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Site- and Regioselective Monoalkenylation of Pyrroles with Alkynes via Cp*Co^{III} Catalysis

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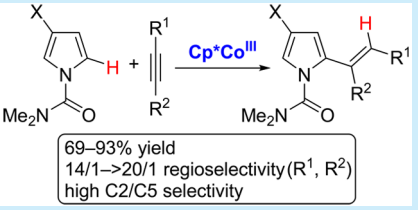
Supporting Information

ABSTRACT: A site-, regio-, *syn*-, and monoselective alkenylation of dimethylcarbamoyl-protected pyrroles proceeded using a catalytic amount of $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ and KOAc. A variety of internal alkynes with several functional groups and a terminal alkyne afforded hydropyrrolation products in a selective manner in good to excellent yield. The site-selectivity (C2/C5 selectivity) observed for C3-substituted pyrroles is noteworthy because Cp*Rh^{III}-catalyzed conditions afforded only a moderate yield and low selectivity. The conditions described here provide general and straightforward access to unsymmetrically mono- and disubstituted pyrrole derivatives.



Pyrrole, one of the simplest nitrogen-containing heterocycles, is a common structural motif in many natural and unnatural biologically active compounds.[1] Therefore, the development of efficient synthetic methods of pyrrole derivatives will accelerate drug discovery and other biological studies. Typical pyrrole synthesis requires condensation of the corresponding nitrogen sources and carbonyl compounds,[2] as represented by Parr–Knorr synthesis.[3] The availability of the starting materials thus often limits the diversity of accessible structures.

Recent progress in transition-metal-catalyzed C–H bond functionalization reactions[4] has opened up alternative routes to substituted pyrrole-containing molecules.[5−8] For installation of the alkenyl moiety, oxidative alkenylation using alkenes has been intensively studied with Pd[5] and other metal catalysts.[6] Direct addition of aromatic C–H bonds to alkynes, the hydroarylation reaction, is another attractive method to introduce alkenyl groups due to the high atom-economy[9] and availability of various alkynes.[10] Transition-metal-catalyzed hydropyrrolation reactions of electron-rich nonactivated alkynes, however, is less well studied than other hydroarylation reactions.[7] This seemingly simple transformation has formidable selectivity issues: mono/diselectivity, regioselectivity of alkyne insertion, *syn*/*anti* selectivity, and site-selectivity of pyrrole C–H bonds (Figure 1). Most of the reported reaction conditions were only optimized for indoles or other substrates and suffer from selectivity issues and/or lack of substrate generality. For example, Yoshikai's conditions using a low-valent cobalt catalyst[7d] and Zeng's conditions using a Ru^{II} catalyst[7f] afforded a bisalkenylated product using only a nonsubstituted pyrrole. π–Acidic metal catalyzed reactions using *N*-alkyl- and *N*-arylpyrroles generally suffer from low selectivity and rarely afford alkenylated products.[7g,10a] Some Ru catalysts were reported to promote branch-selective hydropyrrolation, but only terminal alkynes have been utilized.[7b,e] Cp*Rh^{III}-catalyzed conditions developed by Schipper and Fagnou were only applied to a specific pyrrole bearing the same ester groups at the C3 and C4 positions.[7c] Accordingly, a general catalytic system for the selective hydropyrrolation of internal and terminal alkynes is still in high demand.

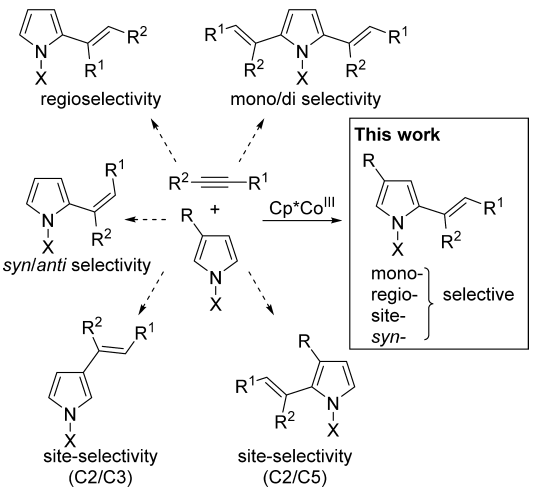


Figure 1. Selectivity issues on hydropyrrolation of alkynes.

