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Regiocontrolled Synthesis of Polysubstituted Pyrroles Starting from Terminal Alkynes, Sulfonyl Azides, and Allenes

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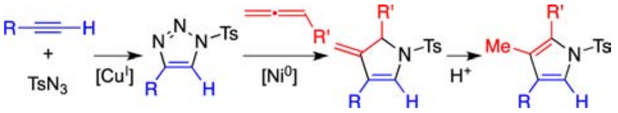
ABSTRACT



1-Sulfonyl-1,2,3-triazoles, readily prepared from terminal alkynes and sulfonyl azides, react with allenes in the presence of a nickel(0) catalyst to produce the corresponding isopyrroles. The initially produced isopyrroles are further converted to a wide range of polysubstituted pyrroles through double bond transposition and Alder-ene reactions.

Pyrroles are privileged structural motifs found in a number of natural products, pharmaceutical compounds, and functional materials. Thus, the development of efficient methods for their synthesis, particularly regiocontrolled synthesis of those containing multiple substituents, from readily accessible compounds is of ever-increasing importance.[1,2]

On the other hand, 4-substituted 1-sulfonyl-1,2,3-triazoles are easily prepared from terminal alkynes and sulfonyl azides by the well-established method using a copper(I) catalyst.[3] It has recently been disclosed that they act as precursors for reactive transition metal complexes of α-imino carbenes.[4−7] If compared with related α-oxo carbene complexes, the nitrogen atom of the α-imino group is considerably more nucleophilic and thus this moiety possibly participates in the cycloaddition reaction with unsaturated compounds to construct *N*-heterocycles. For example, the reactions with nitriles,[5a] alkynes,[5d,6] aldehydes,[5j] and isocyanates[5l] furnish the corresponding imidazoles, pyrroles, oxazolines, and imidazolones, respectively.

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(2) For selected recent examples of pyrrole synthesis, see: (a) Lourdusamy, E.; Yao, L.; Park, C.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7963. (b) Trost, B. M.; Lumb, J.-P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740. (c) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (d) Xu, X.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2011**, *13*, 6122. (e) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926. (f) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (g) Reddy, B. V. S.; Reddy, M. R.; Rao, Y. G.; Yadav, J. S.; Sridhar, B. *Org. Lett.* **2013**, *15*, 464. (h) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140.

(3) (a) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730. (b) Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4952. (c) Liu, Y.; Wang, X.; Xu, J.; Zhang, Q.; Zhao, Y.; Hu, Y. *Tetrahedron* **2011**, *67*, 6294.

(4) For a pioneering work using pyridotriazoles, see: Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757.

(5) For rhodium(II)-catalyzed reactions, see: (a) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (b) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034. (c) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510. (d) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746. (e) Chuprakov, S.; Malik, J. A.; Zibinsky, M.; Fokin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 10352. (f) Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 194. (g) Selander, N.; Fokin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 2477. (h) Miura, T.; Funakoshi, Y.; Morimoto, M.; Biyajima, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17440. (i) Selander, N.; Worrell, B. T.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 13054. (j) Zibinsky, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1507. (k) Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami *Angew. Chem., Int. Ed.* **2013**, *52*, 3883. (l) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 4652. (m) Parr, B. T.; Green, S. A.; Davies, H. M. *J. Am. Chem. Soc.* **2013**, *135*, 4716. For reviews, see: (n) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (o) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371.

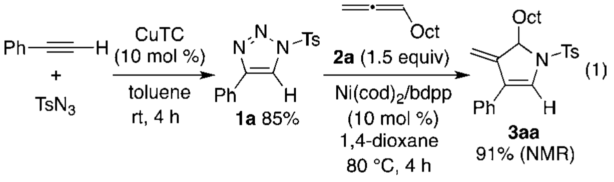
(6) For a nickel(0)-catalyzed reaction, see: Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470.

