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Rhodium-Catalyzed Oxidative Cycloaddition of *N*-*tert*-Butoxycarbonylhydrazones with Alkynes for the Synthesis of Functionalized Pyrroles *via* C(sp^3)–H Bond Functionalization

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Abstract: A rhodium(III)-catalyzed cycloaddition of *N*-*tert*-butoxycarbonylhydrazones with internal alkynes was developed. The reaction features a regioselective α-imino alkyl C(sp^3)–H bond functionalization resulting in selective formation of highly functionalized *NH-free* pyrroles. Our studies showed that utilizing the *N*-*tert*-butoxycarbonyl (*N*-Boc) as the oxidizing directing group is critical for achieving the observed pyrrole formation *versus* the isoquinoline formation. To account for the pyrrole formation, we hypothesized that a prior tautomerization of the *N*-Boc-hydrazones to enamines should occur, followed by regioselective C(sp^2)–H cleavage to form a putative five-membered rhodacycle. Subsequent coupling of the rhodacycle with the alkynes would afford the pyrrole products.

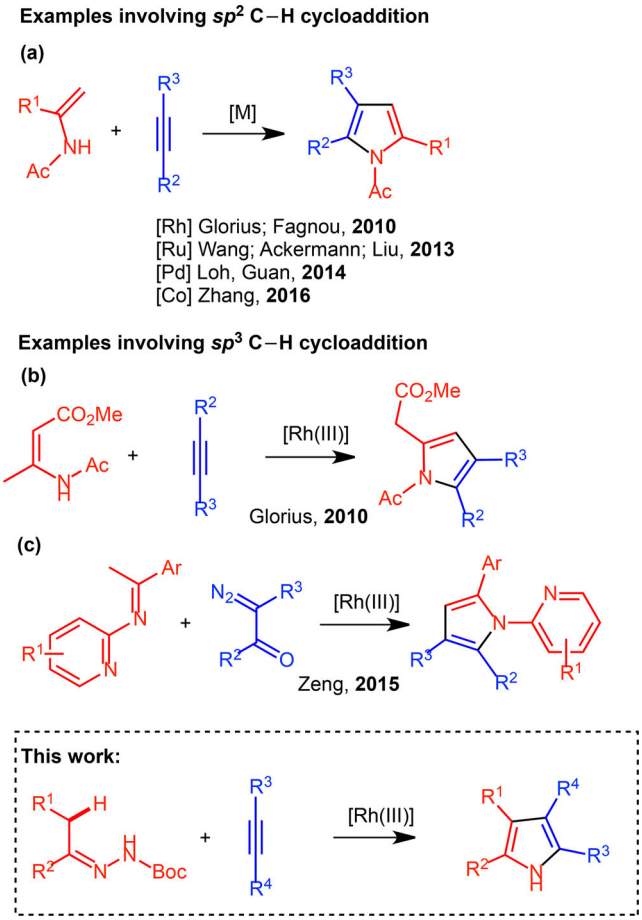
Keywords: alkynes; C–H activation; cycloaddition; nitrogen heterocycles; rhodium

Introduction

Transition metal-catalyzed oxidative C–H bond cycloaddition reactions with alkynes[1,2] and carbenoids[3] are attracting current attention for developing atom-economical syntheses of medicinally valuable heterocycles. The versatility of the transition metal catalysis approach is examplified by the recent advances in indoles and isoquinolines synthesis involving the Cp*Rh^{III}-catalyzed oxidative C(sp^2)–H cycloaddition with *N*-oxyenamines as substrates.[1b,e] With the N–O moieties as oxidizing directing groups, the cycloadditions with alkynes and carbenoids can operate under mild conditions without external oxidants and exhibit high regio- and chemoselectivity.[1–3]