During the course of our studies on Cp*Co^{III}-catalyzed C–H bond functionalization,[11] we reported an alkenylation reaction and alkenylation/annulation reaction of indoles with alkynes.[11b] In addition, Chen and Yu reported a Cp*Co^{III}-catalyzed hydroarylation reaction using various aromatic compounds, including indole.[12] Nevertheless, a hydropyrrolation reaction under high-valent cobalt catalysis[13−15] has not yet been

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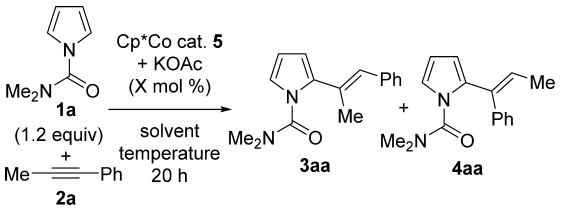
investigated. In this paper, we report a Cp*Co^{III}-catalyzed hydropyrrolation reaction of internal and terminal alkynes with high site-, regio-, *syn*-, and monoselectivity, while Cp*Rh^{III}-catalyzed conditions afforded only low C2/C5 selectivity when unsymmetrically substituted pyrroles were used.

Optimization studies using dimethylcarbamoyl-protected pyrrole **1a**[7c,11b] and alkyne **2a** are summarized in Table 1. We

Table 1. Optimization of Reaction Conditions[a]



entry	X (mol %)	solvent	temp (°C)	yield[b] (%)	3aa/4aa[b]
1	5	DCE	80	67	14/1
2	5	PhCl	80	88	17/1
3	5	toluene	80	91	18/1
4	5	THF	80	47	12/1
5	5	dioxane	80	63	12/1
6	5	TFE	80	13	9/1
7	5	HFIP	80	6	nd
8[c]	2.5	toluene	80	>95	18/1
9[c]	2.5	toluene	60	>95	>20/1
10[c]	2.5	toluene	rt	14	18/1
11[d]	2.5	toluene	60	93[e]	18/1

[a]The reactions were run using **1a** (0.36 mmol) and **2a** (0.30 mmol), $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ **5**, and KOAc in indicated solvent (0.2 M). [b]Determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c]**1a** (0.72 mmol) and **2a** (0.60 mmol) were used. [d]**1a** (0.60 mmol) and **2a** (0.72 mmol) were used. [e]Combined isolated yield of **3aa** and **4aa**.

selected $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ **5** as a catalyst precursor[14a] due to its user-friendly nature.[16] As expected, selective C2-monoalkenylation proceeded to afford monoalkenylated product **3aa** in 67% yield and high selectivity in the presence of 5 mol % of **5** and KOAc in DCE at 80 °C (entry 1). Although a small amount of isomeric product **4aa** was observed (14/1), no other isomers or bis-alkenylated product was identified. Toluene was the best solvent (entries 2−7), and the yield was improved to 91% (entry 3). Ether-type solvents and fluorinated alcohols were inefficient. The catalyst loading was decreased to 2.5 mol % without any loss of the yield (entry 8). Although the reaction also proceeded smoothly at 60 °C, it was very sluggish at room temperature (entries 9, 10). It is noteworthy that monoalkenylated product **3aa** was selectively obtained in 93% isolated yield even when a slight excess amount of alkyne **2a** was used (entry 11). The second alkenylation of **3** did not proceed probably due to unfavorable metallacycle formation that would cause severe steric repulsion between the alkenyl moiety and the directing group (Figure 2).[16]

