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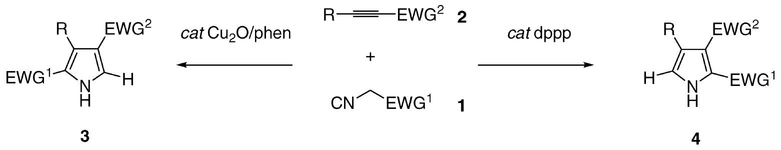

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Copper- or Phosphine-Catalyzed Reaction of Alkynes with Isocyanides. Regioselective Synthesis of Substituted Pyrroles Controlled by the Catalyst

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Abstract: The copper-catalyzed reaction of isocyanides ($CNCH_2EWG^1$) **1** with electron-deficient alkynes ($RC{\equiv}CEWG^2$) **2** gave the 2,4-di-EWG-substituted pyrroles **3** selectively, whereas the phosphine-catalyzed reaction of **1** with **2** afforded the 2,3-di-EWG-subsituted pyrroles **4**. Accordingly, regioselective synthesis of substituted pyrroles has been achieved by merely choosing the catalyst.

Introduction

Carbon−carbon bond formation is one of the most important and fundamental reactions in synthetic organic chemistry. Recent demands for development of environmentally benign processes have led many researchers to the study of eco-chemical transformations. One of the directions of researches to fulfil those requirements is an exploration of atom-economical processes,[1] in which all the atoms in substrates are taken into products. In such processes, no harmful and useless wastes are generated along with production of desired compounds. We envisioned that catalytic direct addition[2] and cycloaddition[3] of carbon pronucleophiles to a carbon−carbon unsaturated bond would bring about highly atom-economical processes as shown in Scheme 1. The ruthenium-catalyzed direct addition of activated methylenes and methines to activated alkynes (Michael reaction)[4] and the palladium-catalyzed direct addition of activated methylenes and methines to nonactivated allenes[5] give the corresponding C−C bond forming products in high yields in atom-economical manner. During the course of investigations on the palladium-catalyzed direct addition of carbon pronucleophiles to nonactivated C−C unsaturated bonds,[6] we found a cyclization of acetylenes tethered with an active methine compound to form carbocycles (hydrocarbonation).[7] Those direct additions are initiated with activation of a C−H bond in pronucleophiles by a metal catalyst, and subsequent insertion of the C−C triple bond into the metal−hydrogen (or metal−carbon) bond accounts for the formation of products. The dimerization of conjugated enynes in the presence of a palladium catalyst gives the 2,6-disubstituted styrenes regioselectively (benzannulation).[8]

In the previous reactions shown in Scheme 1, the ordinary carbon pronucleophiles, $HCR^3(EWG)_2$, were used as the partner of alkynes (or alkenes). It occurred to us that the use of isocyanides, instead of the ordinary pronucleophiles, would bring about a different type of atom-economical process. The reaction of the metalated (or nonmetalated) isocyanides with carbon−carbon and carbon-heteroatom unsaturated bonds is summarized in Scheme 2. The reaction of the two substrates, the nucleophiles and electrophiles, produces the C−C bond forming intermediate **I** which gives the heterocycles (shown in Scheme 2) through further transformations. To the best of our knowledge, the transition metal-catalyzed reaction of isocyanides is rather limited so far, but the application of isocyanides to various transformations has been rapidly expanding these days.[9,10]

We herein report that the copper-catalyzed reaction of isocyanides **1** with activated alkynes **2** produces the 2,4-di-EWG-substituted pyrroles **3** in good yields, whereas the phosphine-catalyzed reaction of **1** with **2** affords the 2,3-di-EWG-substituted pyrroles **4** regioselectively (Scheme 3).[11] This interesting regioreversal of the heteroaromatization stems from the regiodifferentiated addition of the nucleophilic isocyanide to **2**, which is controlled by the catalyst species; the ordinary Michael addition of the metalated isocyanide to the β-carbon

