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Rh(III)-Catalyzed C−C/C−N Coupling of Imidates with α-Diazo Imidamide: Synthesis of Isoquinoline-Fused Indoles

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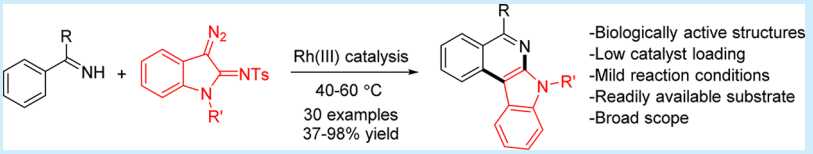
Supporting Information



ABSTRACT: Imidate esters and diazo compounds have been established as bifunctional substrates for the construction of biologically active fused heterocycles via rhodium-catalyzed C−H activation and C−C/C−N coupling. This reaction occurs under mild conditions with high efficiency, step economy, and low catalyst loading.

Isoquinoline-fused indoles are important structural motifs in diverse functional molecules. For example, they exhibit important biological activities including analgesic, anti-inflammatory, and antioxidant effects (Figure 1).[1] They also have found

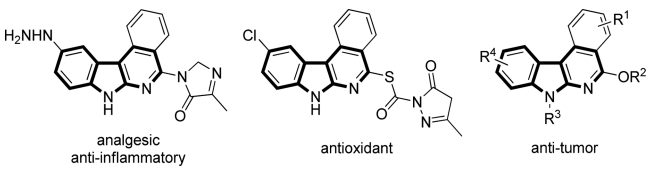
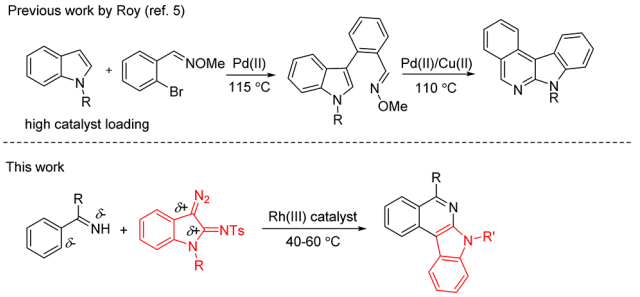


Figure 1. Representative biologically active indoloisquinolines.

applications as materials in organic optoelectronic devices.[2] Among such heterocycles, 7*H*-indolo(2,3-*c*)isoquinolines (Figure 1) are known to have potential antitumor activities and have been used in the treatment of tumors.[1b] However, only very limited methods have been reported for the synthesis of 7*H*-indolo(2,3-*c*)isoquinoline derivatives,[3] which typically start from highly functionalized starting materials and require harsh conditions with low step economy. Therefore, development of highly efficient strategies for the preparation of these compounds under mild conditions is of great significance.

Recently, direct C−H activation of arenes has been extensively investigated as a powerful strategy for the high atom- and step-economical syntheses of complex structures.[4] However, to date, synthesis of indoloisoquinolines via a C−H activation process has been rare. In 2014, Roy and co-workers reported a two-step synthesis of indoloisquinolines via Cu- and Pd-cocatalyzed intramolecular C−H functionalization of indoles, which occurred under high catalyst loading and relatively harsh conditions (Scheme 1).[5] On the other hand, electrophilic diazo compounds have been widely applied as a coupling partner in Rh(III)-catalyzed C−H functionalization of arenes.[6] For instance, in 2012, Yu and co-workers demonstrated the first rhodium-catalyzed intermolecular coupling of diazomalonates with arenes via C−H activation.[7] Subsequently, the groups of

Scheme 1. Synthesis of Indoloisoquinolines via C−H Activation/Annulation



Rovis,[8] Glorius,[9] and others[10] developed annulative couplings between arenes and diazo compounds via Rh(III)-catalyzed C−C/C−N bond formation. Afterward, diverse heterocycles were synthesized via Rh(III)-catalyzed C−H activation.[11] As a continuation of our interest in C−H activation chemistry,[12] we reasoned that α-diazo imidamide as a precursor of a dielectrophilic carbene[13] can electronically match an arene bearing a protic NH directing group, leading to synthesis of such an indolo(2,3-*c*)isoquinoline scaffold (Scheme 1).[14] In this system, the C−C bond formation occurs first via C−H alkylation[15] followed by intramolecular C−N formation. We now report our Rh(III)-catalyzed efficient synthesis of indoloisquinolines via this strategy with aromatization as a driving force.

