An Easy One-Pot Synthesis of Tetrasubstituted 3-Alkynylpyrroles via Multicomponent Coupling Reaction

Xueming Chen,[a] Lei Hou,[b] Xingshu Li*[a]

[a] School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou, 51006, P. R. of China
Fax +86(20)39943050; E-mail: lixsh@mail.sysu.edu.cn

[b] MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou, 510275, P. R. of China

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Abstract: A series of tetrasubstituted 3-alkynylpyrroles were synthesized via a three-component reaction of imines, phenylacetylene, and dialkylzinc. This method provided a new strategy for preparing tetrasubstituted 3-alkynylpyrroles which can be converted into more complex molecules.

Key words: multicomponent reactions, pyrroles, tetrasubstituted 3-alkynylpyrroles

Multicomponent reactions (MCR), in which multiple reactants are combined into the end product, are powerful tools for the introduction of molecular diversity in an efficient, economic, and environmentally friendly way in the synthetic chemistry.[1] In the past decade, a great deal of success have been achieved in this field, and great efforts continue to be made to develop new MCR.[2]

Pyrrole, one of the most important heterocyclic compounds, and its derivatives have become increasingly important in medicinal chemistry and organic synthesis.[3] It has been widely used as antitumor,[4a] anti-inflammatory,[4b,c] antioxidants,[3c] antibacterial,[4d,e] ionotropic,[4f,g] antifungalagents,[4h] poly(ADP-ribose) polymerase inhibitors,[5a] P38kinase,[5b] prolyl-4-hydroxylase,[5c] estrogen receptor β-selective ligands,[5d] AT1-selective angiotensin II receptor antagonists,[5e] and minor groove recognition elements.[5f,g] Especially, 1,2,3,5-tetrasubstituted pyrrole derivatives (**I**, Figure 1) as antimycobacterial agents showed better activity than streptomycin and isoniazid.[6]

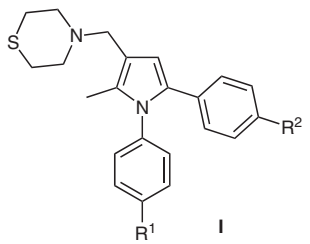
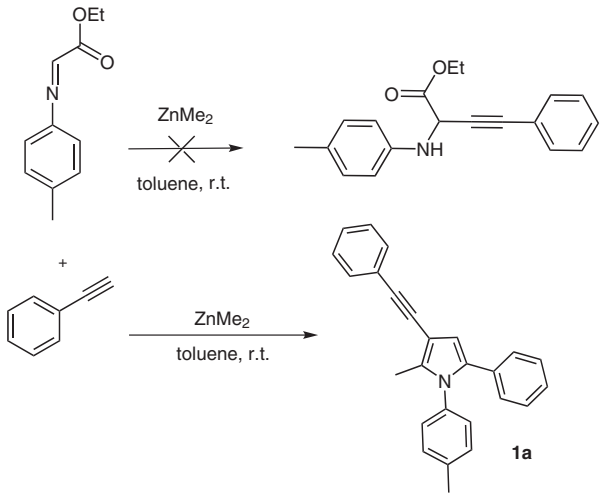


Figure 1

Because of their various usages, many procedures have been developed for the preparation of pyrrole and its derivatives. The classic methods for pyrroles synthesis are: (i) the Hantzsch reaction,[7] which provides pyrroles from the reaction of α-chloromethyl ketones with β-keto esters and ammonia; (ii) the Knorr reaction,[8] a method to prepare pyrroles by the reaction of α-aminoketones derived from α-haloketones with ammonia and β-keto esters; (iii) the Paal Knorr reaction,[9] the reaction of γ-diketone with primary amines (or ammonia) in the presence of various promoting agents.[10] Recently, other strategies including MCR[11] and transition-metal-catalyzed processes[12] have also been investigated.