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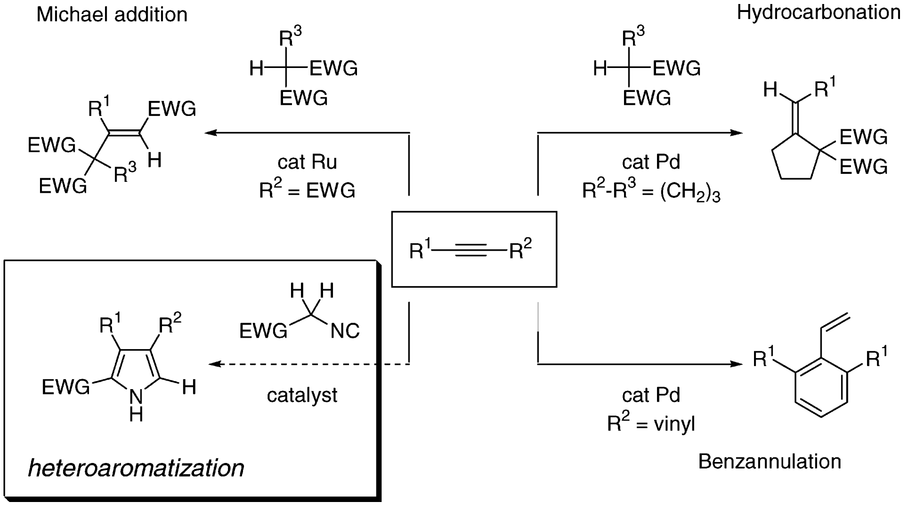
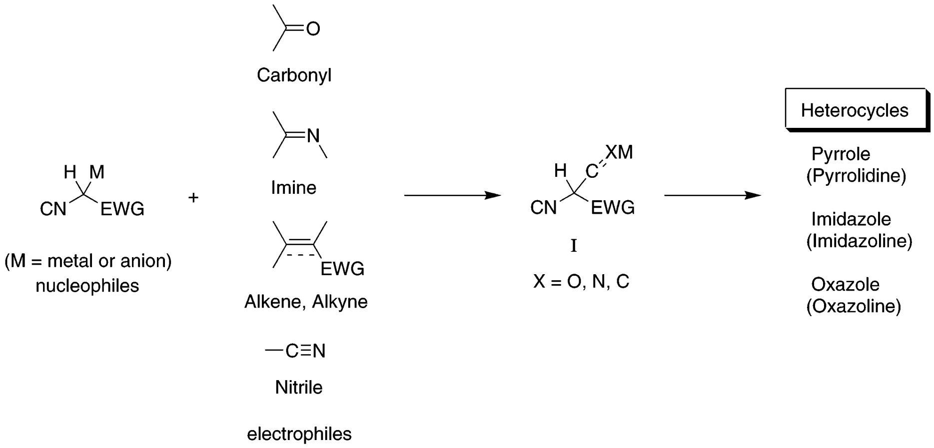
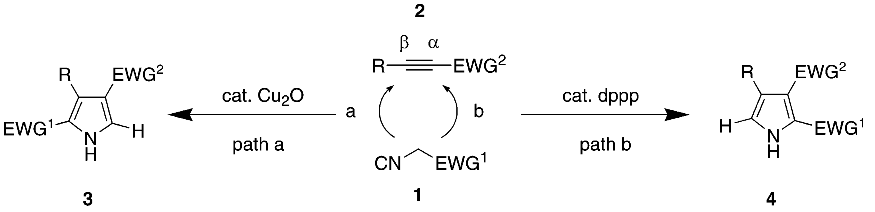
Scheme 1



Scheme 2



Scheme 3



of **2** (path a) gives **3**, while the addition of the nucleophilic isocyanide to the α-carbon attached to EWG^2 affords **4** (path b).

Results and Discussion

Copper-Catalyzed Addition Leading to the Formation of 2,4-Di-EWG-Substituted Pyrroles. Pyrroles are one of the important classes of heterocyclic compounds and found broad use in both synthetic organic chemistry and material science.[12] Pyrroles are often seen as a building block in naturally occurring and biologically active compounds such as chlorophylls and haems. Polypyrroles are known to exhibit conductivity, which can be applied as electric devices. Due to their characteristic

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properties, extensive investigations have been made to elucidate reactivity of pyrrole rings and to develop preparative methods of pyrrole structures.

Many excellent methodologies have been developed for constructing pyrrole rings.[12,13] One of the major strategies for synthesis of pyrroles is dehydrative coupling between ketones and amines. For instance, a condensation of 1,4-diketones with amines is known as the Paal−Knorr synthesis, a combination of α-amino ketones and *β*-dicarbonyl compounds is known as the Knorr synthesis, and a condensation of α-haloketones with *β*-keto ester in the presence of amines is known as the Hantzsh synthesis. The cycloaddition between activated olefins (Michael acceptors) and isocyanides under basic conditions is also a representative method for synthesis of pyrroles. The reaction of nitroalkenes with isocyanoacetates is known as the Barton−Zard synthesis, and the reaction of Michael acceptors and TosMIC (tosylmethyl isocyanide)[14] is called the van Leusen synthesis. These cycloadditions produce desired pyrroles, although they always come with elimination of nitrous acid and toluenesulfinate, respectively.

During the course of research on the cyanamide[15] and the triazole[16] synthesis via the three-component coupling reactions of allyl carbonate, $TMSN_3$, and isocyanides (or alkynes), we discovered that a combination of copper and phosphine catalysts promoted a reaction between ethyl isocyanoacetate **1a** and ethyl 2-butynoate **2a** to produce some cyclized products. A precise analysis of the spectroscopic data revealed that the reaction using Cu_2O and PPh_3 catalysts gave a mixture of 2,4-di(ethoxycarbonyl)-3-methylpyrrole **3a** ($R = Me$, $EWG^1 = EWG^2 = CO_2Et$ in eq 1) and 2,3-di(ethoxycarbonyl)-4-methylpyrrole **4a** ($R = Me$, $EWG^1 = EWG^2 = CO_2Et$ in eq 1) as shown in entry 1 in Table 1. Detailed survey on combination between catalysts and ligands disclosed that Cu_2O and a nitrogen ligand effectively promoted the regioselective formation of the 2,4-di-EWG-substituted pyrrole **3a**. Both alkyl and aromatic amines, such as Pr_3N, *N*-methylmorpholine, and pyridine, worked as a pertinent ligand to afford the expected pyrrole **3a** in moderate yields (entries 2−4). The employment of DBU (1,8-diazabicyclo-[5.3.0]undec-7-ene) decreased the yield of **3a** (entry 5). The diamines, such as TEEDA (*N*,*N*,*N*′,*N*′-tetraethylethylenediamine), phen (1,10-phenanthroline), and bipy (2,2′-dipyridyl), also catalyzed the pyrrole-forming reaction (entries 6−8). Among them, the combination of Cu_2O and phen showed the highest catalytic activity for regioselective formation of **3a**. The formation of **3a** took place by merely using Cu_2O salt, but the yield was slightly lower compared with the yield obtained through the reaction using the Cu_2O and phen catalyst system (entry 9). We also investigated the reactivity of some other copper catalysts, such as CuCl, $Cu(OMe)_2$, and Cu powder, but the yields of **3a** were low (entries 10−12). The rhodium[9b] and ruthenium[4a] complexes promoted the pyrrole formation to some extent (entries 13 and 14). Among the solvents we tested, 1,4-dioxane showed the best result for formation of the pyrrole **3a**. Solvents such as toluene and ethyl acetate produced the desired product **3a** in moderate yields, whereas polar solvents, such as DMF, CH_3CN, and 1,2-dichloroethane, resulted in low yields. When the reaction was carried out at lower temperature (80 °C), a significant decrease of the yield was observed and a prolonged reaction time was required.