Pyrroles are privileged heterocyclic scaffolds present in many pharmaceutical products and functional materials.[4] Analogous to the indoles and isoquinolines synthesis, metal-catalyzed oxidative C–H bond cycloaddition for pyrroles synthesis has also received considerable interest.[5] In 2010, Fagnou[6a] and Glorius[6b] first reported independently the *N*-acetylpyrrole synthesis by $[Cp^*RhCl_2]_2$-catalyzed C(sp^2)–H bond cycloaddition of *N*-acetylenamides with alkynes (Scheme 1a). Later, the research groups of Wang,[7a] Ackermann[7b] and Liu[7c] successfully developed the analogous cycloaddition reactions based on ruthenium catalysis. For other transition metal approaches, Loh's[8a] and Guan's[8b] groups reported the Pd-catalyzed pyrrole synthesis, whereas Zhang and co-workers also developed the related cobalt-catalyzed cycloaddition reaction.[9]

Currently, extensive effort is directed to developing Rh-catalyzed regioselective C(sp^3)–H bond functionalization for C–C and C–X (X = N, B, Si) bonds formation.[10] However, examples for pyrrole synthesis by catalytic regioselective C(sp^3)–H bond functionalization are sparse in the literature.[11] In 2010, Glorius and co-workers pioneered the Cp*Rh(III)-catalyzed oxidative cycloaddition of enamides with alkynes to form pyrroles *via* C(sp^3)–H bond activation, and a Cu(II) salt was employed as co-oxidant (Scheme 1b).[6b] In 2014, Zeng and co-workers reported the Pd-catalyzed C(sp^3)–H bond oxidative cycloaddition of *N*-(2-pyridyl)ketoimines with internal alkynes to form *N*-(2-pyridyl)pyrroles.[11b] Later in 2015, they also developed the Rh-catalyzed cyclization of α-imino C(sp^3)–H bonds with α-acyl diazocarbonyl compounds to form the corresponding pyrroles (Scheme 1c).[11a] In this report, we disclose the Cp*Rh(III)-catalyzed oxidative cycloaddition of *N*-Boc-hydrazones with internal alkynes to afford *NH-*



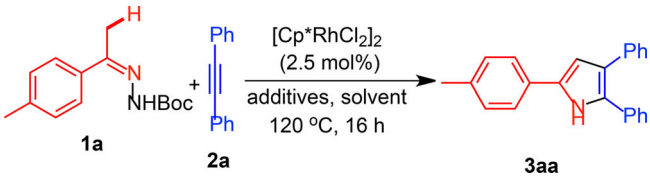
Scheme 1. Selected examples of pyrrole synthesis by metal-catalyzed cycloaddition.

free pyrroles *via* regioselective α-imino C(sp^3)–H bond cycloaddition. This reaction features the N–N bond cleavage for effective product formation and catalyst turnovers without the need for external oxidants.

Results and Discussion

To begin, we reacted 4-methylacetophenone *N*-Boc-hydrazone (**1a**, 0.4 mmol) and diphenylacetylene (**2a**, 0.2 mmol) with $[Cp^*RhCl_2]_2$ (2.5 mol%), CsOAc (25 mol%) and AcOH (3.0 equiv.) in MeCN (2.5 mL) at 120 °C for 16 h, and pyrrole **3aa** was obtained in 68% yield. We were gratified to see that isoquinoline **4aa** was formed in <10% yield (Supporting Information, Table S3).[12] However, when the same protocol was applied to 4-bromoacetophenone *N*-Boc-hydrazone **1f**, no pyrrole or isoquinoline was obtained. After several trials, we found that doubling the solvent volume to 5 mL led to effective formation of pyrrole **3fa** in 60% yield (Supporting Information, S6).[12]

