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Regioselective Formation of α-Vinylpyrroles from the Ruthenium-Catalyzed Coupling Reaction of Pyrroles and Terminal Alkynes Involving C−H Bond Activation

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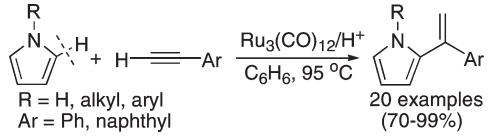
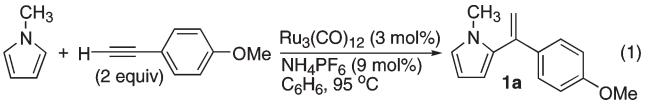


The cationic ruthenium catalyst $Ru_3(CO)_{12}/NH_4PF_6$ was found to be highly effective for the intermolecular coupling reaction of pyrroles and terminal alkynes to give *gem*-selective α-vinylpyrroles. The carbon isotope effect on the α-pyrrole carbon and the Hammett correlation from a series of para-substituted *N*-arylpyrroles ($\rho = -0.90$) indicate a rate-limiting C−C bond formation step of the coupling reaction.

C-Vinylated pyrroles are important building blocks for forming porphyrins and related nitrogen macrocycles as well as for serving as precursors for photoactive polymeric materials.[1] Compared to the traditional arene substitution methods using stoichiometric reagents, transition-metal-catalyzed C−H bond activation methods have been shown to exhibit a number of salient features such as increasing efficiency and reducing wasteful byproducts in introducing the vinyl group directly to pyrroles and related heteroarene compounds.[2] Pd catalysts have been found to be particularly versatile in mediating C−H oxidative coupling reactions of substituted pyrroles, pyridines, and indoles, where the regioselectivity has often been found to be dictated by both the steric and electronic nature of the arene substituents.[3] The direct oxidative arylation of indoles and quinoline *N*-oxides has also been achieved by using Pd catalysts.[4] Cationic Ru-allyl and -vinylidene complexes have been successfully utilized as catalysts for allylation and alkenylation of indoles and pyridine derivatives, respectively.[5] A novel regioselective insertion of alkynes to both Ar−H and Ar−CN bonds of *N*-protected 3-cyanoindoles and related heteroarenes has been achieved by using Ni−phosphine catalysts.[6] Though the *gem*-selective oxidative coupling reaction of indolizines and alkenes has recently been accomplished by using Pd catalysts with bidentate nitrogen ligands,[7] lack of generally reliable *cis*- and *gem*-selective vinylation methods continues to be a major problem in catalytic C−H alkenylation methods for pyrroles and related nitrogen arene compounds, since the formation of *trans*-selective vinyl products is normally favored for these catalytic reactions.

While exploring the scope of the ruthenium-catalyzed coupling reactions involving C−H bond activation, we have recently developed a number of regioselective cyclization methods from the coupling reaction of arylamines and pyrroles with terminal alkynes by using the cationic ruthenium catalytic system $Ru_3(CO)_{12}/NH_4PF_6$.[8] Here we report a highly regioselective formation of α-*gem*-vinylpyrroles from the ruthenium-catalyzed intermolecular coupling reaction of pyrroles and terminal alkynes.



The treatment of *N*-methylpyrrole (1.0 mmol) with 4-ethynylanisole (2.0 mmol) in the presence of $Ru_3(CO)_{12}/NH_4PF_6$ (1:3, 3 mol % Ru) in benzene (3 mL) at 95 °C for 8 h cleanly produced the α-*gem*-vinylpyrrole product **1a** (eq 1). The product was isolated in 99% yield after a simple silica gel column chromatography (CH_2Cl_2/hexanes) and was fully characterized by both spectroscopic methods and elemental analysis. The initial survey of ruthenium catalysts showed that both $Ru_3(CO)_{12}$ and NH_4PF_6 are essential for the catalytic activity. Other selected neutral and cationic ruthenium catalysts, such as $RuCl_3 \cdot 3H_2O$, $(PPh_3)_3RuHCl$, $[(COD)RuCl_2]_x$ $(PCy_3)_2(CO)RuHCl$, and $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$, were not effective in giving the coupling product under the similar reaction conditions.

The scope of the coupling reaction was explored by using the $Ru_3(CO)_{12}/NH_4PF_6$ catalytic system (Table 1). Both *N*-alkyl- and *N*-arylpyrroles were found to react smoothly

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(6) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147.