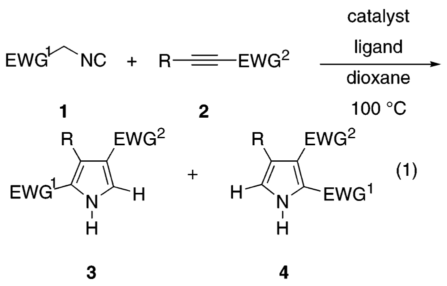

Table 1. Effects of the Metal Catalysts in the Reaction of **1a** and **2a**[a]

entry	catalyst	ligand	NMR yield of **3a**[b], %
1	Cu_2O	PPh_3	35[c]
2	Cu_2O	Pr_3N	50
3	Cu_2O	*N*-methylmorpholine	49
4	Cu_2O	pyridine	46
5	Cu_2O	DBU	22
6	Cu_2O	TEEDA[d]	42
7	Cu_2O	phen[d]	66
8	Cu_2O	bipy[d]	48
9	Cu_2O	none	48
10	CuCl[e]	phen[d]	trace
11	$Cu(OMe)_2$[e]	phen[d]	33
12	Cu powder[e]	phen[d]	33
13	$HRh(PPh_3)_4$	none	26
14	$H_2Ru(PPh_3)_4$	none	41

[a] Unless otherwise noted, the reaction of **1a** (0.5 mmol; $EWG^1 = CO_2Et$ in eq 1) and **2a** (0.7 mmol; $R = Me$, $EWG^2 = CO_2Et$ in eq 1) was conducted in dioxane (1 mL) in the presence of catalyst (25 μmol, 5 mol %) and ligand (100 μmol, 20 mol %) at 100 °C for 6 h. [b] NMR yield using *p*-xylene as an internal standard. [c] **4a** ($R = Me$, $EWG^1 = EWG^2 = CO_2Et$ in eq 1) was obtained in 12% NMR yield. [d] 10 mol % of the ligand was used. [e] 10 mol % of the catalyst was used.

Since the optimal reaction conditions were in hand for the copper-catalyzed heteroaromatization, the reaction of ethyl isocyanoacetate **1a** with various electron-deficient alkynes **2** was carried out and the results are summarized in Table 2. The reaction of ethyl 2-butynoate **2a** with **1a** was conducted with Cu_2O (5 mol %) and phen (10 mol %) in dioxane at 100 °C. The substrate **1a** was consumed in 2 h, and 2,4-di(ethoxycarbonyl)-3-methylpyrrole **3a** was obtained in 64% isolated yield (entry 1). It was possible to use the alkynol **2b** directly without protecting a hydroxyl group, and the corresponding product **3b** was formed in good yield (entry 2). The substrate **2c** attached with a cyclohexyl group produced the pyrrole **3c** in high yield (entry 3); however the bulky *tert*-butyl substituted alkyne **2d** afforded the corresponding product **3d** in only 15% yield (entry 4). The steric congestion around the triple bond seems to diminish the yield of the heteroaromatization reaction. Both ethyl phenylpropiolate **2e** and ethylpropiolate **2f** reacted in a similar

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(14) Leusen, D. v.; Leusen, A. M. v. *Org. React.* **2001**, *57*, 417−666 and references therein.

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(16) (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, 125, 7786−7787. (b) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 2386-2393. (c) Kamijo, S.; Jin, T.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 689−691.

Table 2. Copper-Catalyzed Pyrrole Synthesis Using Various Alkynes **2** and **1a**[a]

entry	R	EWG^2	2	time, h	3	yield, %
1	Me	CO$_2$Et	**2a**	2	**3a**	64
2	HO(CH$_2$)$_4$	CO$_2$Et	**2b**	1	**3b**	65
3	cyclo-C$_6$H$_{11}$	CO$_2$Et	**2c**	2	**3c**	73
4	*t*-Bu	CO$_2$Et	**2d**	3	**3d**	15 (26)[b]
5	Ph	CO$_2$Et	**2e**	2	**3e**	79
6	H	CO$_2$Et	**2f**	1	**3f**	73
7	CO$_2$Et	CO$_2$Et	**2g**	4.5	**3g**	43
8	Ph	COMe	**2h**	1	**3h**	22[c]
9	Ph	CONEt$_2$	**2i**	1	**3i**	11
10	Ph	CN	**2j**	1	**3j**	22
11	Ph	SO$_2$Ph	**2k**	1	**3k**	13