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3aa

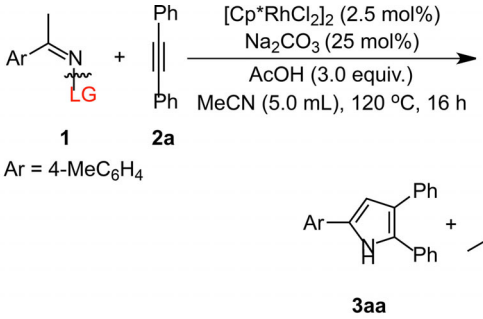
Entry	Solvent (5.0 mL)	Acid (3.0 equiv.)	Base (25 mol%)	Yield [%][b] of **3aa**
1	MeCN	AcOH	CsOAc	70
2[c]	MeCN	AcOH	CsOAc	<5
3	MeCN	AcOH	–	0
4	MeCN	–	CsOAc	0
5[d]	MeCN	AcOH	CsOAc	0
6	MeCN	PivOH	CsOAc	89
7	MeCN	$PhCO_2H$	CsOAc	88
8	MeCN	AcOH	NaOAc	80
9	**MeCN**	**AcOH**	**Na_2CO_3**	**90**
10	dioxane	AcOH	Na_2CO_3	40
11	toluene	AcOH	Na_2CO_3	77
12	DCE	AcOH	Na_2CO_3	42
13	THF	AcOH	Na_2CO_3	78

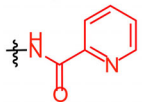
[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (0.2 mmol), and $[Cp^*RhCl_2]_2$ (2.5 mol%) at 120 °C for 16 h.
[b] NMR yields.
[c] Reaction was performed at 60 °C.
[d] Reaction was performed without $[Cp^*RhCl_2]_2$.

To further optimize the reaction, we first examined the reaction temperature. Apparently, performing the reaction at a lower temperature (e.g., 60 °C) led to **3aa** formation in a trace quantity (Table 1, *cf.* entry 1 and 2). The presence of CsOAc, AcOH and $[Cp^*RhCl_2]_2$ is essential, and the absence of any one component resulted in ineffective transformation (entries 3–5). Apart from AcOH, pivalic acid and benzoic acid are equally effective for promoting the pyrrole formation (entries 6 and 7). By examining several acid-base combinations, employing Na_2CO_3 (25 mol%) instead of CsOAc was found to give **3aa** in 90% yield (entry 9). Common organic solvents other than MeCN gave slightly lower product yields (entries 10–13).

It is known that employing oxidizing directing groups is a favourable approach for designing transition metal-catalyzed C–H bond cycloaddition reactions.[13] As shown by Hartwig,[14a] Fagnou[2r] and Glorius,[14b] the catalytic cross-coupling reactions of oximes and benzohydroxamic acids with alkynes afforded indoles and isoquinolones, respectively, in excellent selectivity. It is generally accepted that cleavage of the weak N–O σ-bond facilitates the product formation (*presumably via a sequence of oxidative addition and reductive elimination*) and catalyst turnovers. Recently, Glorius[2c] and co-workers reported

Table 2. Effect of leaving groups (LG).[a,b]



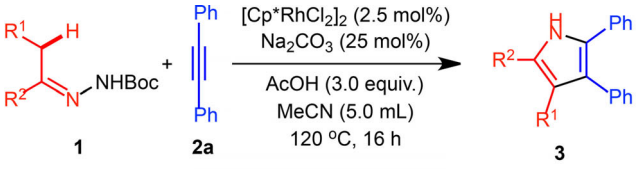
Entry	Leaving groups (LG)	Yield [%][b] 3aa:4aa
1	NHBoc	90:<5
2	OMe	0:75
3	NHAc	0:37
4	NH_2	0:0
5		0:0

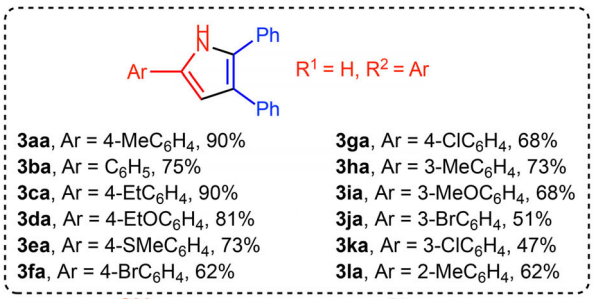
[a] *Reaction conditions:* **1** (0.4 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), Na_2CO_3 (25 mol%) and AcOH (3.0 equiv.) in MeCN (5.0 mL) at 120 °C for 16 h.
[b] Isolated yields.