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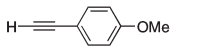
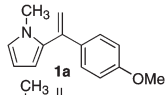
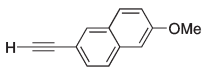
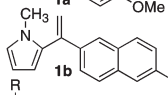
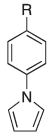
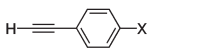
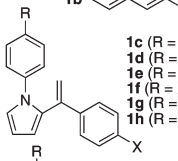
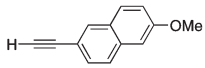
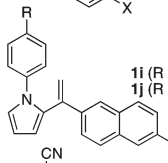
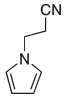
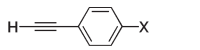
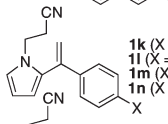
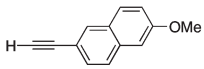
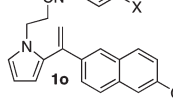
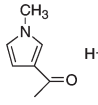
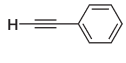
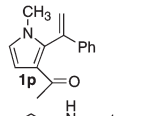
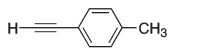
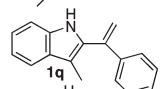
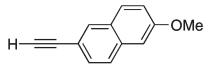
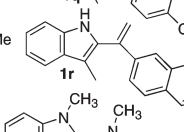
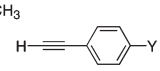
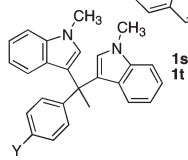
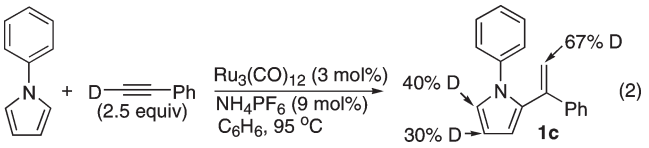
TABLE 1. Coupling Reaction of Pyrroles and Indoles with Terminal Alkynes[a]

entry	pyrrole/indole	alkyne	product (s)	yield (%)
1			 **1a**	99
2			 **1b**	95
3 4 5 6 7 8			 **1c** (R = H, X = H) **1d** (R = H, X = OMe) **1e** (R = CH_3, X = OMe) **1f** (R = X = OMe) **1g** (R = Cl, X = OMe) **1h** (R = F, X = OMe)	90 83 80 78 73 70
9 10			 **1i** (R = H) **1j** (R = OMe)	75 75
11 12 13 14			 **1k** (X = H) **1l** (X = CH_3) **1m** (X = OMe) **1n** (X = NMe_2)	80 83 85 75
15			 **1o**	78
16			 **1p**	81
17			 **1q**	78
18			 **1r**	81
19 20			 **1s** (Y = H) **1t** (Y = CH_3)	85 87

[a]Reaction conditions: pyrrole/indole (1.0 mmol), alkyne (2.0 mmol), $Ru_3(CO)_{12}/NH_4PF_6$ (1:3, 3 mol % Ru), benzene (3 mL), 95 °C, 12−15 h.

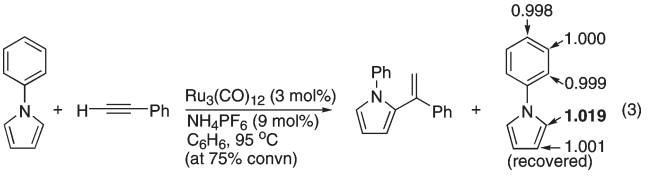
with aryl-substituted terminal alkynes to give the coupling products, in which arylalkynes with a para electron-donating group were found to promote the coupling reaction. Neither aliphatic-substituted terminal alkynes nor internal alkynes gave the coupling products under the similar reaction conditions. The regioselective α-insertion products **1q** and **1r** were obtained for 3-methylindole substrate (entries 17 and 18), while the analogous coupling reaction of *N*-methylindole led to the 2:1 coupling products **1s** and **1t**, resulting from regioselective insertion to the *β*-carbon (entries 19 and 20). The molecular structure of **1d** was also established by X-ray crystallography (Figure S3, Supporting Information).[9]



(2)