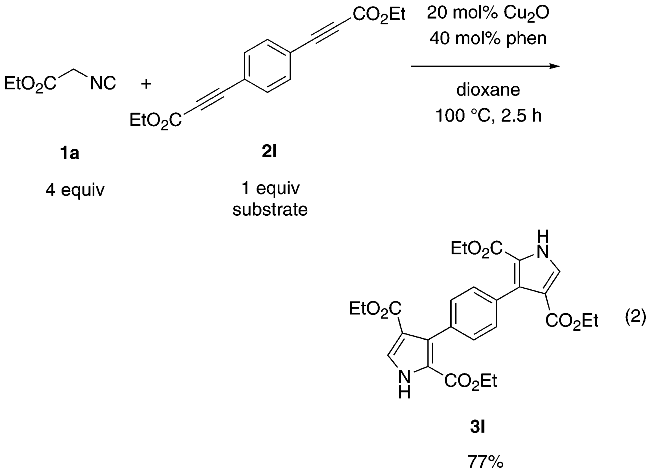
[a] Unless otherwise noted, the reaction between **1a** (0.5 mmol; EWG^1 = CO$_2$Et in eq 1) and **2** (0.6 mmol) was conducted in dioxane (1 mL) in the presence of Cu$_2$O (25 μmol, 5 mol %) and 1,10-phenanthroline (50 μmol, 10 mol %) at 100 °C for the time indicated in Table 2. [b] The yield increased to 26% when 10 mol % Cu$_2$O and 20 mo % phen were used. [c] The oxazoline was obtained in 14% yield.[17]

Table 3. Copper-Catalyzed Pyrrole Synthesis Using Various Isocyanides **1** and **2a**[a]

entry	EWG^1	1	time, h	3	yield, %
1	CO$_2$Me	**1b**	2	**3m**	54
2	CO$_2$ ^{t}Bu	**1c**	3.5	**3n**	71
3	CONEt$_2$	**1d**	4	**3o**	75
4	P(O)(OEt)$_2$	**1e**	24	**3p**	59
5	Ph	**1f**	6	**3q**	46

[a] The reaction between **1** (0.5 mmol) and **2a** (0.6 mmol; R = Me, EWG^2 = CO$_2$Et in eq 1) was conducted in dioxane (1 mL) in the presence of Cu$_2$O (25 μmol, 5 mol %) and 1,10-phenanthroline (50 μmol, 10 mol %) at 100 °C for the time indicated in Table 3.

way to form the pyrroles **3e** and **3f** in high yields, respectively (entries 5 and 6). Highly electron-deficient acetylenedicarboxylate **2g** produced the expected pyrrole **3g** in 44% yield (entry 7). The reactions of the alkynes **2h**−**2k** activated with various electron-withdrawing groups, such as keto, amido, cyano, and sulfonyl group, gave the corresponding pyrroles **3h**−**3k** in low yields (entries 8−11). The diyne **2l** produced the corresponding product **3l** containing two pyrrole rings in 77% yield (eq 2).

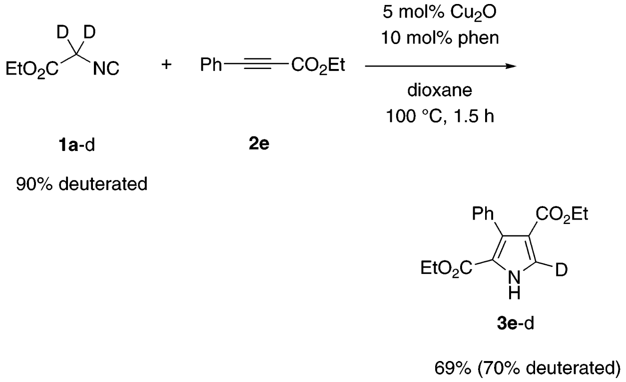


(2)

We next conducted the pyrrole forming reaction employing ethyl 2-butynoate **2a** and a variety of isocyanides **1** (Table 3). The isocyanides having methoxycarbonyl **1b** and *tert*-butoxycarbonyl group **1c** afforded the corresponding pyrroles **3m** and **3n** in 54% and 71% yields (entries 1 and 2). It is clear that installation of sterically bulky *tert*-butyl group in an ester moiety of the isocyanide does not interfere with the progress of the present heteroaromatization. The reactions of the amide **1d** and the phosphonate **1e** gave the expected pyrroles **3o** and **3p** in good to high yields (entries 3 and 4). Surprisingly, benzyl isocyanide **2f** gave the corresponding pyrrole **3q** in 46% yield under the standard reaction conditions (entry 5).

A plausible mechanism for the copper-catalyzed heteroaromatization between isocyanides **1** and electron-deficient alkynes **2** is illustrated in Scheme 4. The reaction starts with activation of a C−H bond of the isocyanides **1** by the influence of Cu$_2$O catalyst. The α-cuprioisocyanide **A** or its tautomer **A′** is formed by the reaction between **1** and Cu$_2$O through the extrusion of H$_2$O.[18] Then, the 1,4-addition of the nucleophilic intermediate **A** and/or **A′** to the alkynes **2**, activated by an electron-withdrawing groups, takes place. The newly generated copper-enolate would intramolecularly attack the isonitrile carbon to generate the cyclized intermediate **B**; this is a formal [3 + 2] cycloaddition process. The C−Cu bond in the intermediate **B** is protonated by isocyanides **1**, and the intermediate **C** is produced with regeneration of the copper-intermediate **A** and/or **A′**. The continuous formation of this active species **A** and/or **A′** makes the catalytic cycle operative. 1,5-Hydrogen shift in the intermediate **C** forms the 2,4-di-EWG-substituted pyrroles **3** as the sole product.