(7) For a silver(I)-catalyzed reaction, see: Liu, R.; Zhang, M.; Winston-McPherson, G.; Tang, W. *Chem. Commun.* **2013**, *49*, 4376.

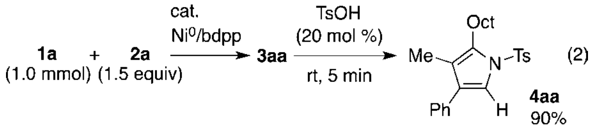
10.1021/ol401340u

We now report a nickel(0)-catalyzed transannulation reaction of 1-sulfonyl-1,2,3-triazoles with allenes.[8] This reaction provides a highly versatile approach to polysubstituted pyrroles starting from terminal alkynes, sulfonyl azides, and allenes with position control of the substituents.

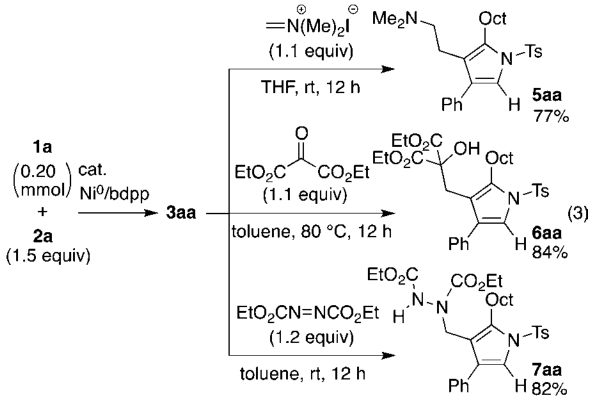
4-Phenyl-1-tosyl-1,2,3-triazole (**1a**) was initially prepared from phenylethyne and tosyl azide according to Fokin's procedure using copper(I) thiophene-2-carboxylate (CuTC) (eq 1).[3b] Then, **1a** (0.20 mmol) was treated with undeca-1,2-diene (**2a**, 1.5 equiv) in 1,4-dioxane at 80 °C in the presence of a nickel(0) catalyst, generated *in situ* from $Ni(cod)_2$ (10 mol %) and *rac*-2,4-bis(diphenylphosphino)pentane (bdpp).[9,10]



The ^1H NMR spectrum of the crude reaction mixture indicated that 3-methylene-2,3-dihydropyrrole **3aa** was formed as a single detectable transannulation product.[2b,11] Thus, the azo moiety (–N=N–) was extruded out of **1a** and instead the allene **2a** was incorporated therein. When the reaction mixture was directly subjected to chromatographic isolation, **3aa** partly underwent double bond transposition to afford a mixture of **3aa** and 3-methyl-2-octyl-4-phenyl-1-tosyl-pyrrole (**4aa**). On the other hand, direct addition of *p*-toluenesulfonic acid to the reaction mixture accelerated the double bond transposition, and **4aa** was isolated in 90% yield (eq 2).

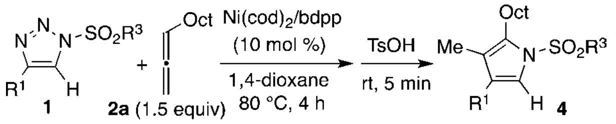


The isopyrrole **3aa** facilely gained aromatic stabilization also by Alder-ene reactions (eq 3).[12] Addition of Echenmoser's salt, diethyl ketomalonate, and diethylazodicarboxylate to the reaction mixture produced the corresponding pyrroles **5aa**, **6aa**, and **7aa**, respectively.



Other 1,4-disubstituted triazoles **1b**–**i** were also prepared from the corresponding terminal alkynes and sulfonyl azides, and the generality of the transannulation reaction was examined (Table 1). Substrates **1b**–**d** possessing aryl groups at the 4-position reacted well with allene **2a** to afford the corresponding pyrroles **4ba**–**da** in yields ranging from 86% to 99% (entries 1–3). Electron-donating and -withdrawing substituents were both tolerated on the benzenesulfonyl group (entries 4 and 5). 4-Alkyl-substituted substrates **1g**–**i** also gave the pyrroles **4ga**–**ia** in good yields (entries 6–8). Given the mechanism proposed below, the low propensity for 1,2-hydride migration is a substantial advantage of the present nickel case.

