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Cyclization of Alkyne−Azide with Isonitrile/CO via Self-Relay Rhodium Catalysis

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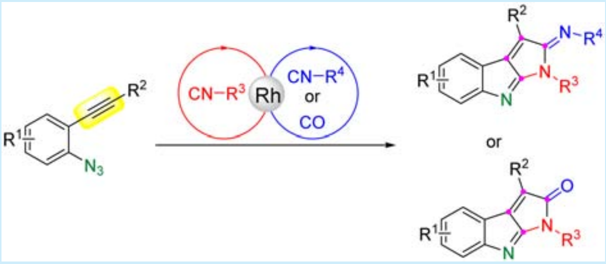
Ⓢ *Supporting Information*

ABSTRACT: A self-relay rhodium(I)-catalyzed cyclization of alkyne−azides with two σ-donor/π-acceptor ligands (isonitriles and CO) to form sequentially multiple-fused heterocycle systems via tandem nitrene transformation and aza-Pauson−Khand cyclization has been developed. In this approach, an intriguing chemoselective insertion process of isonitriles superior to CO was observed. This reaction provides an alternative strategy to synthesize functionalized pyrrolo[2,3-*b*]indole scaffolds.



Polycyclic nitrogen heterocycles are among the most important fused heterocycles, which are found in a range of bioactive natural products and pharmaceuticals. In particular, the pyrrolo[2,3-*b*]indole framework is a key structural motif in a series of medicinal natural products and biologically active molecules,[1] such as physostigmine,[1c] pseudophrynaminol,[1a] flustramine C,[1b] nocardioazine B,[1e] and flustramine P[1d] (Figure 1). Consequently, numerous innovative methods have been developed for constructing this important and attractive structural motif.[1f,2] Traditional strategies involve cyclizations of indoles,[3] tryptamines,[4] and tryptophan derivatives.[5] Recently, Mukai[6] and Saito[7] independently reported a catalytic heterocumulenic Pauson−Khand reaction of alkynylcarbodiimides to prepare pyrrolo[2,3-*b*]indol-2-one ring systems. Moreover, Tu and co-workers[8] achieved a Co(acac)$_2$-catalyzed double insertion of two identical isonitriles into 2-ethynylanilines to obtain functionalized pyrrolo[2,3-*b*]indoles. In spite of the considerable progress that has been disclosed, given the ubiquity and importance of pyrrolo[2,3-*b*]indole derivatives in bioactive molecules and drugs, further exploration and development of diverse and efficient methods for their synthesis are still in great demand.

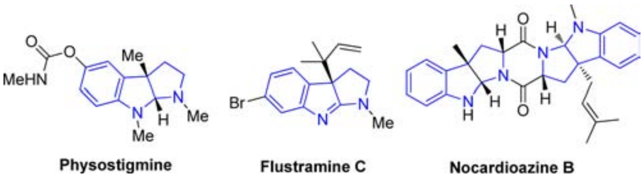


Figure 1. Selected examples of pyrrolo[2,3-*b*]indole-containing natural products.

With the rapid development of nitrene chemistry in recent years, transition-metal-mediated nitrene transformation has become a convenient and promising approach for the synthesis of *N*-containing compounds.[9] Our interest has been focused on the coupling reaction of nitrene precursors with σ-donor/π-acceptor ligands, which provides an efficient route to activate and reorganize unsaturated reactants. In our previous research, we reported a palladium-catalyzed coupling reaction of azides with isonitriles to furnish unsymmetrical carbodiimides.[10] It is well-known that isonitriles, as a class of significant σ-donor/π-acceptor ligands, have been widely applied to constructing versatile nitrogen-containing heterocycles due to their superior reactivity since the pioneering work of Ugi and Passerini.[11,12] Besides, it cannot be ignored that another σ-donor/π-acceptor carbonmonoxide (CO),[13] an isoelectronic species of isonitrile, and π-donor alkynyl group,[14] are also excellent and efficient ligands for the preparation of heterocycles incorporating carbonyl groups and unsaturated carbon−carbon bonds. In particular, isonitriles[12] and CO,[13d,f] as valuable C1 building blocks, were also frequently used in transition-metal-catalyzed cascade reactions to increase the molecular complexity of the products and to construct numerous essential heterocycles efficiently. Thus, we envisioned an atom economic assembly of the three unsaturated ligands with an azide into multiple-fused heterocyclic systems via a relay transition-metal-catalyzed cascade nitrene-coupling/cyclization process. Herein, we report a single rhodium(I)-catalyzed sequential installation of isonitrile and/or CO with 2-azidoalkynylbenzenes to afford two different pyrrolo[2,3-*b*]indole-based heterocyclic compounds (Scheme 1).