We carried out the heteroaromatization between the deuterated isocyanide **1a**−d[9e] and the alkyne **2e** in the presence of the copper catalyst (eq 3). As expected, the reaction gave the pyrrole **3e**−d in 69% yield with 70% content of the deuterium on the pyrrole ring.



(3)

Phosphine-Catalyzed Addtion Leading to the Formation of 2,3-Di-EWG-Substituted Pyrroles.[11] One of the significant advances in the field of synthetic organic chemistry in recent years is development of new catalytic reactions using simple organic molecules, called organocatalysis.[19] Various types of organic molecules have already been revealed to behave as an organocatalyst, and numerous efforts have been made to design more reactive catalysts. Phosphine phosphorus is one of the

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(17) (a) Reference 9a. (b) Saegusa, T.; Murase, I.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 830−833. (c) Ito, Y.; Matsuura, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781−5784.

(18) For Cu$_2$O-catalyzed activation of a C−H bond in isocyanides with extrusion of H$_2$O, see: (a) Reference 17. (b) Ito, Y.; Konoike, T.; Saegusa, T. *J. Organomet. Chem.* **1975**, *85*, 395−401. (c) Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Org. Chem.* **1979**, *44*, 2030−2032. The reactions between copper catalysts and isocyanides have been well studied by Professors Ito and Saegusa; however, we cannot completely exclude the possibility that H−Cu species might act as an active catalyst similar to the case of the Rh-catalyzed reaction of isocyanides in ref 9b. We thank a reviewer for pointing this out.

Scheme 4. A Proposed Mechanism for the Copper-Catalyzed Reaction

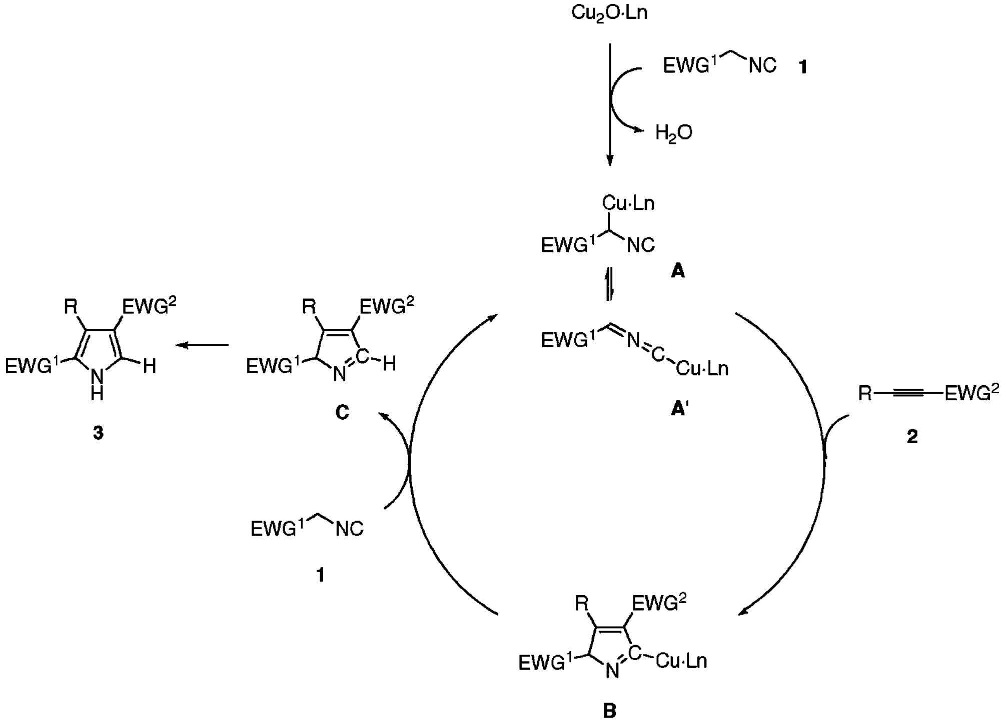


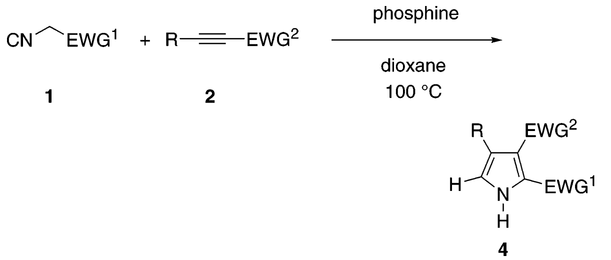
Table 4. Effects of Phosphines in the CuCl-Catalyzed Reaction between **1a** and **2a**[a]

entry	phosphine	NMR yield of **4a**, %[b]
1[c]	PPh_3	50
2	$(p\text{-MeO}-C_6H_4)_3P$	38
3	$(p\text{-CF}_3-C_6H_4)_3P$	0
4	(2-furyl)^{3}P	0
5	$P(OPh)_3$	0
6	$(o\text{-tolyl})_3P$	0
7	PBu_3	34
8	$(\text{cyclohexyl})_3P$	13
9[d]	dppe	50
10[d]	dppp	63
11[d]	dppb	50
12[d]	dppf	25
13[d]	BINAP	0