Table 1. Transannulation of 4-Substituted 1-Sulfonyl-1,2,3-triazoles **1b**–**i** with Undeca-1,2-diene (**2a**)[a]



entry	1	R^1	R^3	4	yield (%)[b]
1	**1b**	4-MeO-C_6H_4	4-Tol	**4ba**	99
2	**1c**	4-CF_3-C_6H_4	4-Tol	**4ca**	86
3	**1d**	3-thienyl	4-Tol	**4da**	86
4	**1e**	Ph	4-MeO-C_6H_4	**4ea**	74
5	**1f**	Ph	4-F-C_6H_4	**4fa**	82
6	**1g**	*n*-Hex	4-Tol	**4ga**	82
7	**1h**	$(CH_2)_4OBz$	4-Tol	**4ha**	81[c]
8	**1i**	Cy	4-Tol	**4ia**	69[d]

[a] Conditions: **1** (0.20 mmol), **2a** (0.30 mmol), $Ni(cod)_2$ (10 mol %), and bdpp (10 mol %) in 1,4-dioxane (4 mL) at 80 °C for 4 h, then at rt for 5 min in the presence of TsOH (20 mol %) unless otherwise noted. [b] Isolated yields. [c] 6 h. [d] 8 h.

Next, the variation of allenes **2** was examined in the reaction of triazole **1a** (Table 2). Monosubstituted allenes **2b**–**f** having primary and secondary alkyl groups gave the corresponding pyrroles **4ab**–**af** in yields ranging from 83% to 90% (entries 1–5). In the case of *tert*-butyl-substituted allene **2g**, the double bond transposition was slow, probably due to steric reasons, to furnish the isopyrrole **3ag** in 87% isolated yield (entry 6). Phenyl-substituted allene **2h** gave the product **4ah** in 58% yield together with unidentified byproducts (entry 7).[13]

Although 1,3-disubstituted cyclic allene **2i** participated in the reaction to afford the pyrrole **4ai** in 57% yield (eq 4),

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(8) The following paper describing a rhodium(II)-catalyzed intramolecular transannulation reaction of 1-sulfonyl-1,2,3-triazoles with allenes recently appeared during preparation of this manuscript: Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696.

(9) Other bisphosphine ligands gave inferior results (NMR yield/%): dppm (0), dppe (0), and dppp (23). Although the bulky monophosphine ligand $[P(n\text{-}Bu)Ad_2]$ was the optimal ligand for the transannulation with alkynes,[6] it failed to effect the transannulation with allenes.

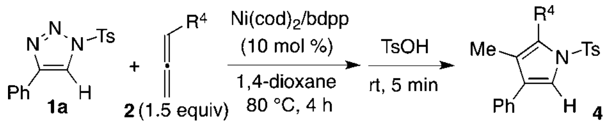
(10) Rhodium(II) catalysts gave inferior results for intermolecular transannulation. For example, **3aa** was not obtained with $Rh_2(OCO\textit{t}Bu)_4$ (1.0 mol %, 80 °C, 4 h, 1,2-dichloroethane).

(11) For the synthesis of isopyrroles, see: Larock, R. C.; Doty, M. J.; Han, X. *Tetrahedron Lett.* **1998**, *39*, 5143.

(12) For related Alder-ene reactions of isoindoles, see: Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797.

(13) Ethoxycarbonyl-substituted allene failed to participate in the transannulation reaction to give a complex mixture.

