

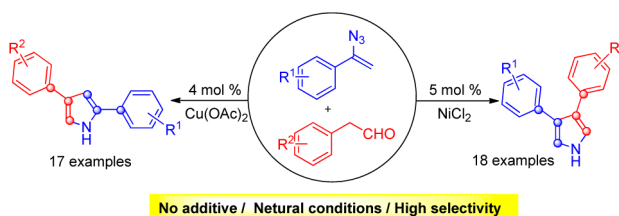
2,4- vs 3,4-Disubstituted Pyrrole Synthesis
Switched by Copper and Nickel CatalystsFeng Chen,[†] Tao Shen,[†] Yuxin Cui,[†] and Ning Jiao^{*,†,‡}

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Received August 13, 2012

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 poly-substituted 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 substituents 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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(1) (a) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109. (b) Cozzi, P.; Mongelli, N. *Curr. Pharm. Des.* **1998**, *4*, 181. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (d) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. (e) Andreani, A.; Cavalli, A.; Granaiola, M.; Guardigli, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Recanatini, M.; Roda, A. *J. Med. Chem.* **2001**, *44*, 4011. (f) Baraldi, P. G.; Nunez, M. C.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bermejo, J.; Esterez, F.; Romagnodi, R. *J. Med. Chem.* **2004**, *47*, 2877. (g) Srivastava, S. K.; Shefali Miller, C. N.; Aceto, M. D.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M. *J. Med. Chem.* **2004**, *47*, 6645.

(2) (a) *Pyrroles, Part II*; Jones, R. A., Ed.; Wiley: New York, 1992. (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517.

(3) (a) *Electronic Materials: The Oligomer Approach*; Müllen, K.; Wegner, G., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) Novak, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207. (c) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465. (d) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17.

(4) For reviews, see: (a) Gossauer, A. In *Methoden der Organischen Chemie* (Houben-Weyl); Kreher, R. P., Ed.; Georg Thieme Verlag: Stuttgart, 1994; E6a, pp 556–798. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2849. (c) Tarasova, O. A.; Nedolya, N. A.; Vvedensky, V. Yu.; Brandsma, L.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 7241. (d) Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411.

(5) For selected examples in recent years, see: (a) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046. (b) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (c) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (d) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (e) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (f) Shindo, M.; Yoshimura, Y.; Hayashi, M.; Soejima, H.; Yoshikawa, T.; Matsumoto, K.; Shishido, K. *Org. Lett.* **2007**, *9*, 1963. (g) St. Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (h) Lu, Y.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5430. (i) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313. (j) Bergner, I.; Wiebe, C.; Meyer, N.; Opatz, T. *J. Org. Chem.* **2009**, *74*, 8243. (k) Ciez, D. *Org. Lett.* **2009**, *11*, 4282. (l) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (m) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312. (n) Bonnamour, J.; Bolm, C. *Org. Lett.* **2011**, *13*, 2012. (o) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *13*, 1062.

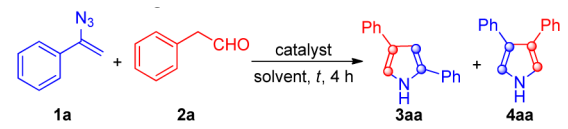
(6) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.

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-partner¹¹ 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-disubstituted 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.

α -Azidostyrene¹² 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.^{12c} We envisioned that 2,4- or

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 atmosphere 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.

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-1H-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-1H-pyrrole (**4aa**) was obtained successfully when nickel chloride (5 mol %) was used as the catalyst without the detection of 2,4-diphenyl-1H-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 % NiCl₂ 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 acid¹³ such as HCl has very low catalytic activity

(7) (a) Fan, X.; Zhang, X.; Zhang, Y. *J. Chem. Res.* **2005**, *11*, 750. (b) Nitta, M.; Kobayashi, T. *Chem. Lett.* **1983**, 1715. (c) Sato, S.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2936. (d) Thompson, B. B.; Montgomery, J. *Org. Lett.* **2011**, *13*, 3289. (e) Hall, M. J.; McDonnell, S. O.; Killoran, J.; O'Shea, D. F. *J. Org. Chem.* **2005**, *70*, 5571. (f) Zhao, W.; Carreira, E. M. *Chem.—Eur. J.* **2006**, *12*, 7254. (g) Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776. (h) Campi, E. M.; Jackson, W.; Nilsson, Y. *Tetrahedron Lett.* **1991**, *32*, 1093. (i) Fan, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43*, 1863. (j) Nitta, M.; Kobayashi, T. *Chem. Lett.* **1983**, 1715. (k) Deady, L. W. *Tetrahedron* **1967**, *23*, 3505. (l) Thorold Rogers, M. A. *J. Chem. Soc.* **1943**, 590.