[a] Unless otherwise noted, the reaction of **2a** (0.6 mmol; R = Me, $EWG^2 = CO_2Et$ in eq 4) and **1a** (0.5 mmol; $EWG^1 = CO_2Et$ in eq 4) was conducted in dioxane (1 mL) in the presence of CuCl (50 μmol, 10 mol %) and phosphine (150 μmol, 30 mol %) at 100 °C for 6 h. [b] NMR yield using *p*-xylene as an internal standard. [c] $CuCl(PPh_3)_3$ (50 μmol, 10 mol %) was used as a catalyst instead of CuCl and PPh_3. [d] Bidentate phosphine (15 mol %) was used.

elements useful for this purpose. It is known that isomerization,[20] cyclization,[21] and addition reactions[22] of electron-deficient alkynes and allenes are catalyzed by organophosphine catalysts.[23] However, pyrrole formation via a formal [3 + 2] cycloaddition between electron-deficient alkynes **2** and isocyanides **1** under a phosphine catalyst is not known so far.[24]

During optimization on the copper-catalyzed addition of **1a** to **2a**, we encountered that the use of CuCl and PPh_3 catalyst produced the 2,3-di-EWG-substituted pyrrole together with trace amounts of the 2,4-di-EWG-substituted one (eq 4; see also entry 1, Table 1). The effects of phosphine additives on the yield of **4a** are summarized in Table 4. Arylphosphines, such as PPh_3 and electron-rich tris(*p*-methoxyphenyl)phosphine, produced the corresponding pyrrole **4a** in moderate yields (entries 1 and 2), whereas electron-deficient tris(*p*-trifluoromethylphenyl)phosphine, tris(2-furyl)phosphine, and triphenyl phosphite did not catalyze the reaction at all (entries 3−5). The sterically congested tri(*o*-tolyl)phosphine also did not promote the reaction either (entry 6). Alkylphosphines, such as PBu_3 and tricyclohexylphosphine, were less effective than PPh_3 (entries 7 and 8). The reactivity of the bidentate phosphines, such as dppe (1,2-bis(diphenylphosphino)ethane), dppp (1,3-bis(diphenylphosphino)propane), and dppb (1,4-bis(diphenylphosphino)butane), were comparable to that of PPh_3 (entries 9−11). Among them,



(4)

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Table 5. Phosphine-Catalyzed Pyrrole Synthesis Using Various Alkynes **2** and **1a**[a]

entry	R	EWG2	2	time, h	4	yield, %
1	Me	CO_2Et	**2a**	2	**4a**	60
2	$CH_3(CH_2)_5$	CO_2Et	**2m**	12	**4b**	73
3	$HO(CH_2)_4$	CO_2Et	**2b**	2	**4c**	59
4	cyclo-C_6H_{11}	CO_2Et	**2c**	24	**4d**	66
5[b]	cyclo-C_6H_{11}	CO_2Et	**2c**	19	**4d**	64
6	*t*-Bu	CO_2Et	**2d**	24	**4e**	–[c]
7	Ph	CO_2Et	**2e**	1.5	**4f**	79
8	*p*-MeO–C_6H_4	CO_2Et	**2n**	3.5	**4g**	79
9	*p*-CF_3–C_6H_4	CO_2Et	**2o**	0.75	**4h**	48
10	isopropenyl	CO_2Et	**2p**	4	**4i**	19
11	H	CO_2Et	**2f**	0.5	**4j**	–[d]
12	CO_2Et	CO_2Et	**2g**	0.5	**4k**	–[d]
13	Ph	COMe	**2h**	1	**4l**	77
14	Ph	$CONEt_2$	**2i**	24	**4m**	17[e]
15	Ph	CN	**2j**	0.5	**4n**	35

[a] Unless otherwise noted, the reaction between **2** (0.5 mmol) and **1a** (0.6 mmol; $EWG^1 = CO_2Et$ in eq 4) was conducted in dioxane (1 mL) in the presence of dppp (75 μmol, 15 mol %) at 100 °C for the time indicated in Table 5. [b] CuCl (25 μmol, 5 mol %) was added. [c] A significant amount of the alkyne **2d** and the isocyanide **1a** was recovered. [d] Complex mixture. [e] The starting alkyne **2i** was recovered in 67% yield.

Table 6. Phosphine-Catalyzed Pyrrole Synthesis Using Various Isocyanides **2** and **1e**[a]

entry	EWG1	1	time, h	4	yield, %
1	$CO_2{}^tBu$	**1c**	2	**4o**	70
2	$CONEt_2$	**1d**	3.5	**4p**	27
3	$P(O)(OEt)_2$	**1e**	24	**4q**	18[b]
4	SO_2(*p*-Me-C_6H_4)	**1g**	24	**4r**	20[b]

[a] The reaction between **1e** (0.5 mmol; R = Ph, $EWG^2 = CO_2Et$ in eq 4) and **2** (0.6 mmol) was conducted in dioxane (1 mL) in the presence of dppp (75 μmol, 15 mol %) at 100 °C for the time indicated in Table 6. [b] A small amount of the starting alkyne **2e** was recovered.

dppp[25] gave the highest yield of the desired pyrrole **4a**. The employment of dppf (1,1′-bis(diphenylphosphino)ferrocene) and BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) did not improve the yield of **4a**. Very interestingly, further studies disclosed that the present heteroaromatization could be catalyzed merely by a phosphine, dppp, without the aid of CuCl. The reaction took place in a wide variety of solvents, such as toluene, 1,2-dichloroethane, 1,4-dioxane, ethyl acetate, and CH_3CN. Among them, dioxane gave the highest yield of **4a**. The reaction proceeded at lower temperature (80 °C); however, a longer reaction time was required.