We embarked on our studies by screening the reaction parameters of the coupling of ethyl benzimidate (**1a**) with α-diazo imidamide **2a** (Table 1). Using $[RhCp^*Cl_2]_2/AgSbF_6$ as a catalyst, desired product **3aa** was isolated in 52% yield in DCE at 80 °C (entry 1). Introduction of PivOH proved to be beneficial and necessary (entries 2−4), which likely facilitated both the C−

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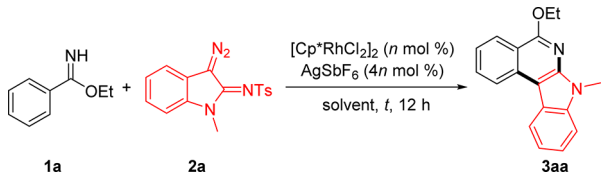
Table 1. Optimization Studies[a]



1a 2a 3aa

entry	*n*	additive (equiv)	solvent	*t* (°C)	yield (%)[b]
1	4		DCE	80	52
2	4	PivOH (1)	DCE	80	67
3	4	TsOH (1)	DCE	80	47
4	4	PivOH (1)	MeOH	80	95
5	4	PivOH (1)	MeOH	80	37[c]
6	4	PivOH (1)	EtOH	80	98
7	2	PivOH (1)	EtOH	80	98
8	2	PivOH (1)	EtOH	40	97
9	2	PivOH (1)	EtOH	25	50
10	1	PivOH (1)	EtOH	40	96
11	2	PivOH (1)	EtOH	40	nd[d]
12	2	PivOH (1)	EtOH	40	87[e]

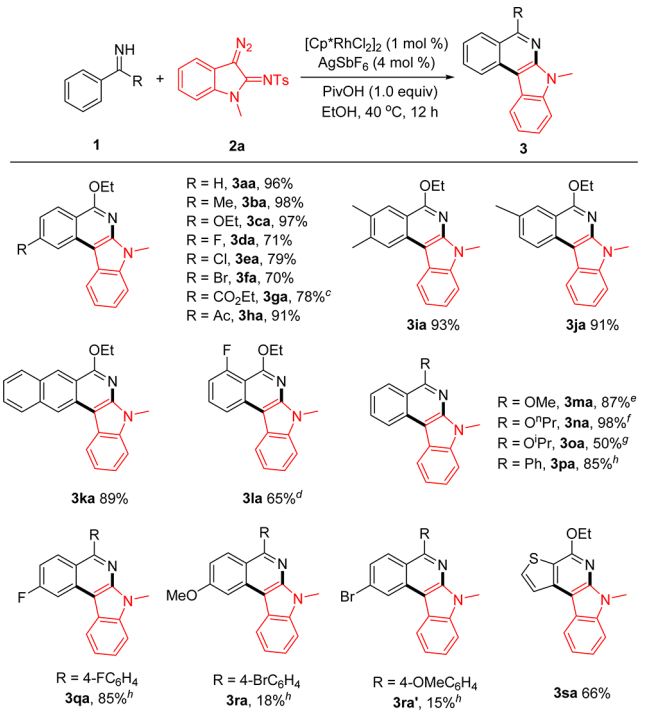
[a]Reactions were carried out using $[RhCp^*Cl_2]_2$ (1 mol %)/$AgSbF_6$ (4 mol %), **1a** (0.2 mmol), and **2a** (0.24 mmol) in a solvent (3 mL) under nitrogen at 40 °C for 12 h. [b]Isolated yield after column chromatography. [c]Reaction was performed with 3-diazo-1-methylindolin-2-one. [d]No rhodium catalyst was used. [e]No $AgSbF_6$ was used.

H activation and the cyclization processes. Screening of the solvents revealed that EtOH was optimal (entry 6), and the same yield was obtained when the catalyst loading was decreased to 2 mol % (entry 7). Poor conversion was observed when the diazo compound was replaced with 3-diazo-1-methylindolin-2-one (entry 5). The reaction proceeded well even at 40 °C (entry 8). The reaction is highly efficient, and even 1 mol % loading of the rhodium catalyst can suffice (entry 10). Control experiments indicated that $[RhCp^*Cl_2]_2$ was necessary (entry 11), but omission of $AgSbF_6$ still gave a good yield (entry 12).