(8) For a symmetric 3,4-diaryl substituted pyrrole synthesis using two equivalent silver acetate as oxidant, see: (a) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. *Org. Lett.* **2010**, *12*, 4066. For 3,4-diaryl substituted pyrrole synthesis through the modification of simple pyrroles, see: (b) Liu, J.-H.; Chan, H.-C.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274.

(9) (a) Holland, G. F. U. S. Pat. 4,282,242, 1981; *Chem. Abstr.* **1981**, *95*, 187068e. (b) Nippon Soda Co., Ltd. Japanese Patent 8179, 672, 1981; *Chem. Abstr.* **1981**, *95*, 187069f. (c) Umio, S.; Kariyone, K. Japanese Patent 6814,699, 1968; *Chem. Abstr.* **1969**, *70*, 87560z.

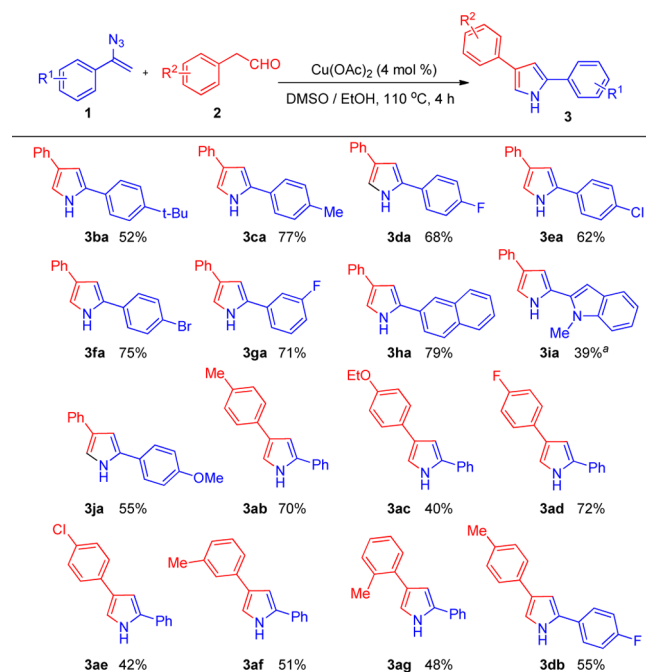
(10) (a) Anderson, H. J.; Loader, C. E.; Xu, R. X.; L Lè, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896. (b) Alizadeh, A.; Rezvanian, A.; Zhu, L.-G. *Tetrahedron* **2008**, *64*, 351.

(11) (a) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094. (b) Chen, F.; Qin, C.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11487.

(12) (a) Hassner, A.; Fowler, F. W. *J. Am. Chem. Soc.* **1968**, *90*, 2869. (b) Hassner, A.; Belinka, Jr. B. A. *J. Am. Chem. Soc.* **1980**, *102*, 6185. (c) Timén, A. S.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339. (d) Singh, P. N.; Carter, C. L.; Gudmundsdóttir, A. D. *Tetrahedron Lett.* **2003**, *44*, 6763. (e) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (f) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (g) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570. (h) Chen, W.; Hu, M.; Wu, J.; Zou, H.; Yu, Y. *Org. Lett.* **2010**, *12*, 3863. (i) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411. (j) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927. (k) Ng, E. P. J.; Wang, Y.-F.; Hui, B. W.-Q.; Lapointe, G.; Chiba, S. *Tetrahedron* **2011**, *67*, 7728. (l) Ng, E. P. J.; Wang, Y.-F.; Chiba, S. *Synlett* **2011**, 783.

for the formation of one of the pyrrole regioisomers (entry 11, Table 1). Therefore, 2,4- and 3,4-disubstituted 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 Disubstituted Pyrrole Formation



* 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-disubstituted 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 NiCl₂-catalyzed 3,4-disubstituted 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-Disubstituted Pyrrole Formation^a

entry	substrate 1	substrate 2	product	yield (%) ^b
1	1b (R ¹ = <i>t</i> -Bu)	2a	4ba	56
2	1c (R ¹ = Me)	2a	4ca	66
3	1d (R ¹ = F)	2a	4da	77
4	1e (R ¹ = Cl)	2a	4ea	50
5	1f (R ¹ = Br)	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 (R ² = OEt)	2c	4ac	40
11	1a (R ² = F)	2d	4ad	82
12	1a (R ² = Cl)	2e	4ae	50
13	1a (R ² = Br)	2h	4ah	50
14	1a	2f	4af	71
15	1a	2g	4ag	61
16	1d	2b	4db	41
17	1h	2b	4hb	55

