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 tetralydrocarbzol-4-one scaffolds, which provided valuable templates for sequential C-H functionalization such as alkylation, alkenyla-tion, amidation and (hetero)arylation at C5-position of tetralydrocarbzol-4-one with different coupling partners. Gram-scale synthesis and further transformation of tetralydrocarbzol-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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Rapid access to polysubstituted tetrahydrocarbazol-4-ones via sequential selective C-H functionalization from *N* -nitrosoanilines

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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 const

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),[2] which greatly promoted the development of its expedient methods, mainly including classic Fischer indole cyclization,[3] 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 form 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* -heterocylces.[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 $[Cp^*RhCl_2]_2$ 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, $[Cp^*RhCl_2]_2$ 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% $[Cp^*RhCl_2]_2$, $AgBF_4$(0.6 mmol, 1.5 equiv.) and PivOH (0.8 mmol, 2 equiv.) at 90°C under Ar for 12 h.

Table 1. Optimization of Reaction Condition A[a]

Entry	Catalyst	Ag Salt	Additive	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	—	DCE	29
2	$[Cp^*IrCl_2]_2$	$AgSbF_6$	—	DCE	ND
3	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	$AgSbF_6$	—	DCE	11
4	$Cp^*Rh(OAc)_2$	$AgSbF_6$	—	DCE	9
5	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	—	DCE	ND
6	$[Cp^*RhCl_2]_2$	$AgBF_4$	—	DCE	40
7	$[Cp^*RhCl_2]_2$	AgF	—	DCE	21
8	$[Cp^*RhCl_2]_2$	$AgNTf_2$	—	DCE	22
9	$[Cp^*RhCl_2]_2$	AgOMs	—	DCE	17
10	$[Cp^*RhCl_2]_2$	$AgPF_6$	—	DCE	19
11	$[Cp^*RhCl_2]_2$	$AgBF_4$	NaOAc	DCE	23
12	$[Cp^*RhCl_2]_2$	$AgBF_4$	HOAc	DCE	17
13	$[Cp^*RhCl_2]_2$	$AgBF_4$	Fumaric acid	DCE	36
14	$[Cp^*RhCl_2]_2$	$AgBF_4$	PivOH	DCE	51
15	$[Cp^*RhCl_2]_2$	$AgBF_4$	PivOH	HFIP	41
16	$[Cp^*RhCl_2]_2$	$AgBF_4$	PivOH	Acetone	57
17[c]	**$[Cp^*RhCl_2]_2$**	**$AgBF_4$**	**PivOH**	**Acetone**	**72**
18[d]	$[Cp^*RhCl_2]_2$	$AgBF_4$	PivOH	Acetone	54

[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 °C under argon for 12 h. [b] Isolated yield.[c] 90 °C.[d] 100 °C. 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 (OCH_3 and CH_3) and electron-withdrawing substituents (CF_3, NO_2 and CO_2CH_3) at the para position of the benzene ring afforded the corresponding products**3ba** -**3ia** in moderate to good yields. When CH_3 and OCH_3 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 CF_3 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 R^2 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-CH_3 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), $[Cp^*RhCl_2]_2$(8 mol %), $AgBF_4$ (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 C^5 -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 $[Cp^*IrCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), PivOH (0.2 mmol) and Ag_2O (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 ^{13}C 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) in the presence of $[Cp^*IrCl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %) as catalysts, AgOPiv (0.6 mmol) and PivOH (0.2 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[a]

Entry	Oxidant	Solvent	Temp. (°C)	Yield (%)[b]
1	Ag_2O	DCE	130	37
2	AgOPiv	DCE	130	44
3	AgO	DCE	130	35
4	AgOPiv	Dioxane	130	57
5	AgOPiv	Toluene	130	50
6	AgOPiv	EtOH	130	trace
7	AgOPiv	Dioxane	110	68
8	**AgOPiv**	**Dioxane**	**100**	**76**

[a] Reaction conditions B: **3aa** (0.2 mmol), **4a** (0.4 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), PivOH (0.2 mmol) and Oxidant (0.6 mmol) in solvent (2 mL) at a temperature under argon for 24 h.[b] 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, whera electron-withdrawing trifluoromethyl (**5c**) may be unfavorable in a lower 22% yield. When replacing methyl with Bn, *n*- Bu and Et at R^2 position, the expected products**5d -5f** and **5k** were well obtained, respectively, and *p* -methylphenyl enriched the diversity of R^3 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** [a,b]

[a] Reaction conditions B: **3aa** ,**3ja** , **3la** , **3na, 3oa, 3pa, 3ai** (0.2 mmol),**4a -g** (0.4 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgSbF_6$ (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 ofC^5 -(hetero)arylation of **3aa** , we subsequently achieved its C^5 -alkylation (**6**), C^5 -alkenylation (**7**) andC^5 -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 C^5 -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 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 $NaBH_3CN$ 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 $AgBF_4$ and PivOH. Then, the active catalyst **I**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 HNO_2.

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 tetralydrocarbzol-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 tetralydrocarbzol-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), $[Cp^*RhCl_2]_2$ (20 mg, 8 mol%), $AgBF_4$ (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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Herein, we have developed a strategy of Rh(III)-catalyzed C–H activation of *N*-nitrosoanilines and iodonium ylides to const