We performed the following kinetic experiments to gain mechanistic insights on the coupling reaction. First, the deuterium-labeling pattern was examined from the treatment of *N*-phenylpyrrole with DC≡CPh (2.5 equiv) and $Ru_3(CO)_{12}/NH_4PF_6$ (1:3, 3.0 mol % Ru) in benzene (3 mL) at 95 °C. The coupling product **1c** showed 67% D on the vinyl as well as 40% on the α-pyrrole positions as determined by both ^1H and ^2H NMR (eq 2). Extensive H/D exchange at the *β*-carbon of pyrrole may be due to a direct metalation by the ruthenium catalyst during or after the coupling reaction. Conversely, the treatment of α,α-dideuterated *N*-phenylpyrrole with HC≡CC_6H_4-*p*-OMe (2 equiv) yielded the product with an extensive H/D exchange on both vinyl (33% D) and α-pyrrole positions. The extensive H/D exchange pattern on the vinyl positions is indicative of rapid and reversible alkynyl and α-pyrrole C−H activation steps.

The deuterium isotope effect study also supported the notion of rapid H/D exchange steps. The rate of the reaction of *N*-phenylpyrrole and 2,5-d_2-*N*-phenylpyrrole with 4-ethynylanisole at 95 °C led to a virtually identical $k_{obs} = 0.14\ h^{-1}$, which translated to $k_{CH}/k_{CD} = 1.1 \pm 0.2$. Similar experiments from the reaction of *N*-phenylpyrrole with HC≡CPh and DC≡CPh also gave a negligible isotope effect of $k_{CH}/k_{CD} = 1.1 \pm 0.1$ (Figure S2, Supporting Information).[9] These results indicate that the α-C−H bond activation of pyrrole is not the rate-limiting step for the catalytic reaction.



(3)

To discern the rate-limiting step of the coupling reaction, we next measured the carbon isotope effect from the coupling reaction of *N*-phenylpyrrole with HC≡CPh by employing Singleton's isotope measurement technique at natural abundance.[10] The most pronounced carbon isotope effect was observed on the α-pyrrole carbon when the ^{13}C ratio of unreacted *N*-phenylpyrrole isolated at 75% conversion was compared to that of the virgin sample (^{13}C(recovered)/^{13}C(virgin) at $C_\alpha = 1.019$, average of 3 runs) (eq 3) (Table S1, Supporting Information). This result is consistent with the C−C bond rate-limiting step of the coupling reaction.

To examine the electronic influence on the pyrrole substrate, the Hammett plot was constructed from the correlation of the relative rates with σ_p for a series of para-substituted *N*-arylpyrroles *p*-X-$C_6H_4NC_4H_4$ (X = OMe, CH_3, H, Cl, F), which led to $\rho = -0.90$ (Figure 1). The promotional effect by electron-releasing group is indicative of a nucleophilic nature of the pyrrole group. An analogous correlation from the reaction of *N*-phenylpyrrole with para-substituted arylalkynes *p*-Y-$C_6H_4C{\equiv}CH$ (Y = OMe, CH_3, H, Br, F) resulted in a similar electronic promotional effect, but with a considerably less negative Hammett ρ value of −0.42. In this case, the negative ρ value suggests a considerable cationic character on the internal alkynyl carbon, which is stabilized by the electron-releasing group of the aryl substituent. These results are consistent with the notion that the C−C bond formation step is promoted by a nucleophilic pyrrole substrate via a cationic transition state.

(9) See the Supporting Information for the experimental details.

(10) (a) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357–9358. (b) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383–3384.

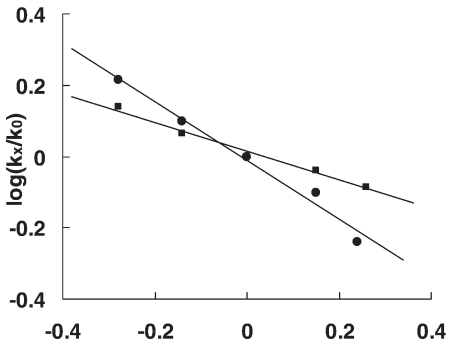
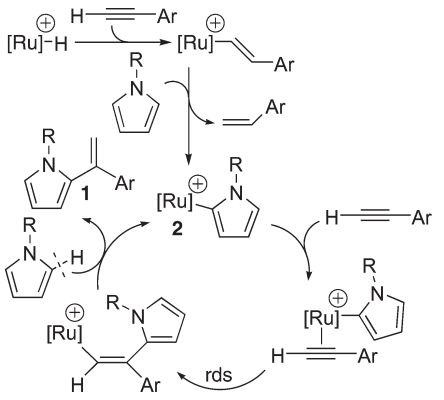


FIGURE 1. Hammett plots of the coupling reaction of para-substituted *p*-X-$C_6H_4NC_4H_4$ (X = OMe, CH_3, H, Cl, F) with PhC≡CH (●) and the reaction of *N*-phenylpyrrole with *p*-Y-C_6H_4C≡CH (Y = OMe, CH_3, H, Br, F) (■).

