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2,4- vs 3,4-Disubsituted Pyrrole Synthesis Switched by Copper and Nickel Catalysts

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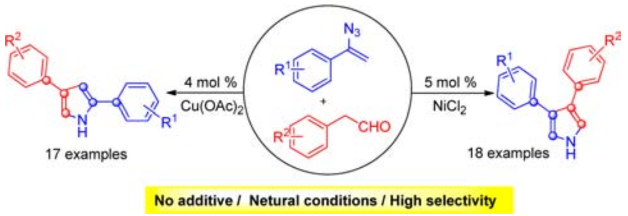
ABSTRACT



A novel and efficient copper or nickel catalyzed highly selective denitrogenative annulation of vinyl azides with aryl acetaldehydes has been developed. 2,4- and 3,4-diaryl substituted pyrroles, which are difficult to synthesize by the reported methods, can be highly regioselectively prepared by this protocol simply switched by the selection of the transition metal catalysts. Compared with the reported acidic or basic conditions for polysubstituted pyrrole synthesis, the present reaction conditions are mild, neutral, and very simple without any additives.

Pyrroles are one of the important classes of heterocyclic compounds as well as building blocks in many synthetic pharmaceutical agents,[1] natural products,[2] and materials science.[3] Various synthetic methods have been developed for the construction of pyrrole structures.[4,5] However, most known approaches are effective for 2,5-di- or polysubstituted pyrroles.[6] New synthetic strategies for the generation of simple aryl-substituted pyrroles are of continuous interest. Particularly, synthetic routes to simple 2,4- or 3,4-diaryl substituted pyrroles are still limited, especially if two different aryl substitutents are required,[7,8] although these compounds have generated considerable interest owing to their remarkable diversity of biological activities,[9] such as antidiabetic,[9a] fungicidal,[9b] or antibacterial[9c]

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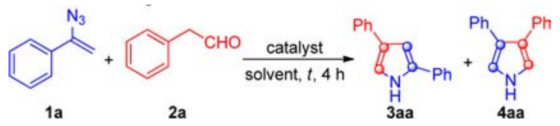
properties. Some limitations, such as equivalent reagents,[7a−c] multiple synthetic steps,[7d−f] harsh reaction conditions with high pressure,[7g,h] and limited substrate scope,[7i−l] are involved in the synthesis of 2,4-diaryl substituted pyrroles. Since the modification of pyrroles by the electrophilic aromatic substitution reactions or lithiation reactions preferred the formation of α-substituted pyrroles, the construction of 3,4-diarylsubstituted pyrroles is very challenging.[8b,10]

On the other hand, establishing methods that can construct different substituted pyrroles in an efficient manner from the same readily accessible substrates continues to be actively pursued. Our continuing interest in reactions using azido reagents as the N-partner[11] has encouraged us to try the catalytic reaction for the construction of diaryl substituted pyrroles. Herein, we report a novel and highly regioselective approach to 2,4- and 3,4-disubsituted pyrroles from readily accessible materials switched by copper and nickel catalyst. Compared to the reported acidic or basic conditions for polysubstituted pyrrole synthesis, the present reaction conditions are mild, neutral and very simple without any additives. In particular, this method provides a new and unique strategy to synthesize asymmetric 3,4-disubstituted pyrroles, which are probably the most difficult to obtain by traditional methods.

Table 1. Screening of The Reaction Conditions[a]



entry	catalyst (mol %)	solvent	*t*/°C	yield (%)[b]	
				3aa	**4aa**
1	Cu(OAc)$_2$ (4)	DMSO	110	56	
2	Cu(OAc)$_2$ (4)	EtOH	110	62	
3[c]	Cu(OAc)$_2$ (4)	DMSO/EtOH	110	80	
4[c]	Cu(OAc)$_2$ (4)	DMSO/EtOH	60	20	
5[c]	Cu(OAc)$_2$ (2)	DMSO/EtOH	110	50	
6[c]	NiCl$_2$ (5)	DMSO/EtOH	110		44
7	NiCl$_2$ (5)	DMAc	110		72
8	NiCl$_2$ (2)	DMAc	110	12	54
9	NiCl$_2$ (5)	DMAc	60	0	0
10		DMAc	110	0	0
11	HCl (10)[d]	DMAc	110	trace	15

[a] Reaction conditions: **1a** (0.6 mmol) and **2a** (0.4 mmol), catalyst, and solvent (1.5 mL) with stirring under argon atomsphere for 4 h. [b] Isolated yields. [c] Mixture solvent with DMSO (0.5 mL) and EtOH (1.0 mL). [d] Concentrated hydrochloric acid (37%) was used.

