBF_4	55
8	$[Ph_3C]BF_4$	77

[a] All the reactions were carried out with **1d** (0.1 mmol), **2a** (0.05 mmol) and Lewis acid (0.01 mmol) in DCE (1.0 mL) at 80 °C for 10 h unless otherwise specified. [b] Isolate yield.

We also investigated the substrate scope of this interesting [4+2] cycloaddition reaction using indole **1d** as substrate to react with a range of THTs and the results are outlined in Scheme 4. For THTs **2e**, **2f**, **2h** and **2j**, in which their aromatic groups having an electron-withdrawing group, the desired cycloadducts **4de**, **4df**, **4dh** and **4dj** were produced in higher yields than those of THTs **2a**, **2b**, **2d** and **2i** (products **4da**, **4db**, **4dd** and **4di**) due to the electronic effect. This formal [4+2] cycloaddition reaction also showed a good functional group tolerance for THTs.

Scheme 4 Substrate scope of [4+2] cycloaddition reaction[a]

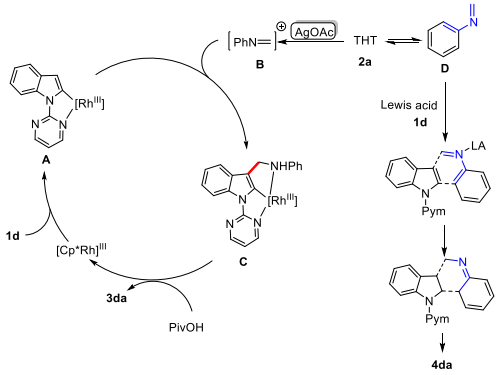


[a] All the reactions were carried out with **1d** (0.1 mmol), **2** (0.05 mmol), and $[Ph_3C]BF_4$ (0.02 mmol) in DCE (1.0 mL) at 80 °C for 10 h unless otherwise specified.

With regard to the reaction mechanism, a plausible mechanistic scenario could be evoked (Scheme 5). Initially, Rh^{III}-catalyzed C–H activation delivers a rhodacycle **A**. AgOAc can assist the dissociation of THT to form a cationic imino species **B**,[15] which accepts a nucleophilic attack from rhodacycle **A** to give intermediate **C**. Protonolysis of intermediate **C** with PivOH produces the final product along with the regeneration of Rh(III) catalyst. In the presence of silver(I) salt, THT has a dissociation equilibrium to give

intermediate **D**, which subsequently undergoes [4+2] cycloaddition with indole **1d** and double bond migration to furnish the corresponding product **4da**.

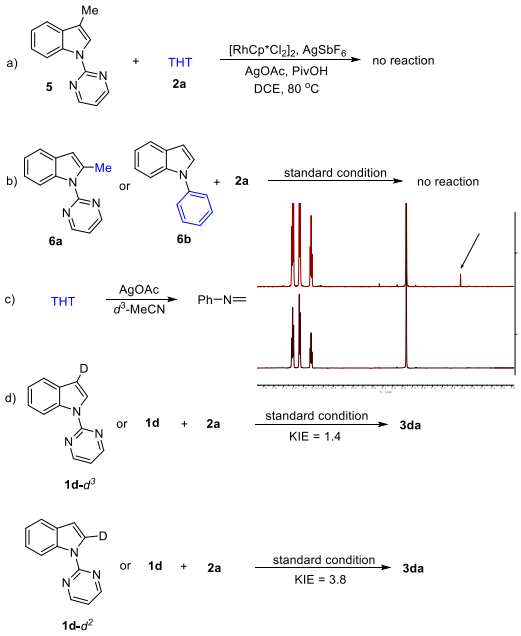
Scheme 5 Plausible reaction mechanisms



To verify the reaction mechanism, several control experiments were conducted. As shown in Scheme 5, we used compound **5** with a methyl substituent at C3 position as substrate in this reaction, and found that no reaction occurred because the reaction site has been blocked out by the methyl group (Scheme 6a). Moreover, indole **6a** with a methyl substituent at C2 position and indole **6b** with a *N*-phenyl group also failed to give the corresponding aminomethylation products under the standard conditions, illustrating that the directing group assisted C-H activation step at indole's C2-position is a dispensable process in this transformation (Scheme 6b). To identify the active imino species generated from THTs, a ^{1}H NMR tracing experiment of THT in d^3-acetonitrile in the presence of AgOAc was performed upon heating and a new signal appearing at δ 3.8 ppm was observed, suggesting that a silver-promoted dissociation of THT took place to give an active imino species upon oxidation (Scheme 6c). Furthermore, the KIE of this reaction was determined to be k_H/k_D = 3.8 for the parallel reactions using **1d** and **1d**-d^2 at low conversion, while the KIE of this reaction was 1.4 if using **1d** and **1d**-d^3 as substrates. These results indicated that the indole's C2–H activation step is probably involved in the turnover-limiting step (Scheme 6d).

Overall, we clarified the role of AgOAc in this C-H functionalization was to promote the dissociation of THT and to oxidize monomer imine **D** into active imino cationic species **B**, which did not change the valence state of rhodium center. The Rh^{III}/Rh^{III} catalytic cycle is more feasible in this reaction.

Scheme 6 Mechanistic investigation



Conclusions

In summary, we have developed a new aminomethylation protocol for indole derivatives with a pyrimidine directing group at C3-position through a Rh^{III}/Ag^{I} relay catalysis in a simple operation. This strategy opens up a new channel to combine metal-catalyzed site selective C-H activation with THTs as imine equivalents using easily accessible substrates. Meanwhile, a Lewis acid catalyzed [4+2] cycloaddition of indoles with THTs has been also discovered, affording tetrahydro-indolo[3,2-*c*]quinolines in good yields under mild conditions. It is expectable that more broad applications can be explored in related areas. The development of other C-H activation involved relay catalysis is undergoing in our laboratory.

Experimental

To an open reaction vessel with a magnetic stirring bar was added **1a** (19.5 mg, 0.1 mmol, 1.0 eq.), **2a** (15.7 mg, 0.05 mmol, 0.5 eq.), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol, 0.05 eq.), $AgSbF_6$ (6.8 mg, 0.02 mmol, 0.2 eq.) and AgOAc (33.1 mg, 0.2 mmol, 2.0 eq). PivOH (10.1 mg, 0.1 mmol, 1.0 eq.) and solvent of DCE (1.0 ml) were added in sequence to the reaction tube. The reaction mixture was stirred in an oil bath at 80 °C for 10 h. After completion of the reaction, the reaction mixture was cooled down to room temperature. After the removal of the volatiles in vacuo, the crude mixture was pre-absorbed on silica gel and purified by a flash column chromatography (silica gel, 300-400 mesh, PE/EA = 8/1), yielding the pure product **3aa** in 83% yield.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2019xxxxx.

Acknowledgement (optional)

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Entry for the Table of Contents

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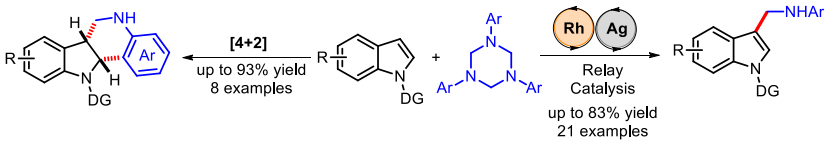

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