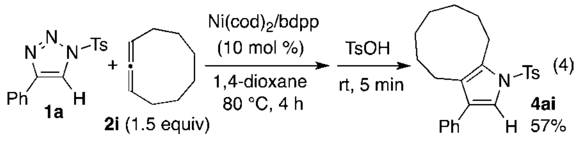
Table 2. Transannulation of 4-Phenyl-1-tosyl-1,2,3-triazole (**1a**) with Allenes **2b**–**h**[a]



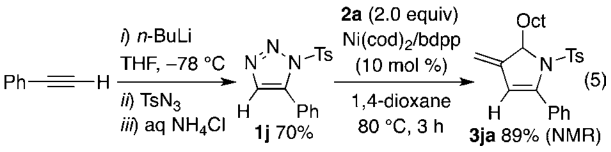
entry	2	R^4	4	yield (%)[b]
1	**2b**	Et	**4ab**	83[c]
2	**2c**	$(CH_2)_2Ph$	**4ac**	90
3	**2d**	$(CH_2)_4OBn$	**4ad**	89
4	**2e**	$(CH_2)_4OSi(t\text{-}Bu)Me_2$	**4ae**	86
5	**2f**	Cy	**4af**	88
6	**2g**	*t*-Bu	**3ag**	87
7	**2h**	Ph	**4ah**	58[d]

[a] The same reaction conditions as those in Table 1 unless otherwise noted. [b] Isolated yields. [c] Using 2.0 equiv of **2b**. [d] Using 3.0 equiv of **2h** and 20 mol % of $Ni(cod)_2$/bdpp for 5 h.

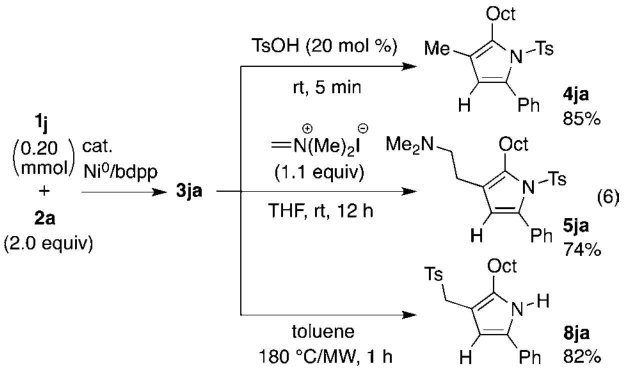
other disubstituted allenes such as penta-2,3-diene and 3-methylbuta-1,2-diene failed to participate in the transannulation reaction and a large amount of triazole **1a** was recovered. The disubstituted allenes were considerably less reactive, and the nickel catalyst deteriorated upon reaction with **1a**.



5-Phenyl-1-tosyl-1,2,3-triazole (**1j**) was prepared from phenylethyne and tosyl azide according to Croatt's procedure via lithium acetylides.[14] The transannulation reaction of **1j** with allene **2a** under the same reaction conditions produced 3-methylene-2,3-dihydropyrrole **3ja**.

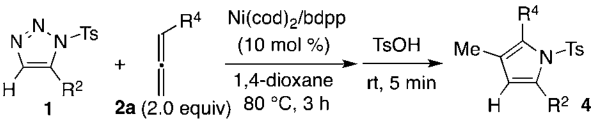


When *p*-toluenesulfonic acid was directly added to the crude mixture of **3ja**, octyl-5-phenyl-1-tosyl-pyrrole (**4ja**) was isolated in 85% yield (eq 6). The isopyrrole **3ja** was also reacted with Echenmoser's salt to produce the pyrrole **5ja** in 74% yield. Interestingly, the tosyl group on the nitrogen transferred onto the *exo*-methylene carbon upon heating **3ja** at 180 °C under microwave irradiation for 1 h, yielding *N*-H pyrrole **8ja** in 82%.[15]



Other 1,5-disubstituted triazoles **1k**–**n** were also prepared from the corresponding terminal alkynes and sulfonyl azides via lithium acetylides, and their transannulation reaction was also examined (Table 3). Substrates **1k**–**n** possessing aryl and alkyl groups at the 5-position afforded the corresponding products **4ka**–**na** in yields ranging from 68% to 80% (entries 1–4). As with the case of 1,4-disubstituted triazoles, various allenes **2** were successfully incorporated into the 1,5-disubstituted triazolyl skeleton of **1j** (entries 5–8). Thus, 2,3,5-trisubstituted pyrroles were selectively synthesized from terminal alkynes, tosyl azide, and allenes.