α-Azidostyrene[12] has been proven to be a useful N-partner participating in various heterocyclic compound syntheses. Recently, Chiba and co-workers reported a significant Mn-catalyzed polysubstituted pyrrole synthesis from α-azidostyrene.[12e] We envisioned that 2,4- or 3,4-diaryl substituted pyrroles could be achieved by the reaction of α-azidostyrene with a selected C-precursor such as acetaldehyde. The preliminary investigation employed α-azidostyrene (**1a**) and 2-phenylacetaldehyde (**2a**) as the substrates. We systematically investigated a number of experimental variables such as catalysts, additives, reaction temperature, time, and solvents and other parameters (see the Supporting Information). Representative results are summarized in Table 1. Interestingly, when the reaction was performed in the presence of copper(II) acetate (4 mol %) at 110 °C in DMSO under argon atmosphere, 2,4-diphenyl-1*H*-pyrrole (**3aa**) was obtained in 56% yield (entry 1, Table 1). The yield was achieved in 62% by using EtOH as the solvent instead of DMSO (entry 2). The reaction was found to proceed more efficiently in a polar solvent. Then the reactions in mixed solvent were investigated. Significantly, the mixed solvent DMSO/EtOH led to the highest yield of **3aa** (80%, entry 3). Low yields were obtained upon reducing the amount of catalyst copper(II) acetate to 2 mol % or decreasing the reaction temperature to 60 °C (entries 4 and 5, Table 1).

We were delighted to find that 3,4-diphenyl-1*H*-pyrrole (**4aa**) was obtained successfully when nickel chloride (5 mol %) was used as the catalyst without the detection of 2,4-diphenyl-1*H*-pyrrole (**3aa**) (entry 6, Table 1). The yield of **4aa** was produced in 72% when DMAc was used as solvent (entry 7). The yield of **4aa** decreased to 50% with the formation of **3aa** (12%) in this reaction condition when 2 mol % NiCl$_2$ was used (entry 8). No product was generated when the reaction temperature was decreased to 60 °C (entry 9). Furthermore, trace products were detected in the absence of catalyst (entry 10, Table 1). Brønsted acid[13] such as HCl has very low catalytic activity

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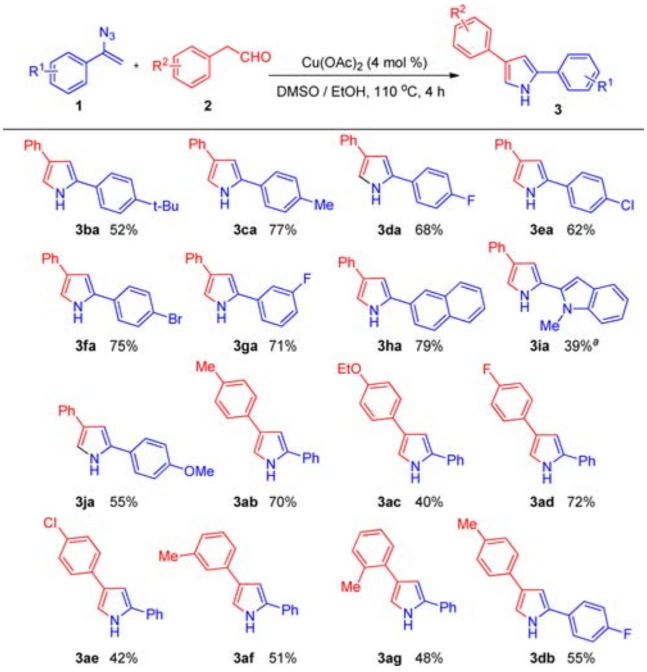
for the formation of one of the pyrrole regioisomers (entry 11, Table 1). Therefore, 2,4- and 3,4-disubsituted pyrroles could be easily and highly regioselectively obtained in high yields just by switching the copper and nickel catalysis.

