Rapid access to polysubstituted tetrahydrocarbazol-4-ones via sequential selective C-H functionalization from N-nitrosoanilines

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Abstract

Herein, we have developed a strategy of Rh(III)-catalyzed C–H activation of N-nitrosoanilines and iodonium ylides to construct novel tetralhydrocarbazol-4-one scaffolds, which provided valuable templates for sequential C-H functionalization such as alkylation, alkenylation, amidation and (hetero)arylation at C5-position of tetralhydrocarbazol-4-one with different coupling partners. Gram-scale synthesis and further transformation of tetralhydrocarbazol-4-one derivatives to Ondansetron and its analogues demonstrated the utility of this protocol, which enabled the concise and diverse construction of biologically active molecules.

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Comprehensive Summary

Herein, we have developed a strategy of Rh(III)-catalyzed C–H activation of N-nitrosoanilines and iodonium ylides to construct novel tetralhydrocarbazol-4-one scaffolds, which provided valuable templates for sequential C-H functionalization such as alkylation, alkenylation, amidation and (hetero)arylation at C5-position of tetralhydrocarbazol-4-one with different coupling partners. Gram-scale synthesis and further transformation of tetralhydrocarbazol-4-one derivatives to Ondansetron and its analogues demonstrated the utility of this protocol, which enabled the concise and diverse construction of biologically active molecules.

Keywords

C–H activation | Cross dehydrogenative coupling | Rhodium catalysis | Iridium catalysis | Heteroarylation
Background and Originality Content

Indole substructures have always been the most important and appealing structural core for the discovery of new drug candidates.\(^1\) In particular, tetrahydrocarbazol-4-one represents a kind of privileged drug scaffold in numerous bioactive molecules, marketed pharmaceuticals and natural products (Figure 1), which greatly promoted the development of its expedient methods, mainly including classic Fischer indole cyclization,\(^2\) Heck-type coupling reactions,\(^4\) oxidative cyclization,\(^5\) and acid-catalyzed cyclization,\(^6\) etc. However, the reported routes often suffer from multi-step processes, harsh conditions, or limited substrate scope. Therefore, it is urgent need to develop an efficient and concise synthetic method.

Figure 1 Bioactive compounds and natural products containing tetrahydrocarbazol-4-one scaffold.

Transition-metal-catalyzed direct C–H functionalization has apparently provided simple and practical pathways for preparing complex molecules from readily available starting materials with the advantage of eliminating the need for prefunctionalization of substrates. Recently, several efforts to construct indole scaffolds have been made in the N-nitroso-directed C–H activation and cyclization with different coupling partners, such as alkynes,\(^7\) alkynols,\(^8\) diazo compounds,\(^9\) sulfoxonium ylides,\(^10\) and cyclopropenones\(^11\) by a traceless, step-economic and cascade approach. However, the discovery of new routes that meet green synthesis goals from readily available raw materials is still desirable. Iodonium ylides, inexpensive, readily available, safe and stable highvalent iodine reagents compared to dangerous and explosive diazonium compounds, were used as effective synthons in few C–H activation.\(^12\) In 2020, Rh(III)-catalyzed C–H bond activation of N-methoxybenzamide with hypervalent iodonium ylides deployed as a carbene precursor has been reported by Maheswari and co-workers.\(^13\) More recently, Kanchupalli’ group developed another Rh(III)-catalyzed \([4+2]\) and \([3+3]\) annulations between indoles and iodonium ylides for rapid synthesis of diverse N-heterocycles.\(^14\)