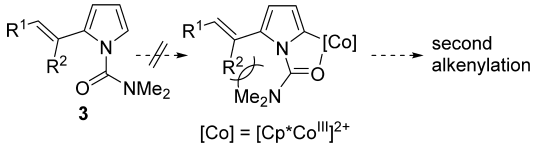
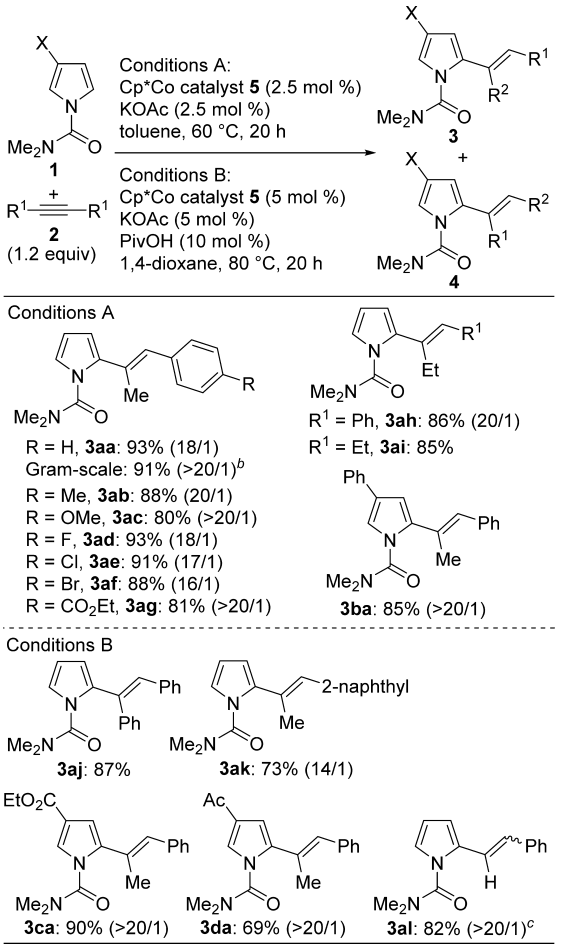


Figure 2. Unfavorable second alkenylation.

Scheme 1 shows the substrate scope of the Cp*Co^{III}-catalyzed hydropyrrolation. The electronic property of the alkynes hardly

Scheme 1. Substrate Scope[a]



[a]All the indicated yields are combined yields of **3** and **4** after isolation. The ratios in parentheses are those of **3**/**4** determined by ^{1}H NMR analysis of the crude mixture. [b]5 mmol scale, 46 h.[c]**1** (0.36 mmol), **2** (0.30 mmol), and PivOH (50 mol %) were used, and the reaction was run at 110 °C. *E*/*Z* ratio >20/1.

affected the reactivity, and substrates with various functional groups on the phenyl group afforded the products in high yields (**3aa**−**3ag**). Both aryl and alkyl groups on the alkynes were also compatible to afford the products in good yields (**3ah**, **3ai**). A gram-scale reaction successfully afforded **3aa** in 91% yield with high selectivity although a longer reaction time was required. On the other hand, several alkynes and pyrroles were less reactive under the above optimized conditions (Conditions A). Additional studies revealed that the addition of a catalytic amount of pivalic acid to promote the protonation step in the catalytic cycle improved the reactivity.[17] Under the newly optimized conditions (Conditions B), diphenylacetylene **2j** and 1-(2-naphthyl)-1-propyne **2k** afforded the hydropyrrolation products in good yields and selectivity. When pyrroles bearing C3-substituents were used as a substrate, the less hindered C5-position was selectively alkenylated to give **3ba**, **3ca**, and **3da** in 69−90% yields along with a tiny amount of the corresponding C2-alkenylated products. Terminal alkynes were also applicable by increasing the reaction temperature to 110 °C and the amount of pivalic acid to 50 mol %; alkenylation product **3al** was obtained in

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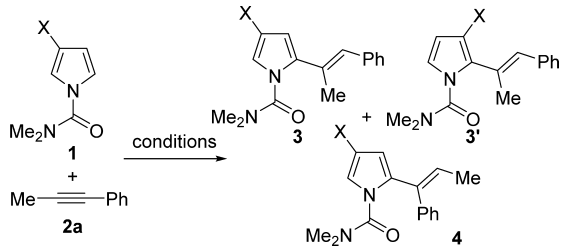
82% yield, but a small amount of the *Z*-isomer was observed in this case.

The high site-selectivity observed for 3-substituted pyrroles under Cp*Co^{III} catalysis is remarkable because the corresponding rhodium catalysis did not work well for these substrates under our optimized conditions or Schipper's conditions,[7c] as shown in Table 2. Almost no reaction proceeded between **1c** and **2a** when

Table 2. Comparison of Cobalt and Rhodium Catalysis

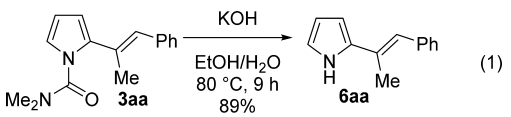


entry	conditions	**1** (−X)	yield (%)	**3**/**3′**/**4**[e]
1	Conditions B[a]	**1c** (−CO_2Et)	90[d]	100/6/4
2	Rh instead Co[b]	**1c** (−CO_2Et)	trace	–
3	Rh (ref 7c)[c]	**1c** (−CO_2Et)	40[e]	100/59/–
4	Conditions B[a]	**1d** (−Ac)	69[d]	100/3/4
5	Rh (ref 7c)[c]	**1d** (−Ac)	17[e]	100/17/–