SCHEME 1



A plausible mechanistic rationale for the coupling reaction is illustrated on the basis of these results (Scheme 1). We propose that the catalytically active cationic Ru-pyrrolyl species **2** is initially formed from an α-C−H insertion of pyrrole followed by the elimination of an arylalkene. In support of this hypothesis, the formation of styrene (3%) was observed from the catalytic coupling reaction of *N*-phenylpyrrole with PhC≡CH as detected by both ^{1}H NMR and GC−MS.[9] Both negligible k_H/k_D isotope effect and extensive H/D exchange patterns on the coupling reaction are consistent with a rapid and reversible C−H bond activation step. The observation of the pronounced α-carbon isotope effect on the pyrrole substrate provides strong evidence for the rate-limiting C−C bond formation step. A relatively high negative Hammett ρ value from the correlation of para-substituted *N*-arylpyrroles indicates that the C−C bond formation step is promoted by the nucleophilic nature of the α-metalated pyrrolyl species **2**. The formation of *gem*-selective pyrrole product **1** can readily be rationalized by invoking a regioselective insertion of pyrrole to the internal alkynyl carbon in forming sterically less demanding Ru-vinyl species.[11] The migratory insertion of alkynes constitutes one of the well-known organometallic elementary reactions,[12] and the C−C bond forming rate-determining step has been proposed in other ruthenium-catalyzed arene C−H coupling reactions.[13]

In summary, the cationic ruthenium catalyst $Ru_3(CO)_{12}$/NH_4PF_6 was found to be highly effective for mediating the regioselective intermolecular coupling reaction of pyrroles and alkynes to give α-*gem*-vinylpyrroles. Both carbon isotope effect and Hammett study support a mechanism of the coupling reaction involving rate-limiting C−C bond formation step. The catalytic coupling reaction provides a reliable, atom-economical method for directly introducing synthetically useful *gem*-vinyl group to pyrroles and indoles.

Experimental Section

Representative Procedure of the Catalytic Reaction. In a glovebox, $Ru_3(CO)_{12}$ (22 mg, 0.030 mmol), NH_4PF_6 (16 mg, 0.10 mmol), pyrrole (1.0 mmol), and an alkyne (2.0 mmol, 2 equiv) were dissolved in 3 mL of benzene solution in a 25 mL Schlenk tube equipped with a magnetic stirring bar. The tube was brought out of the glovebox and was stirred in an oil bath set at 95 °C for 12−15 h. The tube was cooled to room temperature, and the crude product mixture was analyzed by GC−MS. The solvent was removed under a rotary evaporator, and analytically pure organic product was isolated by a column chromatography on silica gel (CH_2Cl_2/hexanes).

2-[1-(4-Methoxyphenyl)ethenyl-1-methylpyrrole (**1a**) was synthesized from the reaction of *N*-methylpyrrole (81 mg) with 4-ethynylanisole (265 mg) following the general procedure. For **1a**: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.2−6.9 (m, 4H), 6.7−6.1 (m, 3H), 5.46 (d, J = 1.6 Hz), 5.15 (d, J = 1.6 Hz), 3.81 (s, 3H), 3.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 160.5, 142.4, 134.6, 134.4, 129.1, 124.4, 114.8, 113.8, 110.9, 107.9, 55.4, 35.1; HREI (*m*/*z*) calcd for $C_{14}H_{15}NO$ (M^+) 213.1154, found 213.1144.

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Supporting Information Available: Experimental details, characterization data of the products, and X-ray crystallographic data of **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) As the reviewers pointed out, alternative mechanistic pathways involving cationic Ru-acetylide or direct metalation of pyrrole substrate can also be considered (for example, see recently proposed mechanisms in ref 8). While these mechanistic paths cannot readily explain the *gem*-selective formation of the coupling products, they could not be rigorously ruled out on the basis of available data.

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(13) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834 and references cited therein.