With the establishment of the optimal conditions, we first defined the scope and generality with respect to aryl imidates (Scheme 2). Aryl imidates bearing both electron-donating and -withdrawing groups at the *para* position of the phenyl ring all coupled smoothly with diazo **2a** to afford the annulated products (**3ba**–**3ha**) in good to excellent yields. The molecular structure of **3fa** was unambiguously confirmed by X-ray crystallography (CCDC 1482471). Introduction of a *meta* substituent was also tolerated, and the reaction occurred at the less hindered site, furnishing the products in excellent yields (**3ia**–**3ka**). An *ortho* fluoro group was also compatible (**3la**, 65%) at a slightly higher temperature. Besides the ethyl ester, other alkyl esters of the imidate also coupled smoothly in high yields (**3ma**–**3na**), although the isopropyl imidate reacted with lower efficiency (**3oa**). In the coupling of these alkyl esters, the corresponding alcohol was employed as the solvent to avoid transesterification. The imidate substrate is not limited to alkyl esters, and even benzophenone NH imines all reacted with high efficiency (**3pa** and **3qa**), wherein using electronically biased diarylmethanimine substrates afforded two regioisomeric products, **3ra** and **3ra′**. Notably, the arene substrate was smoothly extended to a thiophene ring in good yield (**3sa**).

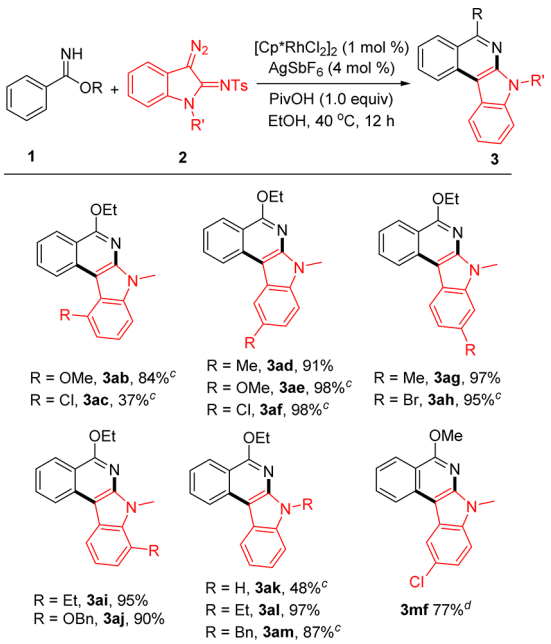
We next examined the scope of the diazo substrate. It was found that introduction of electron-donating and halogen groups at the 4-, 5-, 6-, and 7-positions of the indole ring was fully tolerated (Scheme 3). However, introduction of a 4-chloro

Scheme 2. Substrate Scope of Aryl Imidates[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (4 mol %), PivOH (0.2 mmol), EtOH (3 mL), 40 °C under N_2 for 12 h. [b]Isolated yield. [c]$[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 40 °C. [d]$[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 60 °C. [e]With MeOH (3 mL). [f]With ^{n}PrOH (3 mL). [g]With ^{i}PrOH (3 mL). [h]$[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), MeOH (3 mL), 60 °C.

Scheme 3. Substrate Scope of 3-Diazoindolin-2-imines[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (4 mol %), PivOH (0.2 mmol), EtOH (3 mL), 40 °C under N_2 for 12 h. [b]Yield of isolated product. [c]$[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 60 °C. [d]$[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), MeOH (3 mL), 60 °C.

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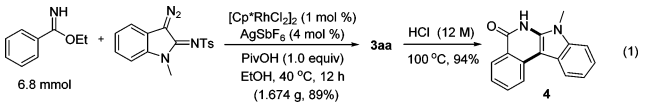
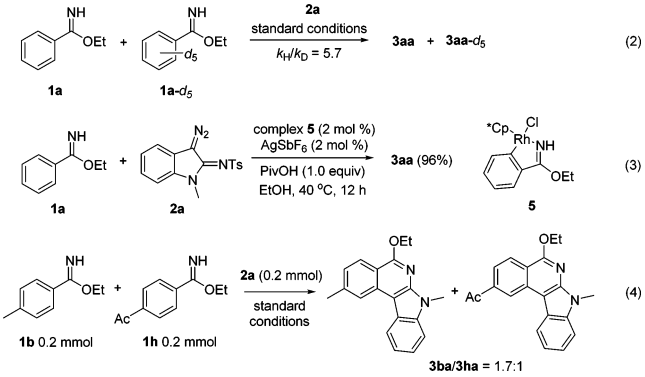
substituent of indole retarded the coupling (**3ac**, 37%), as a result of the electronic and steric effects. Other N-substituted indoles, such as *N*-ethyl and *N*-benzyl indoles, coupled with high yields (**3al**, **3am**). Notably, N-unprotected diazo indole was also viable for this transformation albeit with slightly lower efficiency (**3ak**). Product **3mf** with potent antitumor activity was synthesized in good yield.[5]