To our knowledge, unexpected side reactions are common phenomena in late transition-metal-catalyzed nitrene transformations. An intriguing issue is whether a single rhodium catalyst can perform the sequential coupling/cyclization with specific unsaturated ligands, namely isonitriles, CO, and alkynes. We began our investigation by reacting azidobenzene with *tert*-butyl isocyanide (**2a**) and CO, respectively, in the presence of

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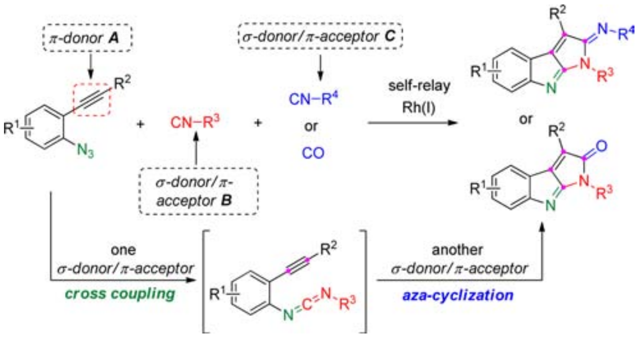
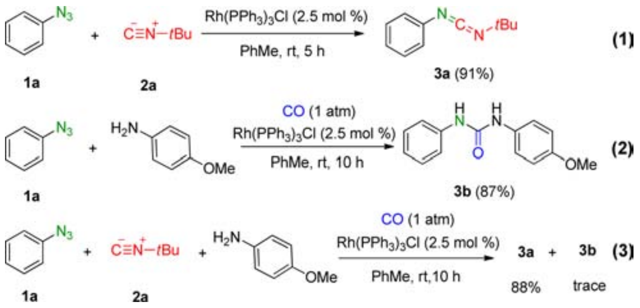
Scheme 1. Self-Relay Rh(I)-Catalyzed Cyclization of Alkyne−Azides with Two Sequential σ-Donor/π-Acceptor Ligands (Isonitriles and CO)



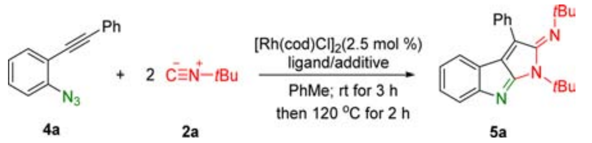
Rh(PPh$_3$)$_3$Cl as catalyst (Scheme 2). To our delight, rhodium catalysts showed remarkable reactivity and selectivity. Carbodiimide (**3a**), the coupling product of azide (**1a**) and isonitrile (**2a**), could be obtained in 91% yield (eq 1). Meanwhile, the three-component reaction of azide, CO, and arylamine also gave urea in good yield (eq 2). To further evaluate the relative reactivity of isonitrile and CO, an intermolecular competition experiment was conducted (eq 3). Surprisingly, the result revealed that isonitrile showed vastly superior reactivity to CO for Rh(I)-catalyzed transformation with azide, which presumably could be rationalized in terms of stronger coordination of isonitrile to transition-metal atoms as well as the heterogeneous nature of carbonylation with CO.