Although a lot of methods for the synthesis of pyrroles have been reported, it is still challenging to prepare polysubstituted pyrroles with various substituents directly from readily available materials. To the best of our knowledge, there have been no reports for the preparation of tetrasubstituted 3-alkynylpyrroles by one-pot coupling reaction. Herein, we disclose the synthesis of these pyrrole derivatives via the one-pot reaction of imines, phenylacetylene, and dialkylzincs.

In our study of enantioselective addition of phenylacetylene to imines,[13] we found that the reaction of ethyl 2-(4-methylphenylimino)acetate with phenylacetylene in the presence of dimethylzinc did not give the normal propargylamines. Instead, it afforded a three-component coupling product, 1-(4-methylphenyl)-2-methyl-5-phenyl-3-(phenylethynyl)-1*H*-pyrrole (**1a**, Scheme 1) and its structure was confirmed by X-ray crystallographic analysis (Figure 2).[14]



Scheme 1 Synthesis of tetrasubstituted 3-alkynylpyrrole

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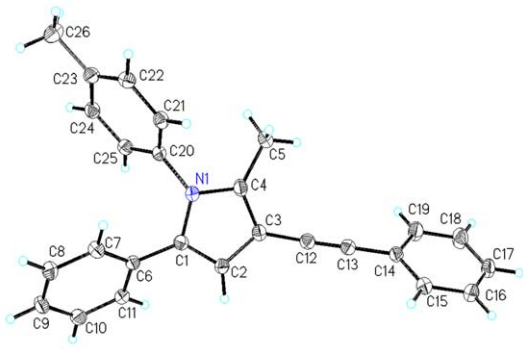
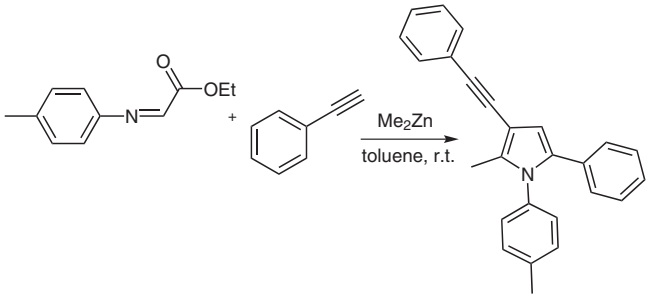


Figure 2 ORTEP drawing of compound **1a** at 50% probability

The possible mechanism for the three-component coupling reaction is shown in Scheme 2. First, reaction of imine **1** with dimethylzinc gave the amino acid derivative **2**. In the presence of excessive dimethylzinc, intermediate **2** then reacted with phenylacetylene to form a tertiary alcohol **3**, similar to the reaction of aliphatic esters with alkynyl lithium.[15] Finally, the intramolecular cyclization of **3** and subsequently dehydration led to the target product **1a**.

Some other reaction parameters such as the choice of solvent, equivalents of phenylacetylene, and dimethylzinc were examined, and the results are summarized in Table 1. The equivalents of phenylacetylene and dimethylzinc were rather significant for the yields of the reaction. The best result was obtained when the imine was treated with six equivalents of phenylacetylene and dimethylzinc at room temperature (Table 1, entry 4). However, when the temperature was decreased to 0 °C, only trace products were obtained (Table 1, entry 6). Other solvents, such as dichloromethane and tetrahydrofuran were also screened for the reaction, 53% yield was obtained in dichloromethane but very low yield was obtained in THF as the solvent (Table 1, entries 7 and 8).