Table 3. Transannulation of 5-Substituted 1-Sulfonyl-1,2,3-triazoles **1j**–**n** with Various Allenes **2**[a]



entry	1	R^2	2	R^4	4	yield (%)[b]
1	**1k**	$4\text{-MeO-}C_6H_4$	**2a**	Oct	**4ka**	80
2	**1l**	$4\text{-}CF_3\text{-}C_6H_4$	**2a**	Oct	**4la**	71
3	**1m**	*n*-Hex	**2a**	Oct	**4ma**	68
4	**1n**	Cy	**2a**	Oct	**4na**	73
5	**1j**	Ph	**2b**	Et	**4jb**	77
6	**1j**	Ph	**2d**	$(CH_2)_4OBn$	**4jd**	85
7	**1j**	Ph	**2f**	Cy	**4jf**	71
8	**1j**	Ph	**2j**	$(CH_2)_3CN$	**4jj**	85[c]

[a] Conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Ni(cod)_2$ (10 mol %), and bdpp (10 mol %) in 1,4-dioxane (4 mL) at 80 °C for 3 h, then at rt for 5 min in the presence of TsOH (20 mol %). [b] Isolated yields. [c] TsOH (110 mol %).

It is generally difficult in organic reactions to discern different alkyl groups of similar electronic as well as steric characters. Therefore, regiocontrolled synthesis of pyrroles having multiple alkyl substituents presents a significant challenge.[2c] For example, the nickel(0)-catalyzed transannulation reaction of **1a** with pent-2-yne gave an almost 1:1 mixture of two isomeric pyrroles.[6,16] We applied the nickel(0)-catalyzed transannulation reaction with allenes to the synthesis of pyrrole having

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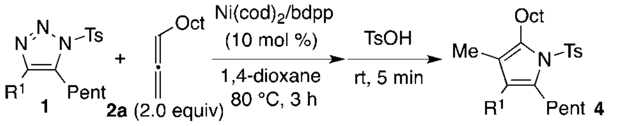
(14) Meza-Aviña, M. E.; Patel, M. K.; Lee, C. B.; Dietz, T. J.; Croatt, M. P. *Org. Lett.* **2011**, *13*, 2984.

(15) The tosyl group of isopyrrole **3aa** failed to transfer under the same reaction conditions. For a precedence of N- to C-transfer of a sulfonyl group with dihydropyridones, see: Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653.

(16) See the Supporting Information for more details.

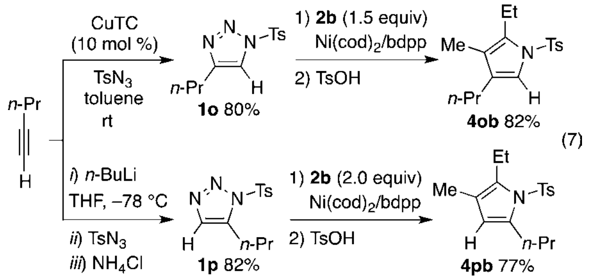
Table 4. Transannulation of 4-Substituted 5-Pentyl-1-tosyl-1,2,3-triazoles **1q**−**u** with Undeca-1,2-diene (**2a**)[a]



entry	1	R^1	4	yield (%)[b]
1	**1q**	Me	**4qa**	73
2	**1r**	Si(*t*-Bu)Me$_2$	**4ra**	78[c]
3	**1s**	C(O)*n*-Pr	**4sa**	90
4	**1t**	C(O)Ph	**4ta**	86
5	**1u**	CO$_2$Bn	**4ua**	99

[a] The same reaction conditions as those in Table 3 unless otherwise noted. [b] Isolated yields. [c] Adding 4.0 equiv of **2a** in two portions.