Scheme 2. Rh(I)-Catalyzed Coupling Reactions of Azide with Isonitrile or CO



Based on the results of these initial experiments and given the diversity and flexibility of isonitrile, we chose *tert*-butyl isocyanide (**2a**) and 2-azidoalkynylbenzene (**4a**) as the model substrates to evaluate the feasibility of installation of two σ-donor/π-acceptor ligands to afford pyrrolo[2,3-*b*]indoles (Table 1). At the initial investigation, we found that the combination of [Rh(cod)Cl]$_2$ and bidentate phosphine ligands could apparently effect the reaction. After examination of several bidentate phosphine ligands with different bite angles, the desired product was obtained in modest yields (Table 1, entries 1−4). To enhance the reactivity, we surveyed a number of additives. To our delight, a noticeable improvement in yield was observed by addition of Cu(I) salts, which facilitate more efficient reactions than zinc and silver salts did (Table 1, entries 6−10). Finally, pyrrolo[2,3-*b*]indole (**5a**) was obtained in 81% yield when DPPP was used as ligand and CuI (10 mol %) as additive (Table 1, entry 11). Notably, without any ligands and additives the target product could only be detected in trace amounts (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions[a]



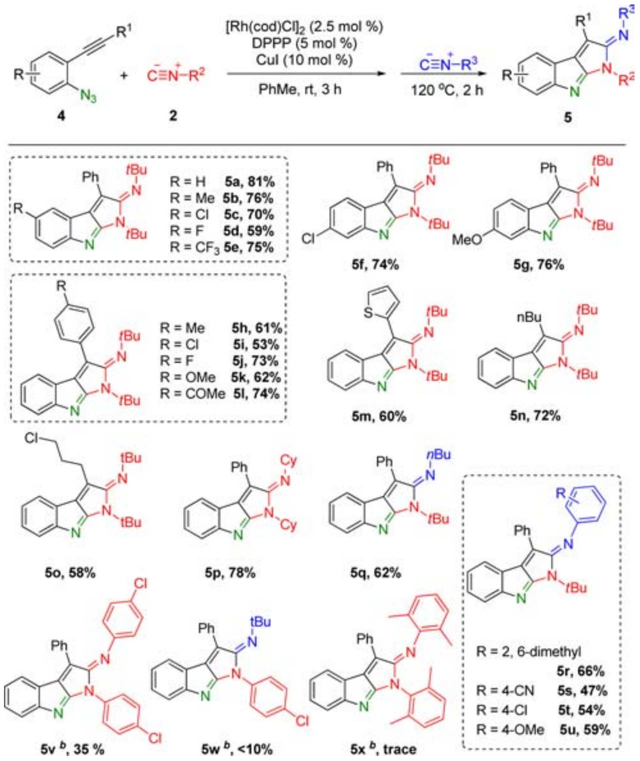
entry	ligand (mol %)	additive (mol %)	yield[b] (%)
1	DPPM (5)		55
2	DPPP (5)		57
3	DPPE (5)		62
4	DPPB (5)		61
5			trace
6	DPPP (5)	AgSbF$_6$ (5)	trace
7	DPPP (5)	Zn(OTf)$_2$ (5)	trace
8	DPPP (5)	CuI (5)	72
9	DPPP (5)	CuCl (5)	65
10	DPPP (5)	CuBr (5)	76
11	DPPP (5)	CuI (10)	81
12	DPPE (5)	CuI (10)	75
13[c]		CuI (10)	trace

[a]Reaction conditions: **4a** (0.1 mmol), PhMe (2 mL), and **2a** (0.1 mmol) were added, the mixture was reacted at room temperature for 3 h, and then **2a** (0.11 mmol, 0.1 M in PhMe) was added by syringe at 120 °C for 2 h. [b]Isolated yields. [c]No [Rh(cod)Cl]$_2$ was added. DPPM = bis(diphenylphosphino)-methane. DPPP = 1,3-bis(diphenylphosphino)propane. DPPE = 1,2-bis(diphenylphosphino)ethane. DPPB = 1,4-bis(diphenylphosphino)butane.