We carried out the phosphine-catalyzed heteroaromatization of various electron-deficient alkynes **2** with ethyl isocyanoacetate **1a** under the optimal conditions; dppp (15 mol %) in dioxane at 100 °C, and the results are summarized in Table 5. The reaction between **2a** and **1a** was completed in 2 h to give 2,3-di(ethoxycarbonyl)-4-methylpyrrole **4a** in 60% isolated yield (entry 1). The alkyne **2m** bearing hexyl group afforded the pyrrole **4b** in 73% yield (entry 2). Even the unprotected alkynyl alcohol **2b** could be used directly as a starting material and the corresponding product **4c** was obtained in 59% yield (entry 3). The reaction of the alkyne **2c** attached with a cyclohexyl group proceeded smoothly to produce the desired product **4d** in 66% yield after 24 h (entry 4). When the same reaction was carried out in the presence of a catalytic amount of CuCl, the reaction time was reduced without affecting the yield of **4d** (entry 5).[26] In the case of the alkyne **2d** bearing a bulky *tert*-butyl group, no reaction took place even after 24 h and a significant amount of the starting materials was recovered (entry 6). The reactions of aromatic acetylenes **2e**, **2n**, and **2o** gave the corresponding pyrroles **4f**, **4g**, and **4h**, respectively (entries 7–9). The introduction of an electron-donating group on the aromatic ring slightly retarded the consumption of the substrate, though the product **4g** was obtained in high yield (entry 8). On the contrary, the introduction of an electron-withdrawing group shortened the reaction time but the yield of **4h** remained moderate (entry 9). The reaction of the conjugated enyne **2p** took place chemoselectively at the alkyne moiety and produced the corresponding pyrrole **4i**, although the yield was modest (entry 10). The reaction of the terminal acetylene **2f** and the highly electron-deficient acetylenedicarboxylate **2g** gave a complex mixture of unidentified products, probably due to the polymerization of acetylenes (entries 11 and 12). It is worthy to mention that the acetylenes bearing keto **2h**, amido **2i**, and cyano group **2j** served as a starting material to afford the corresponding pyrroles **4l**–**4n**, respectively (entries 13–15).

We next examined the phosphine-catalyzed heteroaromatization between ethyl phenylpropiolate **2e** and the various isocyanides **1c**–**1d**, and **1g** (Table 6). Installation of the bulky *tert*-butyl group in the ester moiety, as in **1c**, did not affect the reaction progress, and the corresponding pyrrole **4o** was produced in 70% yield (entry 1). The isocyanides having amido **1d** and phosphonate **1e** and sulfonyl group **1g** afforded the corresponding pyrroles **4p**, **4q**, and **4r**, respectively, however the yields were rather low (entries 2–4). Benzyl isocyanide **1f** did not give the desired pyrrole under the present conditions, and recovery of the starting materials was observed.

A plausible mechanism for the phosphine-catalyzed heteroaromatization is depicted in Scheme 5. The reaction is most probably initiated by 1,4-addition of the nucleophilic phosphine to the activated alkynes **2** to form the zwitterionic intermediate **D**.[27] This step induces umpolung of reactivity of the activated alkyne **2**. The abstraction of an acidic proton in the isocyanide **1** gives the cationic intermediate **E** and the carbanion **1′**.[28] The carbanion would attack the carbon bearing EWG^2 of **E**,[29] and the newly formed anionic center would attack the isocyanide carbon of **1′** to form the cyclic intermediate **F**; this is a formal [3 + 2] cycloaddition process. Intramolecular proton migration and elimination of the phosphine catalyst produce the intermediate **G**. Subsequent 1,5-hydrogen shift furnishes the pyrrole **4** as a product.

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(25) The reactions using dppp as a catalyst: (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819–10820. (b) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670–5671. (c) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7579–7596.