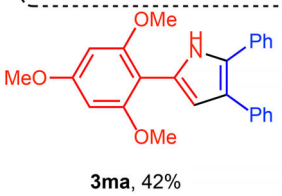
a catalytic oxidative C(sp^2)–H bond cycloaddition of some Boc-protected hydrazines with alkynes to form indoles, and the N–N bond was found to be an effective oxidizing directing group. In this work, we have examined a series of hydrazones bearing different terminal leaving groups for the catalytic cycloaddition with alkynes (Table 2). With *N*-Boc as a leaving group, facile cycloaddition of 4-methylacetophenone *N*-Boc-hydrazone **1a** with diphenylacetylene **2a** furnished pyrrole **3aa** in 90% yield with isoquinolines **4aa** being formed in <5% yield. Importantly, the analogous reactions with 4-methylacetophenone hydrazones bearing NHAc and OMe leaving groups produced isoquinoline **4aa** exclusively without any pyrrole formation. Hydrazones with picolinamide and NH_2 leaving groups are ineffective substrates; neither pyrroles nor isoquinolines were obtained.

With these optimized conditions in hand, reactions of various *para*-substituted acetophenone *N*-Boc hydrazones with diphenylacetylene **2a** were examined, and the corresponding pyrroles **3aa**–**3ga** were obtained in 62–90% yields (Table 3). The molecular structure of the pyrrole product **3ea** has been confirmed by X-ray crystallography (Figure 1).[15] In these cases, isoquinoline formation resulting from the *ortho* C(sp^2)–H bond activation was insignificant (Supporting Information, Table S1).[12] For acetophenone *N*-Boc-hydrazones bearing substituents located at other

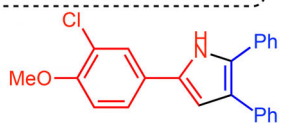
Table 3. Scope of *N*-Boc-hydrazones.[a,b]



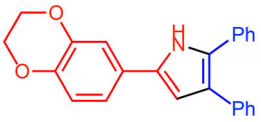




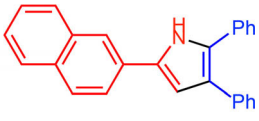
3ma, 42%



3na, 63%

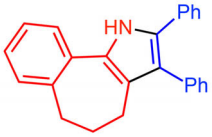


3oa, 45%

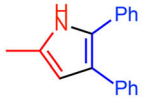


3pa, 72%

3qa, 75%



3ra, 42%



3sa, 32%[c]

[a] *Reaction conditions:* **1** (0.4 mmol) and **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), Na_2CO_3 (25 mol%) and AcOH (3.0 equiv.) in MeCN (5.0 mL) at 120 °C for 16 h.
[b] Isolated yields.
[c] *Reaction conditions:* **1s** (0.8 mmol) and **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), Na_2CO_3 (25 mol%) and AcOH (3.0 equiv.) in MeCN (5.0 mL) at 120 °C for 2 h.

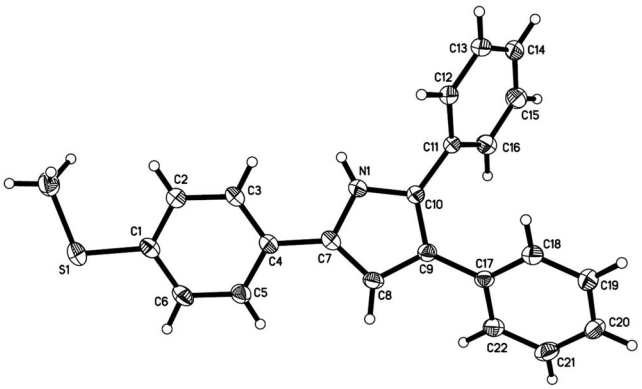


Figure 1. Molecular structure of 5-[4-(methylthio)phenyl]-2,3-diphenyl-1*H*-pyrrole (**3ea**).

positions on the aryl ring, successful cycloadditions were also achieved to give pyrroles **3ha–3oa** in 42–73% yields. As expected, the cycloaddition of a naphthyl-substituted acetophenone *N*-Boc hydrazone furnished pyrrole **3pa** in 72% yield.