Having identified the optimal conditions, we next focused on examining the generality of the catalytic bicycloaddition involving two isonitriles (Scheme 3). A variety of substituted 1-azido-2-(phenylethynyl)benzenes bearing halogen, electron-rich, and electron-poor groups on the aromatic ring gave the desired products in good yields (**5b**−**e**). Notably, those substituents at the C4 or C5 positions of the ring are well tolerated (**5f**,**g**). For substrates bearing halogen and other electron-donating or -withdrawing groups on the aromatic ring at the end of the triple bond, desired products were obtained in moderate to good yields (**5h**−**l**), and electron-donating groups exhibit better reactivity than electron-withdrawing groups. Besides aryl substituents, substrates containing heterocyclic (**5m**) or simple alkyl groups (**5n**,**o**) on the alkyne moiety were smoothly converted into the corresponding pyrrolo[2,3-*b*]indole products. In addition, isocyanocyclohexane also gave a better result (**5p**, 78%). More importantly, selective and sequential installation of two different isonitriles proved to be amenable for the process. As for the second isonitrile, bearing either a linear alkyl group like *n*-Bu (**5q**) or aryl groups substituted by a sterically encumbered 2,6-dimethyl group or electronic 4-Cl, 4-CN, and 4-MeO groups, all could be introduced into the pyrrolo[2,3-*b*]indole scaffold in comparable yields (**5r**−**u**). When the first insertion was an aryl isonitrile, designed product could also be obtained (**5v**,**w**).

To further explore the diversity of products generated by our reaction, we turned our attention to another prominent σ-donor/π-acceptor ligand carbon monoxide, which has become a common carbonylation reagent due to its low cost and ready availability, and has even been applied in industry. In our method, CO was employed as a crucial synthon to build intricate heterocyclic compounds containing carbonyl groups. As mentioned above, compared with its isoelectronic isonitriles counterparts, CO exhibits inferior reactivity in coupling reactions

Scheme 3. $[Rh(cod)Cl]_2$-Catalyzed Reactions of Alkyne−Azides with Two Isonitriles[a]

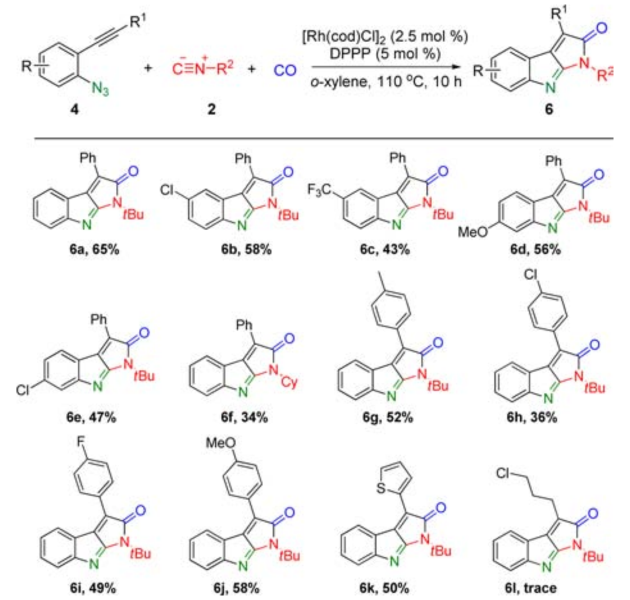


[a]Reaction conditions: **4** (0.15 mmol), PhMe (2 mL), and **2** (0.15 mmol) were added, the mixture was reacted at rt for 3 h, and then another portion of **2** (0.165 mmol, 0.1 M in PhMe) was added by syringe at 120 °C for 2 h. Isolated yields were given. [b]**4** (0.15 mmol), dioxane (2 mL), and **2** (0.15 mmol) were added without CuI, the mixture was reacted at rt for 10 min, and then another portion of **2** (0.165 mmol, 0.1 M in dioxane) was added by syringe at 120 °C for 2 h.