Scheme 1. Copper Catalyzed 2,4 Disubsituted Pyrrole Formation

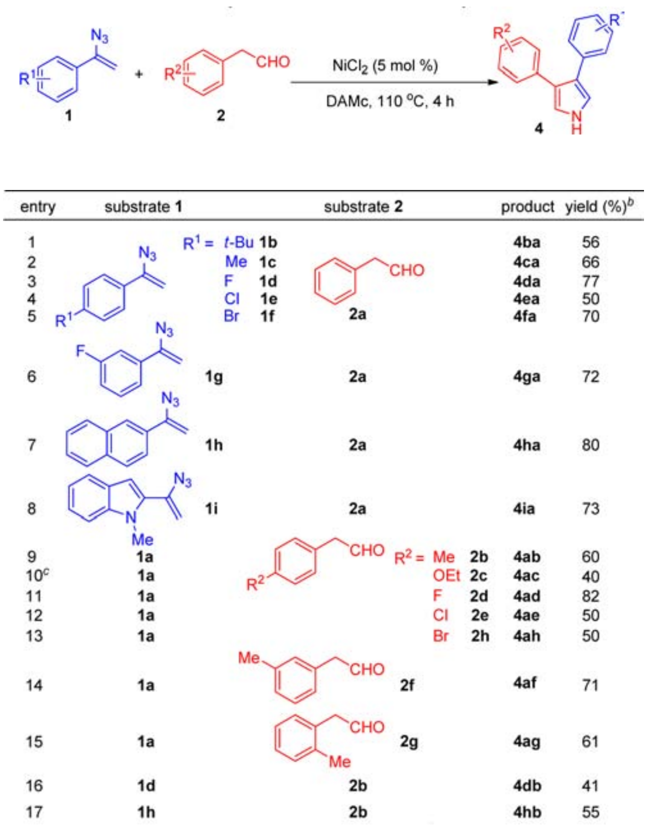


[a] 10% **4ia** was obtained.

After optimizing the reaction conditions, we subsequently investigated the substrate scope of this highly regioselective protocol (Scheme 1 and Table 2). Under the Cu-catalysis conditions, various desired 2,4-disubsituted pyrroles were obtained in moderate to good yields from corresponding substituted vinyl azides and phenylacetaldehydes (Scheme 1). The structure of **3aj** was further proven by X-ray diffraction (see the Supporting Information). The reaction efficiencies were not significantly affected by the substituted groups at different position (*para*, *meta*, or *ortho*-position) of the aromatic ring of vinyl azides. Additionally, halo-substituted vinyl azides and phenylacetaldehydes performed well under the standard conditions generating the halosubstituted products. Furthermore, the heteroaryl-substituted substrate 2-(1-azidovinyl)-1-methyl-1*H*-indole (**3i**) was a compatible substrate with the formation of **3ia** in 39% yield (Scheme 1).

Then $NiCl_2$-catalyzed 3,4-disubsituted pyrrole formation was investigated (Table 2). The substrate scope is also broad, with various substituted vinyl azides and phenylacetaldehydes leading to the corresponding asymmetric 3,4-disubstituted pyrroles in moderate to good yields. All these reactions performed with high regioselectivities under the Cu- and Ni-catalysis, respectively (Scheme 1 and Table 2).

Table 2. Nickel Catalyzed 3,4-Disubsituted Pyrrole Formation[a]



entry	substrate 1	substrate 2	product	yield (%)[b]
1	R^1 = t-Bu **1b**	**2a**	**4ba**	56
2	Me **1c**	**2a**	**4ca**	66
3	F **1d**	**2a**	**4da**	77
4	Cl **1e**	**2a**	**4ea**	50
5	Br **1f**	**2a**	**4fa**	70
6	**1g**	**2a**	**4ga**	72
7	**1h**	**2a**	**4ha**	80
8	**1i**	**2a**	**4ia**	73
9	**1a**	R^2 = Me **2b**	**4ab**	60
10[c]	**1a**	OEt **2c**	**4ac**	40
11	**1a**	F **2d**	**4ad**	82
12	**1a**	Cl **2e**	**4ae**	50
13	**1a**	Br **2h**	**4ah**	50
14	**1a**	**2f**	**4af**	71
15	**1a**	**2g**	**4ag**	61
16	**1d**	**2b**	**4db**	41
17	**1h**	**2b**	**4hb**	55

[a] Reaction conditions: see entry 7, Table 1. [b] Isolated yields. [c] The reaction temperature is 130 °C.

To probe the reaction mechanism of the regioselective formation of 2,4- and 3,4-disubsituted pyrrole, a series of control experiments have been designed and tested. As 2*H*-azirine[12a−d] is assumed to be an intermediate of the transformation, the reactions of phenylacetaldehyde (**2a**) with 3-(naphthalen-2-yl)-2*H*-azirine **5** were conducted under copper and nickel catalyzed system, respectively (eq 1, 2). It was interesting that 3-(naphthalen-2-yl)-4-phenyl-1*H*-pyrrole (**4ha**) was obtained as the sole product in 30 and 90% yield, respectively, in the both Cu- or Ni-catalyzed reactions (eq 1, 2). No 2-(naphthalen-2-yl)-4-phenyl-1*H*-pyrrole (**3ha**) was detected under the Cu-catalytic conditions (eq 1). These results indicate that 2*H*-azirines could be the key intermediate in the Ni-catalysis but not involved in the Cu-catalyzed reactions. Furthermore, the results of isotopic labeling experiments demonstrate the differences of these two catalytic systems. The reaction of **1a** and **2a** catalyzed by $Cu(OAc)_2$ using DMSO-d_6 (0.6 mL) and CD_3OD (0.6 mL) as solvent produced product **[d]-3aa** in 69% yield with 80% of 3-*H* deuterated (eq 3). In contrast, no hydrogen was deuterated of the