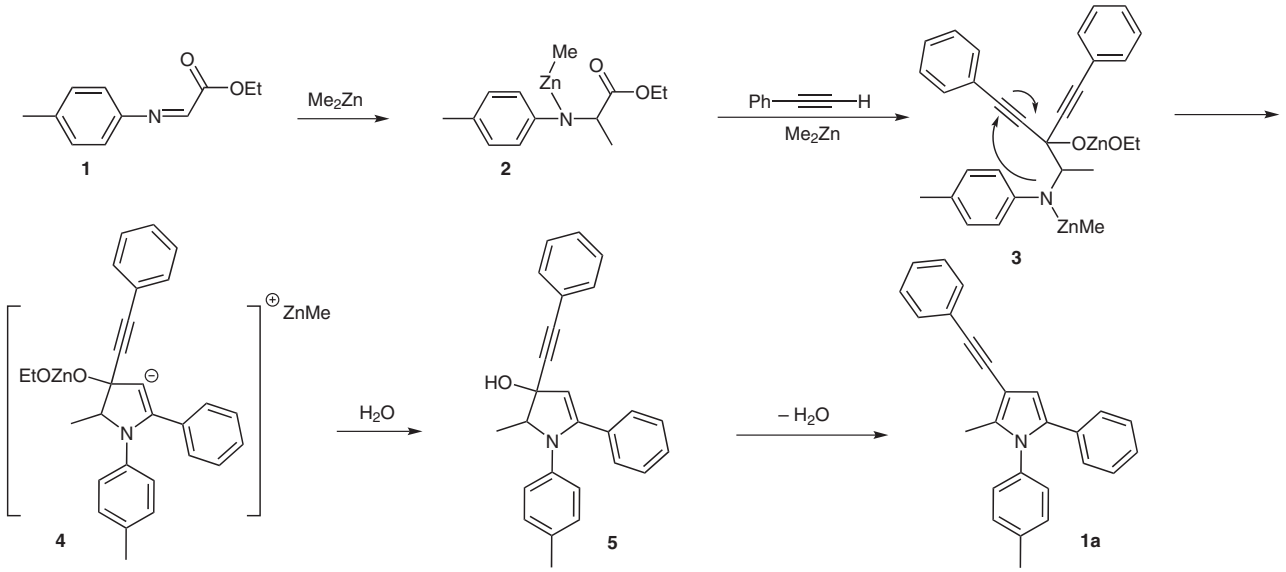
Table 1 One-Pot Syntheses of Tetrasubstituted 3-Alkynylpyrroles in Various Reaction Conditions



Entry	Solvent	Phenylacetylene (equiv)	$ZnMe_2$ (equiv)	Yield (%)[a]
1	toluene	2	3	20
2	toluene	3	3	37
3	toluene	5	5	46
4	toluene	6	6	67
5	toluene	6	7	61
6	toluene	6	6	trace (0 °C)
7	CH_2Cl_2	6	6	53
8	THF	6	6	5

[a] Isolated yield.

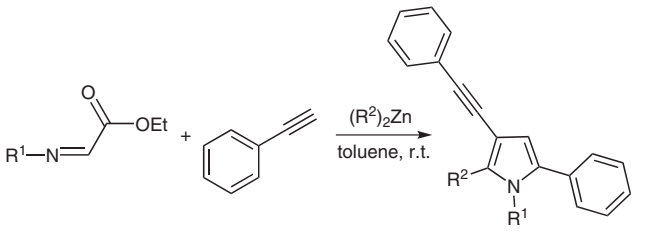
In order to extend the scope of this reaction to the synthesis of important tetrasubstituted 3-alkynylpyrroles, other imines and diethylzinc were tested under the established optimal reaction conditions.[16] The results shown in Table 2 indicated that imines with substituted groups at the *para* position of the phenyl ring were favorable for the reaction (51–67% yields were obtained, Table 2, entries 1–6). However, imines derived from aniline or 3-methyl



Scheme 2 Possible mechanism for the formation of tetrasubstituted 3-alkynylpyrroles

aniline gave relatively lower yields (Table 2, entries 7–10, 35–46% yield). Furthermore, *ortho*-substituted imines and the imine derived from 3-chloride aniline did not give the corresponding products (Table 2, entries 11 and 12).