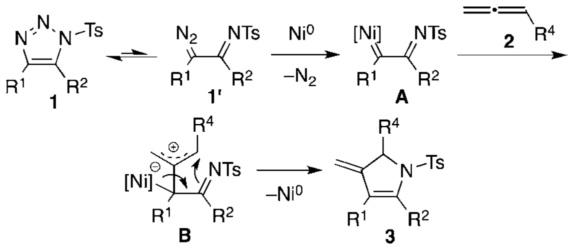
three different alkyl groups (eq 7). Thus, 1,4- and 1,5-disubstituted triazoles **1o** and **1p** were prepared starting from pent-1-yne, as mentioned above. Each of them was subjected to the transannulation reaction with pent-1,2-diene (**2b**). The following double bond transposition selectively furnished 2-ethyl-3-methyl-4-propyl-1-tosyl-pyrrole (**4ob**) and 2-ethyl-3-methyl-5-propyl-1-tosyl-pyrrole (**4pb**), respectively.



(7)

4,5-Disubstituted 1-sulfonyl-1,2,3-triazoles were also prepared according to Croatt's procedure.[14] The 1,3-dipolar cycloaddition reaction of a lithium acetylide with tosyl azide gave rise to a 4-lithiated triazole, which was then reacted with electrophiles such as methyl iodide, chlorosilane, and acid chlorides. The resulting 4-substituted 5-pentyl-1-tosyl-1,2,3-triazoles were reacted with **2a** under the standard reaction conditions (Table 4). Substrates **1q** and **1r** possessing methyl and silyl groups at the 4-position were smoothly transformed to the corresponding fully substituted pyrroles **4qa** and **4ra** (entries 1 and 2). In particular, substrates **1s**−**u** possessing a carbonyl group at the 4-position were highly reactive to quantitatively afford the pyrroles **4sa**−**ua**, probably due to the enhanced electrophilicity of the nickel carbene intermediate (entries 3−5).

Scheme 1. Plausible Mechanism for the Nickel(0)-Catalyzed Synthesis of Isopyrrole **3** from Triazole **1** and Allene **2**



A plausible mechanism for the production of isopyrrole **3** from triazole **1** and allene **2** is depicted in Scheme 1. First, a reversible ring−chain tautomerization of 1-sulfonyl-1,2,3-triazole **1** generates α-diazo imine **1′**.[17] The generated **1′** reacts with nickel(0) in an irreversible manner to afford α-imino nickel carbene **A** with extrusion of molecular nitrogen. Nucleophilic addition of allene **2** to the electrophilic carbene center of **A** occurs in preference to 1,2-hydride migration (*vide supra*) to furnish zwitterionic intermediate **B**. With the allyllic cation moiety of **B**, a more positive charge is distributed at the more substituted carbon. The anionic nickel of **B** releases an electron pair, which flows into the imine moiety to make the nitrogen atom nucleophilic enough to couple with the more substituted, and hence more positively charged, allylic carbon atom. Thus, the isopyrrole **3** is selectively formed.

In conclusion, we have reported a new synthetic pathway to polysubstituted pyrroles. Although it is difficult to synthesize them with position control of multiple substituents, the present protocol renders it possible to selectively synthesize isomeric pairs of polysubstituted pyrroles **4aa**/**4ja**, **4ba**/**4ka**, **4ab**/**4jb**, **4ob**/**4pb**, **5aa**/**5ja**, etc., in which the positions of the multiple substituents are different. It is also demonstrated that not only 1,4-disubstituted triazoles but also 1,5-disubstituted and 1,4,5-trisubstituted ones are easily accessible precursors of reactive α-imino carbene complexes.

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Supporting Information Available. Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) McKinney, M. A.; Patel, P. P. *J. Org. Chem.* **1973**, *38*, 4059.

The authors declare no competing financial interest.