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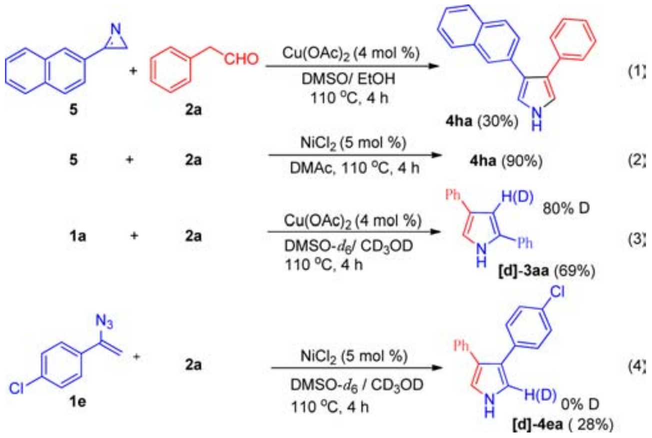
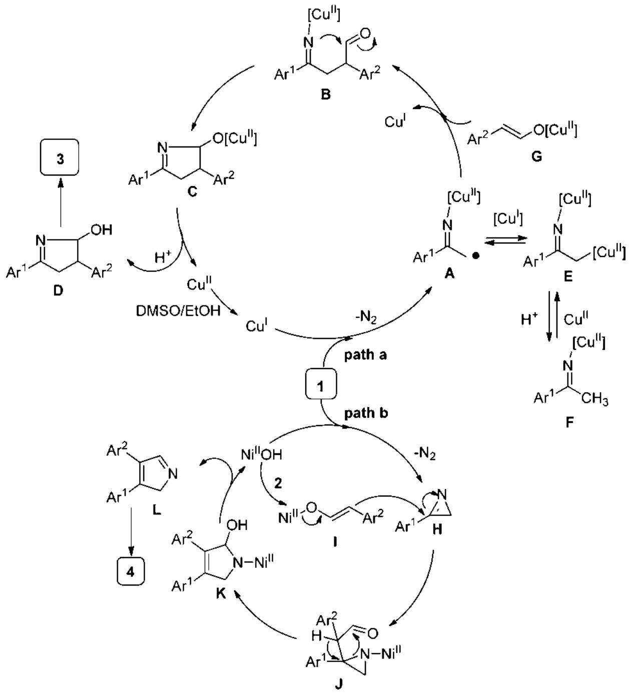
3,4-disubsituted pyrrole for nickel catalyzed reaction using DMSO-d_6 and CD_3OD as solvent (eq 4).

On the basis of above experimental observations, plausible mechanisms for these highly regioselective transformations are proposed. For the Cu-catalyzed 2,4 disubsituted pyrrole formation (path a, Scheme 2), $Cu(OAc)_2$ might be initially reduced by DMSO/EtOH to form a CuI species or by disproportionation[14] to form a CuI species.[12j] Then, the radical intermediates **A** are generated through a denitrogenative decomposition pathway of the vinyl azide.[12j] Subsequently, the radical coupling of enol tautomers of the phenylacetaldehydes with the intermediates **A** generates the intermediates **B**, which undergo nucleophilic attack to the aldehyde leading to the addition intermediates **C**. Subsequent protonation generates the intermediates **D**, and dehydration of intermediates **D** yields the target 2,4-disubsituted pyrroles. The protonation of the Cu-*aza*-enolates **E** could be proved by the results of isotopic labeling experiments (eq 3).



For the Ni-catalyzed 3,4-disubsituted pyrrole formation (path b, Scheme 2), $NiCl_2$ promoted thermal denitrogenative decomposition of the vinyl azide **1a** generates 2*H*-azirines **H**, which could not be produced in the presence of Cu-catalyst. Subsequent nucleophilic attack by the enol tautomers of the phenylacetaldehydes affords the intermediates **J**. Intramolecular ring-opening of intermediates **J** yields five-membered species **K**. The following *β*-OH elimination produces the 2*H*-pyrroles **L** and Ni complexes, which react with **2** to regenerate enol intermediates **I**. Finally 3,4-disubsituted pyrroles are achieved via the tautomerition of intermediates **L**.

Scheme 2. Proposed Mechanisms



In summary, we have demonstrated a novel and efficient copper or nickel catalyzed highly regioselective denitrogenative annulation of vinyl azides with aryl acetaldehydes. 2,4- and 3,4-diaryl substituted pyrroles, which are difficult to synthesize by the reported methods, can be high selectively prepared by this protocol simply switched by the selection of the transition metal catalysts. Compared with the reported acidic or basic conditions for polysubstituted pyrrole synthesis, the present reaction conditions are mild, neutral and very simple without any additives. Further investigation of the scope and synthetic application of these reactions are ongoing in our group.

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Supporting Information Available. Experimental details, NMR spectra analysis of the products, and crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.