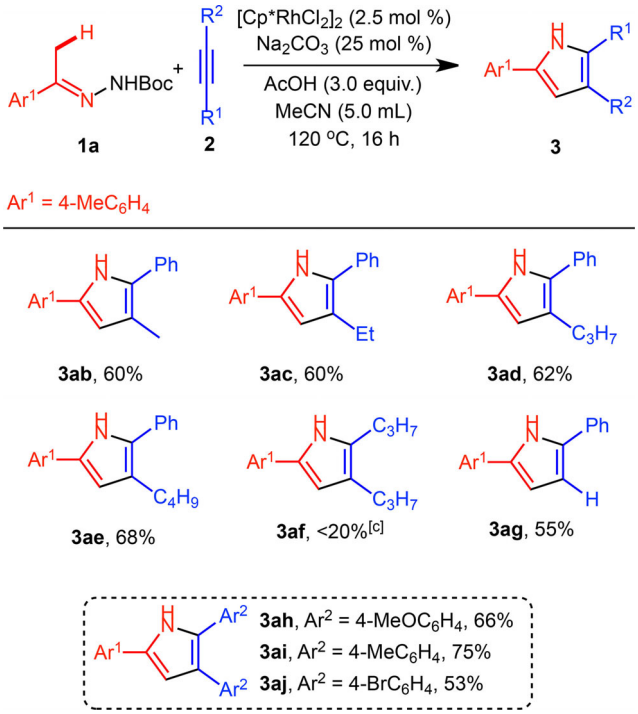
For the Rh(III)-catalyzed C(sp^3)–H bond functionalization, examples concerning the functionalization of primary C(sp^3)–H bonds are well documented.[10] However, functionalizations of the analogous secondary C(sp^3)–H bond are less common.[16] In this work, when an ethyl phenyl ketone-derived *N*-Boc-hydrazone was subjected to the Rh-catalyzed cycloaddition reaction with diphenylacetylene, effective functionalization of the secondary α-imino C(sp^3)–H bond was achieved to give pyrrole **3qa** in 75% yield. Nonetheless, the analogous reaction with the substrate bearing an *n*-propyl imino substituent was sluggish; isoquinoline **4va** was obtained in 23% yield, with the desired pyrrole **3va** being formed in <5% yield.[12] An *N*-Boc-hydrazone containing a seven-membered carbocyclic ketone moiety was found to undergo effective cycloaddition to produce the tricyclic pyrrole **3ra** in 42% yield with <10% isoquinoline formation. Yet, the analogous cycloaddition of the *N*-Boc-hydrazone containing a six-membered carbocyclic ketone afforded isoquinoline **4ua** in 90% yield.[12] In this work, when an *N*-Boc-hydrazone *derived from acetone* was employed as substrate, effective C(sp^3)–H bond cycloaddition was achieved to give the α-methylpyrrole **3sa** in 32% yield.

With 4-methylacetophenone *N*-Boc-hydrazone **1a** as substrate, the alkyne scope has also been examined (Table 4). The reaction with 1-phenyl-1-propyne **2b** under the Rh-catalyzed conditions furnished pyrrole **3ab** as a single regioisomer. Similar results were obtained for the analogous reactions with 1-phenyl-1-butyne **2c**, 1-phenyl-1-pentyne **2d** and 1-phenyl-1-hexyne **2e**. When 4-octyne **2f** was employed as the coupling partner, isoquinoline **4af** became a major product (60%), and the desired pyrrole **3af** was formed in <20% yield. This finding implies that the transition state for successful pyrrole formation should be rather sensitive to steric factors. Having such a hypothesis in mind, we anticipated that employing a bulkier substituent such as a trimethylsilyl (TMS) group on the alkyne would hinder the pyrrole formation. Interestingly, the reaction of phenylsilylacetylene **2g** with **1a** gave the desilylated 2,5-diarylpyrrole **3ag** in 55% yield with a minor isoquinoline formation (<5%). Effective cycloadditions were also achieved with some substituted diphenylacetylenes, and pyrroles **3ah–3aj** were obtained in 53–75% yields.