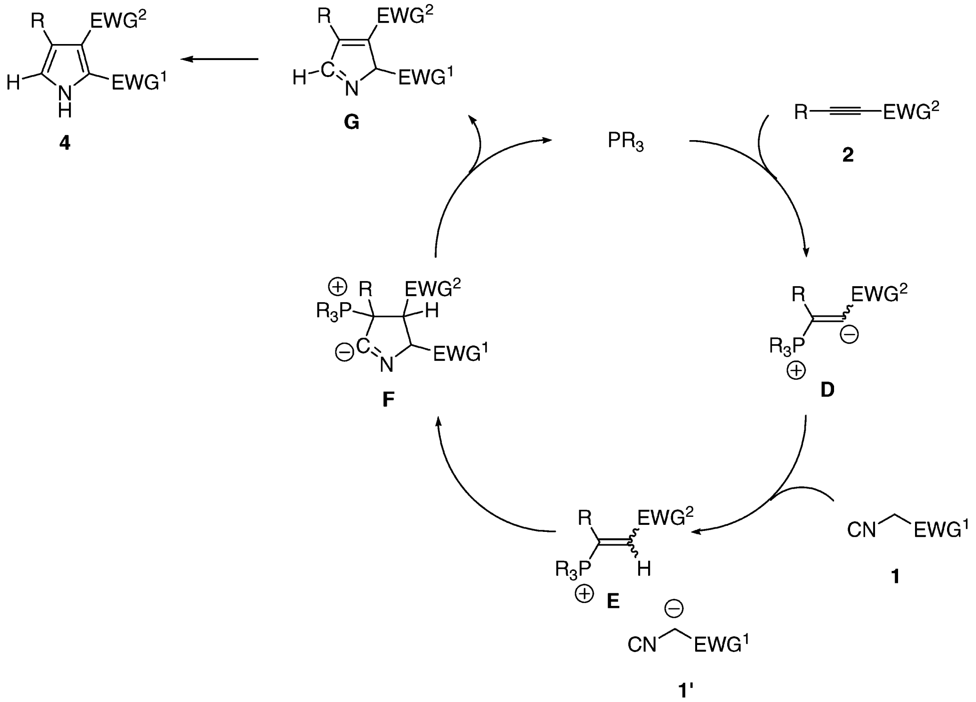
(26) The copper effect might be explained as follows, although it is speculative. CuCl catalyst coordinates both dppp and the isocyanide. This complexation makes it easy to generate the anionic species **1′** in Scheme 5 and stabilizes the derived intermediate as a copper-enolate. Moreover, the ligation between the phosphine in **E** and the copper-enolate of **1′** accelerates the formation of the cyclized intermediate **F**. The combination of CuCl and isocyanides has been studied in ref 17c.

(27) (a) Reference 23. (b) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. *J. Org. Chem.* **2003**, *68*, 871–874. (c) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244. (d) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683.

(28) The pK_a value of isocyanides is slightly larger than those of the corresponding cyanides; see: (a) Castejon, H.; Wiberg, K. B. *J. Org. Chem.* **1998**, *63*, 3937–3942. (b) Bordwell, F. G.; Branca, J. C.; Bares, J. E.; Filler, R. *J. Org. Chem.* **1988**, *53*, 780–782 [pK_a of methyl cyanoacetate = 12.8].

(29) Similar types of inverse 1,4-addition reactions have been reported; see: (a) Hanédanian, M.; Loreau, O.; Taran, F.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 7035–7038. (b) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677–4679.

Scheme 5. A Proposed Mechanism for the Phosphine-Catalyzed Reaction



Conclusion

We have developed new synthetic procedures for the regiocontrolled formation of pyrroles via a formal [3 + 2] cycloaddition of isocyanides **1** and electron-deficient alkynes **2**. The present heteroaromatization proceeds smoothly under either a copper or a phosphine catalyst, and the two distinct regioisomeric pyrroles can be obtained selectively by merely choosing the catalyst conditions. The reaction under a catalytic amount of Cu_2O and phen gives 2,4-di-EWG-substituted pyrroles, whereas the reaction under dppp catalyst affords 2,3-di-EWG-substituted pyrroles selectively. This interesting switching of the regioselectivity is due to umpolung of the reactivity of the alkynes **2**, depending on the catalyst conditions. As mentioned in Scheme 4, the nucleophilic isocyanide **A** generated by a C−H activation with Cu_2O undergoes the ordinary 1,4-addition to **2** leading to **3**, whereas the 1,4-adduct of PR_3 to **2** makes the α-carbon attached to EWG electrophilic (**E** in Scheme 5) and thereby the carbanion of **1** attacks the α-position of **E** leading to **4**.

Experimental Section

Representative Procedure for the Copper-Catalyzed Reaction Leading to the Formation of 2,4-Di-EWG-Substituted Pyrroles. To a 1,4-dioxane solution (1 mL) of Cu_2O (3.6 mg, 25 μmol) and 1,10-phenanthroline (9.0 mg, 50 μmol) were added ethyl butynoate **2a** (70 μL, 0.6 mmol) and ethyl isocyanoacetate **1a** (55 μL, 0.5 mmol) under an Ar atmosphere. The solution was stirred at 100 °C for 2 h. After the consumption of **1a**, the reaction mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified by column chromatography (silica gel, *n*-hexane/AcOEt 50:1 to 3:1) to afford 2,4-di(ethoxycarbonyl)-3-methylpyrrole **3a** in 64% yield (72.1 mg).

Representative Procedure for the Phosphine-Catalyzed Reaction Leading to the Formation of 2,3-Di-EWG-Substituted Pyrroles. To a 1,4-dioxane solution (1 mL) of 1,3-bis(diphenylphosphino)propane (dppp) (30.9 mg, 75 μmol) were added ethyl isocyanoacetate **1a** (66 μL, 0.6 mmol) and ethyl butynoate **2a** (58 μL, 0.5 mmol) under an Ar atmosphere. The solution was stirred at 100 °C for 2 h. After the consumption of **2a**, the reaction mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified by column chromatography (silica gel, *n*-hexane/AcOEt 50:1 to 3:1) to afford 2,3-di(ethoxycarbonyl)-4-methylpyrrole **4a** in 60% yield (67.1 mg).

Acknowledgment. We are grateful to the members in the Research and Analytical Center for Giant Molecules at the Graduate School of Science, Tohoku University for measurement of NMR spectra and mass spectra and elemental analysis.

Supporting Information Available: Analytical data for the 2,4-di-EWG-substituted pyrroles **3** and 2,3-di-EWG-substituted pyrroles **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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