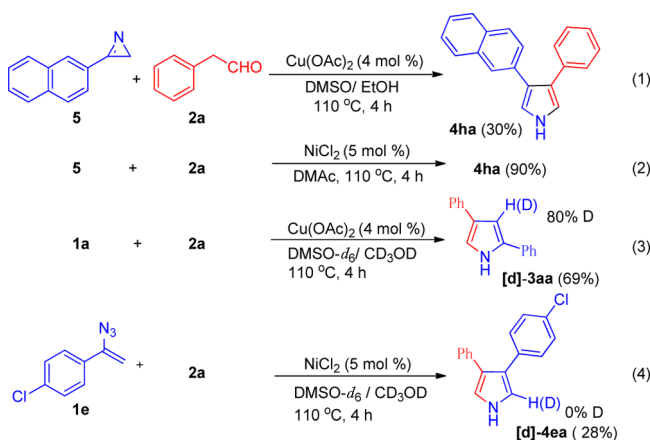
^a Reaction conditions: see entry 7, Table 1. ^b Isolated yields. ^c The reaction temperature is 130 °C.

To probe the reaction mechanism of the regioselective formation of 2,4- and 3,4-disubstituted 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 CD₃OD (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

(13) (a) Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, 76, 9353. (b) Schmidt, R. K.; Mütther, K.; Mück-Lichtenfeld, C.; Grimme, S.; Oestreich, M. *J. Am. Chem. Soc.* **2012**, 134, 4421.

3,4-disubstituted pyrrole for nickel catalyzed reaction using DMSO- d_6 and CD $_3$ OD as solvent (eq 4).

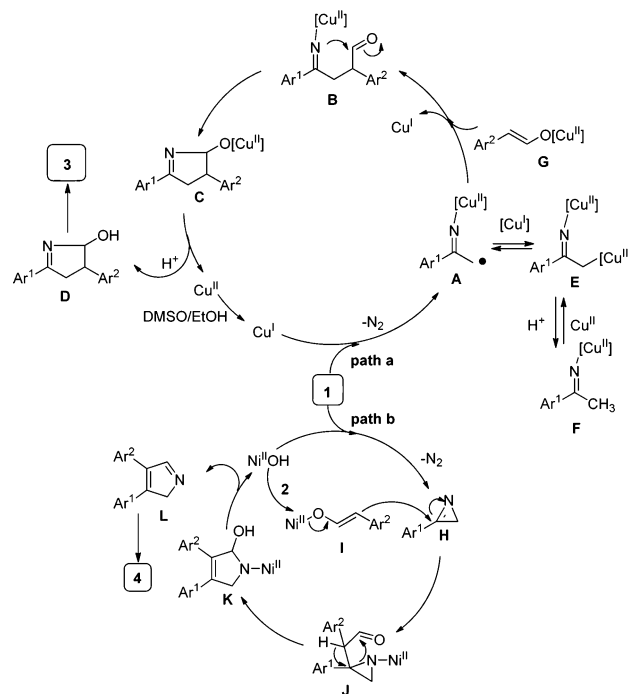
On the basis of above experimental observations, plausible mechanisms for these highly regioselective transformations are proposed. For the Cu-catalyzed 2,4-disubstituted pyrrole formation (path a, Scheme 2), Cu(OAc) $_2$ might be initially reduced by DMSO/EtOH to form a Cu I species or by disproportionation¹⁴ to form a Cu I 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-disubstituted 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-disubstituted 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-disubstituted pyrroles are achieved via the tautomerization of intermediates **L**.

(14) (a) Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gomez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Solà, M.; Llobet, A.; Stack, T. D. P. *J. Am. Chem. Soc.* **2010**, *132*, 12299. (b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 1147. (c) Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2009**, 2899. (d) Ribas, X.; Jackson, D. A.; Donnadiou, B.; Mahia, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2991. (e) Li, Y.; Li, Z.; Xiong, T.; Zhang, Q.; Zhang, X. *Org. Lett.* **2012**, *14*, 3522.

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.

Acknowledgment. Financial support from National Basic Research Program of China (973 Program 2009CB825300), National Science Foundation of China (No. 21172006), and Peking University are greatly appreciated. We thank Guolin Wu in this group for reproducing the results of **3ab** and **4da**.

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>.

The authors declare no competing financial interest.