The catalytic pyrrole formation developed in this work features the regioselective α-imino C(sp^3)–H bond functionalization *versus* the aryl C(sp^2)–H bond functionalization (isoquinoline formation). As shown earlier, replacing the *N*-Boc group of the substrate with an NHAc or OMe group resulted in exclusive isoquinoline formation *via* the aryl C(sp^2)–H bond functionalization. Presumably, successful pyrrole formation is associated with the *N*-Boc group to direct the C(sp^3)–H bond functionalization by the Rh(III) complex. To understand the observed selectivity for the α-imino C(sp^3)–H bond functionalization, the cycloaddition of the deuterated *N*-Boc-hydrazone **1t** with diphenylacetylene was performed under our optimized conditions. The expected **3ta** was obtained in 90% yield *without any loss of deuterium* on the phenyl ring (Scheme 2a). This result implies that the *N*-Boc group should play a key role in directing the kinetically competitive C(sp^3)–H bond functionalization.

Moreover, after subjecting 4-methylacetophenone *N*-Boc-hydrazone **1a** to the Rh(III)/AcOD/CD_3CN system at 120 °C *in the absence of diphenylacetylene* for 20 min, 50% deuterium incorporation was detected at the α-imino methyl and the *N*-Boc groups (Scheme 2b). This result may suggest that the imine-enamine tautomerization could have been promoted by the Rh(III) catalyst coordinated to the *N*-Boc group.

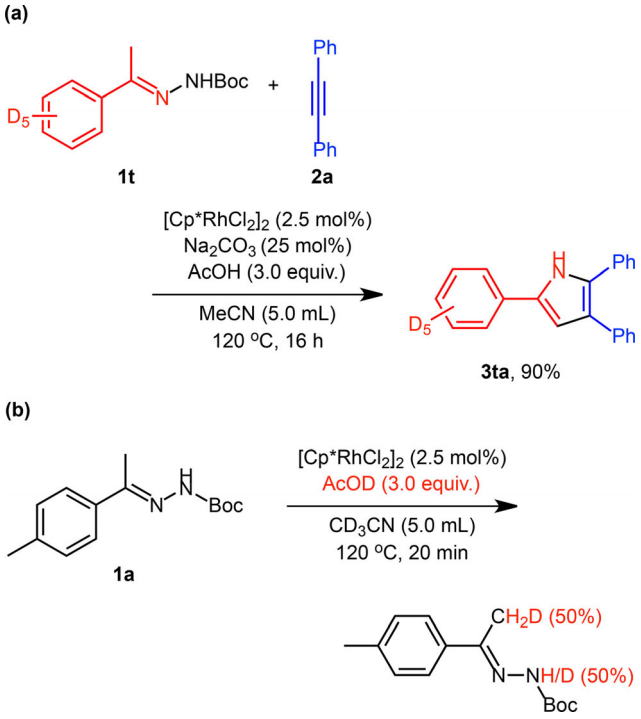
Table 4. Scope of alkynes.[a,b]



[a] *Reaction conditions:* **1a** (0.4 mmol) and **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), Na_2CO_3 (25 mol%) and AcOH (3.0 equiv.) in MeCN (5.0 mL) at 120 °C for 16 h.

[b] Isolated yields.

[c] NMR yield, isoquinoline **4af**: 60% yield.