Based on the continuous efforts of our group in building drug-like heterocyclic compounds through transition-metal-catalyzed C–H bond activation, we further accomplished an efficient synthesis of the tetrahydrocarbazol-4-one scaffold via a Rh(III)-catalyzed traceless and cascade reaction of hypervalent iodonium ylides with N-nitrosoanilines under mild reaction conditions (Scheme 1). More importantly, the tetrahydrocarbazol-4-one derivatives constructed by the first-step C–H activation provided valuable templates for further modification, fulfilling the rapid and modular generation of molecular complexity through sequential multicomponent C–H activation. For example, C\(^5\)-selective alkylation, alkenylation, amidation and (hetero)arylation of tetrahydrocarbazol-4-one derivatives have successfully been achieved by sequential transition metal catalyzed C–H functionalization with commercially available materials. To the best of our knowledge, Rh(III)-catalyzed annulation of N-nitrosoanilines with iodonium ylides and sequential C\(^5\)-H functionalization of tetrahydrocarbazol-4-ones have not been reported previously. We believe the desired analogues may help in the search of new biologically active compounds and drug discovery by creation of diverse chemical space.

Scheme 1 Design of Rh(III)-catalyzed annulation of N-nitrosoanilines with iodonium ylides and sequential C–H functionalization.

Results and Discussion

As a starting point, we conducted the annulation reaction between N-nitroso-N'-methylaniline (1a) and 2-(phenyl-λ\(^3\)-iodaneylidene)cyclohexane-1,3-dione (2a) in the presence of \([\text{Cp}^*\text{RhCl}_2]\) and AgSbF\(_6\) in DCE at 80 °C as the initial catalytic conditions, and fortunately isolated the desired product 3aa in 29% yield (Table 1, entry 1). Among the tested catalysts, \([\text{Cp}^*\text{RhCl}_2]\) still showed the highest catalytic activity (entries 2-5). Further reaction optimization by examining Ag salts revealed that AgBF\(_4\) was conducive to this reaction, providing 3aa in 40% yield (entries 6-10). Then, a screening of additives demonstrated that PivOH gave a better yield (entries 11-14), and the yield of 3aa was increased to 57% when the reaction was conducted in acetone (entries 15 and 16). Subsequently, performing the reaction at 90°C exhibited a higher reaction efficiency with 72% isolated yield (entry 17). Briefly, the optimal results could be obtained when...
1a (0.4 mmol) and 2a (0.6 mmol, 1.5 equiv.) in acetone were treated with 8 mol% [Cp*RhCl2]2, AgBF4(0.6 mmol, 1.5 equiv.) and PivOH (0.8 mmol, 2 equiv.) at 90 oC under Ar for 12 h.

Table 1. Optimization of Reaction Condition A

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ag Salt</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>[Cp*RhCl2]2</td>
<td>AgSbF6</td>
<td>—</td>
<td>DCE</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>[Cp*IrCl2]2</td>
<td>AgSbF6</td>
<td>—</td>
<td>DCE</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>[Cp*Rh(CH3CN)3][SbF6]2</td>
<td>AgSbF6</td>
<td>—</td>
<td>DCE</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>[Cp*Rh(OAc)2]</td>
<td>AgSbF6</td>
<td>—</td>
<td>DCE</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>[Cp*Co(CO)I2]</td>
<td>AgSbF6</td>
<td>—</td>
<td>DCE</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>—</td>
<td>DCE</td>
<td>40</td>
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<tr>
<td>7</td>
<td>[Cp*RhCl2]2</td>
<td>AgF</td>
<td>—</td>
<td>DCE</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>[Cp*RhCl2]2</td>
<td>AgNTf2</td>
<td>—</td>
<td>DCE</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>[Cp*RhCl2]2</td>
<td>AgOMs</td>
<td>—</td>
<td>DCE</td>
<td>17</td>
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<tr>
<td>10</td>
<td>[Cp*RhCl2]2</td>
<td>AgPF6</td>
<td>—</td>
<td>DCE</td>
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<tr>
<td>11</td>
<td>[Cp*RhCl2]2</td>
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<td>NaOAc</td>
<td>DCE</td>
<td>23</td>
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<td>HOAc</td>
<td>DCE</td>
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<td>13</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>Fumaric acid</td>
<td>DCE</td>
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<tr>
<td>14</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>PivOH</td>
<td>DCE</td>
<td>51</td>
</tr>
<tr>
<td>15</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>PivOH</td>
<td>HFIP</td>
<td>41</td>
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<tr>
<td>16</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>PivOH</td>
<td>Acetone</td>
<td>57</td>
</tr>
<tr>
<td>17c</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>PivOH</td>
<td>Acetone</td>
<td>72</td>
</tr>
<tr>
<td>18d</td>
<td>[Cp*RhCl2]2</td>
<td>AgBF4</td>
<td>PivOH</td>
<td>Acetone</td>
<td>54</td>
</tr>
</tbody>
</table>