To demonstrate the synthetic utility of the catalytic system, gram-scale synthesis of **3aa** was performed in high yield. Further hydrolysis of **3aa** in concentrated hydrochloric acid/1,4-dioxane led to isoquinolone **4** in excellent yield (eq 1).



Several experiments have been performed to explore the mechanism. To probe this C−H activation process, an intermolecular kinetic isotope effect experiment was measured using **1a** and **1a**-d_5 in the coupling with **2a** (eq 2). A rather large

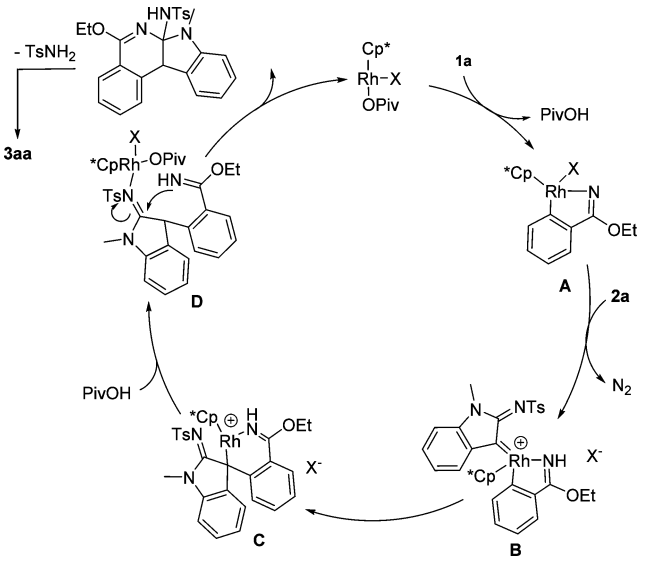


k_H/k_D value of 5.7 indicated that cleavage of the C−H bond is likely involved in the turnover-limiting step. Furthermore, rhodacyclic complex **5**[16] was designated as a catalyst for the coupling of imidate **1a** with diazo **2a**, and the corresponding annulated product was isolated in excellent yield (eq 3), indicating the relevancy of C−H activation. Moreover, an intermolecular competition between **1b** and **1h** under standard conditions pointed to the conclusion that an electron-rich imidate reacted preferentially (eq 4).

On the basis of these preliminary results, a plausible pathway is proposed starting from an active [RhCp*(OPiv)X] (X = OPiv or SbF_6) species (Scheme 4). Coordination and C−H activation of the imidate ester deliver rhodacycle **A**. Subsequent coordination of the diazo substrate is followed by extrusion of N_2 to give a rhodium carbenoid intermediate **B**. Migratory insertion of the Rh−Ar bond into the carbene generates a six-membered spiro-rhodacycle **C** that undergoes protonolysis, leading to alkylated intermediate **D**. An intramolecular nucleophilic addition/elimination process eventually releases the Rh(III) species and furnishes product **3aa**.

In summary, we have developed an efficient system of Rh(III)-catalyzed C−H activation of imidate esters for construction of 7*H*-indolo(2,3-*c*)isoquinolines under mild conditions with aromatization as a driving force. A broad scope of both aryl imidates and diazo compounds has been established. This coupling features the employment of bifunctional imidate esters and α-diazo imidamide. Efficient and concise protocols to access

Scheme 4. Proposed Mechanism



such important fused heterocycles may find applications in the synthesis of complex biologically active products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01284.

Crystallographic data for **3fa** (CIF)

General procedures, characterization data, and copies of the NMR spectra of all new products (PDF)

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Author Contributions

†H.W. and L.L. contributed equally.

Notes

The authors declare no competing financial interest.

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