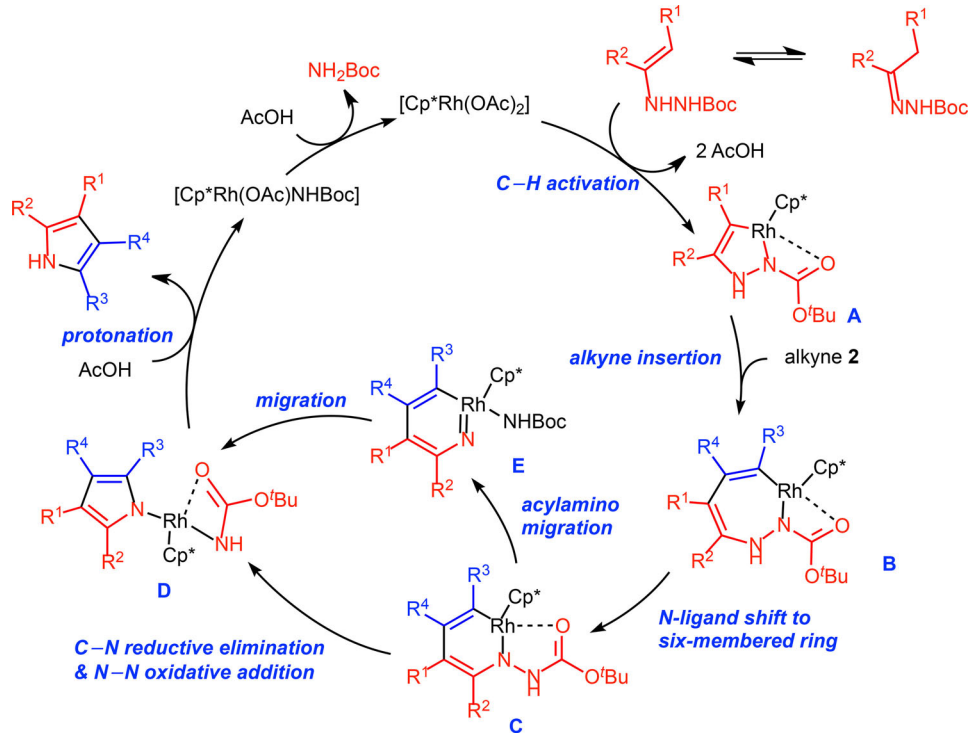


Scheme 2. H/D exchange experiments.

A plausible reaction mechanism is depicted in Scheme 3. The reaction should be initiated by the coordination of the enamine isomer of the *N*-Boc-hydrazone **1** to the Rh(III) center,[17] followed by the cleavage of the C(sp^2)–H bond to form rhodacycle **A**. The complex **A** is presumably stabilized by the Boc group.[18] After alkyne insertion, the 7-membered intermediate **B** would undergo the N-ligand shift to give the 6-membered rhodacycle **C**.[19] Reductive elimination *via* oxidative addition of the N–N bond to the Rh(III) should produce species **D**. Protonation by acetic acid should furnish the desired pyrrole product. An alternative route involving a Rh(V) nitrene intermediate **E** by acylamino migration is also possible.[20] Subsequent carbon-migration to the nitrene ligand on species **E** should produce species **D**.

Conclusions

In summary, we have developed a Rh(III)-catalyzed oxidative cycloaddition of *N*-Boc-hydrazones with internal alkynes. Our study shows that the *N*-Boc group is essential for the selective pyrrole formation. The reaction provides a direct route to highly functionalized pyrroles *via* direct C(sp^3)–H bond functionalization. This reaction offers an expedient access to *NH-free* pyrroles, which are key structural scaffolds of many pharmaceutical products and functional materials.



Scheme 3. Plausible reaction mechanism.

Experimental Section

General

All the solvents and reagents were obtained from commercial sources and used without purification unless stated otherwise. All glasswares were dried overnight at 150 °C prior to use. All the Rh-catalyzed reactions were performed without specific protection from air or moisture. Thin layer chromatography was performed on silica gel plates. Flash column chromatography was performed on a silica gel (Merck, 230–400 mesh) column. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 MHz spectrometer. The chemical shift (δ) values are given in ppm and are referenced to residual solvent peaks; carbon multiplicities were determined by DEPT-135 experiments. Coupling constants (J) were reported in hertz (Hz). The NMR yield values were determined with dibromomethane (6.98 μL) as internal standard, which shows a singlet signal at $\delta_H = 4.9$ ppm in CD_2Cl_2. Mass spectra and high resolution mass spectra (HR-MS) were obtained on a VG MICROMASS Fison VG platform, a Finnigan Model Mat 95 ST instrument, or a Brüker APEX 47e FT-ICR mass spectrometer. X-ray crystallographic study was performed using a Bruker CCD area detector diffractometer.