a Reaction condition A: 1a (0.4 mmol), 2a (0.6 mmol), Catalyst (8 mol %), Ag Salt (0.6 mmol) and Additive (0.8 mmol) in solvent (3 mL) at 80 oC under argon for 12 h. b Isolated yield. c 90 oC. d 100 oC. DCE: 1,2-dichloroethane. HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol.

With the optimal reaction conditions established, we first explored the substrate versatility of N-nitrosoanilines and iodonium ylides, respectively (Scheme 2). Generally, all the reactions could proceed smoothly in moderate to excellent yields. By first, N-nitrosoanilines 1a-1t with various substituents installed on the para, meta or ortho position of the benzene ring as well as N atom were examined with 2a, and smoothly transformed into the desired compounds 3aa-3ta in 25-80% yields. Introducing halogens (F, Cl, Br), electron-donating substituents (OCH3 and CH3) and electron-withdrawing substituents (CF3, NO2 and CO2CH3) at the para position of the benzene ring afforded the corresponding products 3ba-3ia in moderate to good yields. When CH3 and OCH3 were placed at 3-position of the benzene ring, 3ja and 3ka were offered in 53% and 54% yield, respectively, superior to 3la with a CF3 substituent. Moreover, O-fluorosubstituted N-nitroaniline 1m was also tolerated under the standard condition A. It was worth mentioning that the substituent on the nitrogen atom was not limited to a methyl, but could be favorably extended to Et (3na, 67%), n-Bu (3oa, 57%), Bn (3pa, 49%), and even p-Methylphenyl (3qa, 30%). More importantly, this transformation was also compatible with N-nitroso-tetrahydroquinoline independent of electronic factors (3ra-3ta), which greatly broaden its application scope. Then, iodonium ylides were also investigated. A variety of iodonium ylides (2b-2i) smoothly reacted with 1a to afford the desired products 3ab-3ai in moderate to good yields. For example, iodonium ylides bearing a methyl, dimethyl or phenyl at R2 position could be well delivered to the desired products 3ab, 3ac and 3ae in 67%, 69% and 56% yields, respectively. Besides, 4-F, 4-Cl, 4-Br and 4-CH3 phenyl substituted substrates were favored to provide 3af-3ai in 42%-72% yields. What’s more, five-membered iodine ylide (2d) was converted to 3ad at a high yield of 72%.

Scheme 2. Substrate Scope for 3 a,b
a Reaction condition A: 1 (0.4 mmol), 2 (0.6 mmol), [Cp*RhCl₂]₂ (8 mol %), AgBF₄ (0.6 mmol) and PivOH (0.8 mmol) in acetone (3 mL) at 90 °C under argon for 12 h. b Isolated yield.

After constructing a preliminary knowledge of the optimal reaction conditions and substrates diversity, we were further intrigued by the structure of 3aa, because the carbonyl group of its tetrahydrocarbazol-4-one possibly acted as a new directing group to selectively catalyze cross dehydrogenative coupling (CDC) reaction between the C⁵-position of 3aa and other (hetero)arenes. To verify our idea, we chose 3aa (0.2 mmol) and 4a (0.4 mmol) as template substrates and treated them with [Cp*IrCl₂]₂ (5 mol %), AgSbF₆ (20 mol %), PivOH (0.2 mmol) and AgOPiv (0.6 mmol) in 1,2-dichloroethane (DCE) at 130 °C under argon for 24 h. To our delight, the desired product 5a could be attained in 37% isolated yield (Table 2, entry 1), and its exact structure has been verified by the ¹H and ¹³C NMR spectroscopy, mass spectrometry data and X-ray crystallographic analysis (see Figure S2 in the Supporting Information). The detailed reaction condition optimization was shown in Table 2. Finally, we treated 3aa (0.2 mmol) and 4a (0.4 mmol) as additives in 2 mL of dioxane where 5a was obtained in 76% isolated yield at 100 °C under argon for 24 h (Table 2, entry 8).