with azides. Taking advantage of this difference in reaction rates, we achieved selective incorporation of both isonitrile and CO into the product in a single operation. Next, we explored the substrate scope of our strategies involving the cyclization of isonitriles and CO. The results were summarized in Scheme 4. Compared with two isonitriles, the introduction of two kinds of σ-donor/π-acceptor ligands gave the corresponding products with relatively lower yield. Variation of electronic nature or positions at the phenyl ring of aryl azides did not affect the reactivity significantly (**6a**−**e**). Azidoalkynylbenzenes bearing different substituents (including Me, Cl, F, and OMe) at the aromatic alkyne moieties could react well to deliver products (**6g**−**j**) in moderate yields. Moreover, isocyanocyclohexane is also compatible in the transformation, albeit in low yield (**6f**). However, though heterocyclic substituents at the alkynyl terminal position were well tolerated under the conditions (**6k**), aliphatic substituents showed little reactivity (**6l**).

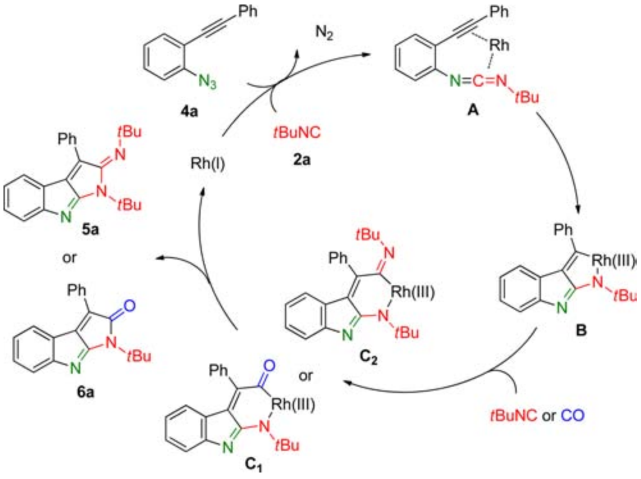
A plausible mechanism for the formation of pyrrolo[2,3-*b*]indoles is shown in Scheme 5, which generally involves two processes including Rh(I)-catalyzed cross-coupling of azides with isonitriles and an aza-Pauson−Khand cyclization. Initially, an important intermediate alkynyl carbodiimide **A** was generated with release of N_2.[15] Next, the alkynyl carbodiimides intermediate **A**, through π-complexation with Rh(I) and an oxidative cyclometalation step, could form a new intramolecular C−C bond and afford rhodacycle species **B**. Further insertion of another σ-donor/π-acceptor ligand (isonitrile or CO) into the Rh−C bond of species **B** results in the generation of rhodium complex **C**. Finally, the two different pyrrolo[2,3-*b*]indole derivatives were produced following a reductive elimination process with regeneration of the active rhodium(I) catalyst.

Scheme 4. $[Rh(cod)Cl]_2$-Catalyzed Reactions of Alkyne−Azides with Isonitriles or CO[a]



[a]Reaction conditions: **4** (0.15 mmol), **2** (0.15 mmol), *o*-xylene (2 mL) reacted at 110 °C for 10 h under CO (1 atm). Isolated yields were given.

Scheme 5. Proposed Mechanism



In summary, we have developed a self-relay Rh(I)-catalyzed cascade reaction that enabled the assembly of two different σ-donor/π-acceptor ligands sequentially to form multiple-fused heterocyclic systems via relay-catalyzed nitrene transformation and sequential cyclization processes. This protocol provides an alternative and facile strategy to construct the pyrrolo[2,3-*b*]indole scaffold, which served as a pivotal structural motif of many useful natural products and drug molecules. Moreover, we have examined the reactivity of isonitriles and CO in this reaction. The result shows that isonitriles possess superior reactivity to their isoelectronic counterpart CO in either coupling reaction with azides or the aza-Pauson−Khand-type cyclization. Further investigations into other promising σ-donor/π-acceptor ligands and applications to the synthesis of diverse and useful compounds combined with the booming nitrene chemistry are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03570.

> Experimental procedures along with characterization data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(15) For the generation of alkynyl carbodiimide **A**, there are three possible pathways: [3 + 2] cyclization followed with 1, 2-migration, direct isonitrile insertion, or Rh(I)-nitrene mechanism. For more details, see the Supporting Information.