General Procedure for Rh(III)-Catalyzed Cycloaddition of *N*-Boc hydrazones with Alkynes for the Synthesis of Pyrrole 3

A 10 mL-sealed tube equipped with a magnetic stirrer was charged with $[Rh(Cp^*)Cl_2]_2$ (3.2 mg, 2.5 mol%), Na_2CO_3 (5.3 mg, 25 mol%), *N*-Boc-hydrazone **1** (0.4 mmol) and MeCN (5.0 mL). Alkyne **2** (0.2 mmol) and AcOH (34.3 μL, 0.6 mmol) were added sequentially. The mixture was then stirred and heated at 120 °C for 16 h. After cooling to room temperature, the crude mixture was filtered through Celite® and concentrated under reduced pressure. The residue was then purified by flash column chromatography (hexanes/ethyl acetate, 9:1, v/v) to give the desired product **3**.

5-[4-(Methylthio)phenyl]-2,3-diphenyl-1*H*-pyrrole (**3ea**) was isolated as a pale yellow solid; yield: 50 mg (73%); mp 185–186 °C; $R_f = 0.6$ (hexanes/ethyl acetate 85:15, v/v). The solid was redissolved in a minimum amount of DCM; diffusion with hexane gave a pale yellow solid. ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 2.55$ (s, 3H), 6.72 (d, $J = 2.8$ Hz, 1H), 7.23–7.27 (m, 1H), 7.30–7.45 (m, 11H), 7.54 (d, $J = 8.4$ Hz, 2H), 8.58 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta =$ 136.68 (C), 136.42 (C), 133.05 (C), 131.74 (C), 129.28 (C), 129.10 (C), 128.68 (CH), 128.32 (CH), 127.50 (CH), 127.13 (CH), 126.99 (CH), 125.94 (CH), 125.74 (C), 124.09 (CH), 123.77 (C), 108.27 (CH), 15.72 (CH_3); HR-MS (ESI): $m/z =$ 341.1233, calcd. for $C_{23}H_{19}NS^+$: 341.1223.

General Procedure for Preparation of *N*-Boc-hydrazones 1

A 100-mL round-bottom flask equipped with a magnetic stirrer was charged with aryl ketone **6** (5 mmol), acetic acid (29 μL, 0.5 mmol) and EtOH (30.0 mL). The mixture was stirred and heated under reflux for 15 min. Then *tert*-butyl carbazate (0.990 g, 7.5 mmol) was added to the mixture and subjected to reflux. Upon completion as indicated by TLC, the crude mixture was concentrated under reduced pressure. The solid remaining was then filtered and recrystallized with a minimum amount of hot DCM. The desired product **1** was used without further purification.

Typical Procedure for Preparation of 1s

A 100-mL round-bottom flask equipped with a magnetic stirrer was charged with acetone (40 mL), acetic acid (0.2 mL) and *tert*-butyl carbazate (5 g, 37.8 mmol). The mixture was subjected to reflux for 1 h under a nitrogen atmosphere. The crude mixture was cooled and the resulting suspension was filtered off. The filtrate was concentrated under reduced pressure. The residue solid was then recrystallized with a minimum amount of hot DCM. The desired product **1s** was used without further purification. Compound **1s** was obtained as a white solid; yield: 6.37 g (98%); mp 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H), 1.73 (s, 3H), 1.90 (s, 3H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.02$ (C), 149.87 (C), 80.56 (C), 28.16 (CH_3), 25.23 (CH_3), 16.05 (CH_3).

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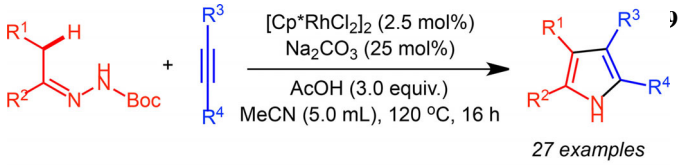
Rhodium-Catalyzed Oxidative Cycloaddition of *N*-*tert*-Butoxycarbonylhydrazones with Alkynes for the Synthesis of Functionalized Pyrroles *via* C(sp^3)–H Bond Functionalization



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