**Table 2. Optimization of Reaction Condition B**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ag₂O</td>
<td>DCE</td>
<td>130</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>AgOPiv</td>
<td>DCE</td>
<td>130</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>AgO</td>
<td>DCE</td>
<td>130</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>AgOPiv</td>
<td>Dioxane</td>
<td>130</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>AgOPiv</td>
<td>Toluene</td>
<td>130</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>AgOPiv</td>
<td>EtOH</td>
<td>130</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>AgOPiv</td>
<td>Dioxane</td>
<td>110</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>AgOPiv</td>
<td>Dioxane</td>
<td>100</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions B: 3aa (0.2 mmol), 4a (0.4 mmol), [Cp*IrCl₂]₂ (5 mol %), AgSbF₆ (20 mol %), PivOH (0.2 mmol) and Oxidant (0.6 mmol) in solvent (2 mL) at a temperature under argon for 24 h. <sup>b</sup> Isolated yield.

Afterwards, we further investigated the corresponding substrate scope under the standard condition B. As shown in Scheme 3, the 7-methyl substituted tetrahydrocarbazol-4-one derivative 3ja was easily transformed into 5b in a moderate efficiency, where electron-withdrawing trifluoromethyl (5c) may be unfavorable in a lower 22% yield. When replacing methyl with Bu, n-Bu and Et at R² position, the expected products 5d-5f and 5k were well obtained, respectively, and p-methylphenyl enriched the diversity of R³ substituent (5g). Besides, a series of substituted thiophenes and furans were also tolerated, where electron-rich thiophene rings had higher reaction efficiencies (5h-5n).

**Scheme 3. Substrate Scope for 5**

<sup>a</sup> Reaction conditions B: 3aa, 3ja, 3la, 3na, 3oa, 3pa, 3ai (0.2 mmol), 4a-g (0.4 mmol), [Cp*IrCl₂]₂ (5 mol %), AgSbF₆ (20 mol %), PivOH (0.2 mmol) and AgOPiv (0.6 mmol) in dioxane (2 mL) under argon for 24 h. b Isolated yield.

Encouraged by the success of C⁵-(hetero)arylation of 3aa, we subsequently achieved its C⁵-alkylation (6), C⁵-alkenylation (7) and C⁵-amidation (8) by treating 3aa with tert-butyl-3-ethyl 2-diazomalonate, 3-buten-2-ol and 3-phenyl-1,4,2-dioxazolidin-5-one, respectively (Scheme 4). The structures of products 7 and 8 were unambiguously established by the single crystal X-ray diffraction analyses (see Figures S3 and S4 in the Supporting Information). These transformations will provide simpler routes for the synthesis of highly-functionalized tetrahydrocarbazol-4-one derivatives, which could be further modified to obtain biologically active compounds.
Scheme 4. The C⁵-alkylation, alkenylation and amidation of 3aa.