[a]**1** (0.30 mmol), **2** (0.36 mmol), **5** (5 mol %), KOAc (5 mol %), and PivOH (10 mol %) in dioxane (0.2 M), 80 °C, 20 h. [b]**1** (0.30 mmol), **2** (0.36 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (5 mol %), KOAc (5 mol %), and PivOH (10 mol %) in dioxane (0.2 M), 80 °C, 20 h. [c]**1** (0.30 mmol), **2** (0.33 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (5 mol %), PivOH (5 equiv) in DCE (0.4 M), 90 °C, 24 h. [d]Isolated yield. [e]Determined by ^{1}H NMR analysis of the crude mixture.

5 was replaced with $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ under our optimized conditions B (entry 2). Although Schipper's conditions using $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ and an excess amount of pivalic acid afforded the products in moderate yield, the C5/C2 selectivity was only 100/59 (entry 3). A similar tendency was observed for 3-acetylpyrrole derivative **1d** (entries 4, 5). Although moderate selectivity was observed under the rhodium catalysis in this case, only 17% combined yield was obtained. These differences in the site-selectivity between Cp*Co^{III} and Cp*Rh^{III} catalysis probably reflect the difference in the ionic radius between cobalt and rhodium. Steric repulsion between the Cp* ligand and the substituent (X) would be enhanced by the smaller ionic radius of cobalt.[11e,14q] The requirement for a large amount of pivalic acid under Cp*Rh^{III} catalysis might indicate higher stability of the alkenylrhodium intermediate and slower protodemetalation compared with alkenylcobalt intermediate.

Finally, removal of the dimethylcarbamoyl group of **3aa** was accomplished to afford NH-free pyrrole **6aa** in 89% yield by heating with KOH in aqueous ethanol (eq 1).[7c]



(1)

A plausible catalytic cycle is shown in Figure 3. The catalytically active species **I** would be generated from **5** and KOAc. Coordination of pyrrole **1** and subsequent C−H metalation assisted by a carboxylate base[18] would afford metallacyclic intermediate **III**. Formation of another possible

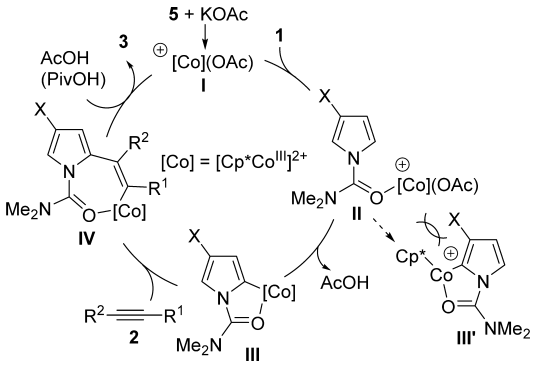


Figure 3. Plausible catalytic cycle.

metallacycle **III′** would be hampered by steric repulsion between the Cp* ligand and the substituent X. Insertion of alkyne (**IV**) and protodemetalation by AcOH or PivOH would generate the catalyst with the release of product **3**. Alkenylcobalt **IV** would be less stable than the corresponding alkenylrhodium species, and therefore only a catalytic amount of carboxylic acid efficiently would promote the final protonation step while the Cp*Rh^{III}-catalyzed conditions required excess amounts of PivOH to achieve a good yield.

In summary, site-, regio-, *syn*-, and monoselective alkenylation reaction of dimethylcarbamoyl-protected pyrroles with alkynes catalyzed by $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ **5** was developed. In addition to excellent functional group compatibility and generality, higher site-selectivity of the substituted pyrroles were observed compared with previously reported conditions using a Cp*Rh^{III} catalyst, probably due to the smaller ionic radius of cobalt.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02997.

Experimental procedures, characterization data, and copy of NMR spectrum (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Other directing groups and catalyst precursors were ineffective under the optimized conditions. See Table S1 in the Supporting Information.
(17) See Table S2 in the Supporting Information for more details on the optimization studies using terminal alkyne **2l**.
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