To further evaluate the application potential of the prepared carbazolone derivatives, we first performed a gram-scale preparation of 3sa in 48% isolated yield (Scheme 5a). Then, 3aa was used as a universal precursor to synthesize potentially active molecules through functional group conversion (Scheme 5b). First, 3aa was reacted with Pb(OAc)₄ in dichloromethane (DCM) at room temperature for 12 h to give the unexpected oxidation product 9. Surprisingly, both double bond and carbonyl group of 3aa were reduced to afford tetrahydrocarbazole 10 in 61% yield when treating 3aa with NaBH₃CN in acidic solution. Moreover, the carbonyl group of 3aa was easily reacted with hydroxylamine hydrochloride to yield oxime, which further underwent a Beckmann rearrangement reaction under PPA and gave the ring-expanding lactam 11 in 70% yield. More importantly, carbazolone derivatives 3 could be used to prepare Ondansetron (12a) and its analogues (12b and 12c), a marketed drug treating vomiting caused by chemotherapy and radiotherapy, through simple two-step reactions (Scheme 5c).[15] Notably, our methods and products could find great applications in drug synthesis.

Scheme 5. Gram-scale Preparation and Conversion of 3.

To gain insight into the reaction mechanism, we subsequently performed some mechanistic experiments. First, the H/D exchange experiment under the standard condition A showed that the C–H activation was reversible (Scheme 6a). Then, the intermolecular competition experiment was performed between N-methyl-N-(p-tolyl)nitrous amide 1e and N-methyl-N-(4-(trifluoromethyl)phenyl)nitrous amide 1g, and the mole ratio of 3ea/3ga was up to 2.6, indicating that the electron-donating substituent may be more conducive to the reaction (Scheme 6b).

Scheme 6. Preliminary Mechanistic Investigations

On the basis of the preliminary mechanistic experiments and literature precedents, a conceivable reaction mechanism was proposed in Scheme 7. First, the catalyst is activated in the presence of AgBF₄ and PivOH. Then, the active catalyst breaks the ortho C–H bond of 1a to form a five-membered Rh intermediate II, which subsequently captures 2a and gives the Rh-carbene species IV with the release of IPh. The intermediate IV undergoes a cyclohexanedione carbene migration insertion into C(Ar)-Rh bond and a sequential protonation, providing the intermediate VI and the active Rh. Finally, the intermediate VI undergoes an intramolecular enol interconversion and cyclization to afford the carbazolone derivative 3aa, accompanying by the departure of a molecule of HNO₂.

Scheme 7. Proposed Reaction Mechanism.

Conclusions

In conclusion, we have developed a Rh(III)-catalyzed C–H activation of N-nitrosoanilines and iodonium ylides to construct novel tetrahydrocarbazol-4-one scaffolds, which provided valuable templates for sequential C–H functionalization such as alkylation, alkenylation, amidation and (hetero)arylation at C⁵-position of tetrahydrocarbazol-4-one with diverse coupling partners. The protocol showed mild reaction conditions and good functional group tolerance. This transformation enabled the multiple C–H modification of pharmaceuticals, and the concise construction of biologically active molecules.

Experimental

General Procedure for the Synthesis of 3

A pressure tube was charged with 1 (0.4 mmol) and 2 (0.6 mmol), [Cp*RhCl₂]₂ (20 mg, 8 mol%), AgBF₄ (116 mg, 0.6 mmol) and PivOH (81.7 mg, 0.8 mmol) in acetone (3 mL) under Ar. The reaction mixture was stirred at 90°C for 12 h. After the reaction was completed, the reaction mixture was cooled to room temperature and filtered over celite. The solvent was then removed under vacuum and the residue was purified by silica gel chromatography with PE/EA=5:1-2:1 to afford the corresponding 3.

Supporting Information
The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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References


The Authors

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**Left to Right:** Authors Names

Entry for the Table of Contents

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Herein, we have developed a strategy of Rh(III)-catalyzed C–H activation of *N*-nitrosoanilines and iodonium ylides to construct novel tetrahydrocarbazol-4-one scaffolds, which provided valuable templates for sequential C-H functionalization such as alkylation, alkenylation, amidation and (hetero)arylation at *C*₅-position of tetrahydrocarbazol-4-one with different coupling partners. Gram-scale synthesis and further transformation of these scaffolds demonstrated the utility of this protocol, which enabled the concise and diverse construction of biologically active molecules.