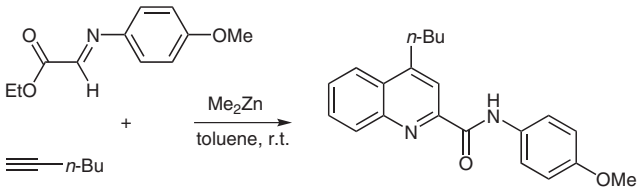
Table 2 One-Pot syntheses of Tetrasubstituted 3-Alkynylpyrroles[a]



Entry	R^1	R^2	Product	Yield (%)[b]
1	4-MeC_6H_4	Me	**1a**	67
2	4-MeC_6H_4	Et	**1b**	56
3	4-$MeOC_6H_4$	Me	**2a**	60
4	4-$MeOC_6H_4$	Et	**2b**	54
5	4-ClC_6H_4	Me	**3a**	55
6	4-ClC_6H_4	Et	**3b**	51
7	Ph	Me	**4a**	46
8	Ph	Et	**4b**	40
9	3-MeC_6H_4	Me	**5a**	37
10	3-MeC_6H_4	Et	**5b**	35
11	3-ClC_6H_4	Me	**5a**	–
12	2-ClC_6H_4	Me	**6a**	–

[a] Imine (1.0 mmol), phenylacetylene (6 mmol), and ZnR_2 (6 mmol).
[b] Isolated yield.

Aliphatic alkyne such as hex-1-yne was also investigated for the domino reaction of imines, alkyne, and dialkylzinc. It is very interesting that quinoline derivative was obtained under the same reaction conditions (Scheme 3) and the result showed that it reacted through a different pathway. Further study for the interpretation of proposed mechanism are under way.



Scheme 3 Reaction of imines, alkyne, and dialkylzinc

The one-pot four-component reaction of amine, ethyl glyoxylate, phenylacetylene, and dimethylzinc was also carried out (Scheme 4) and the result showed that it was possible to perform the reaction in such a procedure. However, it was obviously that the reaction of three-component was favorable for rising the yields.

In conclusion, a series of tetrasubstituted 3-alkynylpyrroles were synthesized via a three-component reaction of imines, phenylacetylene, and dialkylzinc. This work represents a very simple method to generate these useful tetrasubstituted 3-alkynylpyrroles. Further studies on the biological activities of these compounds are under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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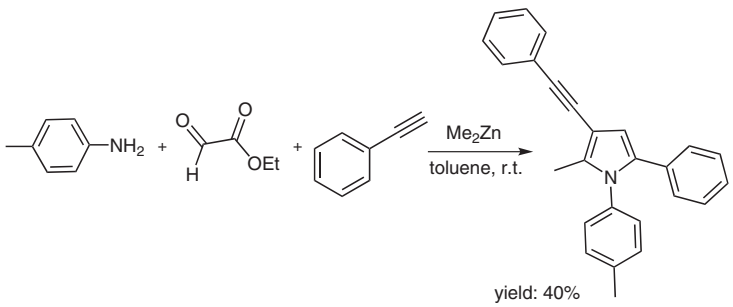
References and Notes

(1) (a) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (c) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (e) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471. (f) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (g) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (h) Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

(2) (a) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427. (b) List, B.; Castello, C. *Synlett* **2001**, 1687. (c) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestiopolov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans,



Scheme 4 One-pot, four-component reaction of amine, ethyl glyoxylate, phenylacetylene, and dimethylzinc

D. H. *Org. Lett.* **2002**, *4*, 423. (d) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147. (e) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309. (f) Cheng, J. F.; Chen, M.; Arthenius, T.; Nadzen, A. *Tetrahedron Lett.* **2002**, *43*, 6293. (g) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485. (h) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435. (i) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. (j) Barluenga, J.; Perez-Sanchez, I.; Swero, M. G.; Ruhio, E.; Florez, J. *Chem. Eur. J.* **2006**, *12*, 7225. (k) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. (l) Crich, D.; Bowers, A. *Org. Lett.* **2007**, *9*, 5323. (m) Guo, S. H.; Liu, Y. H. *Org. Biomol. Chem.* **2008**, *6*, 2064.

(3) (a) Hayakawa, Y.; Kawasaki, K.; Seto, H. *Tetrahedron Lett.* **1992**, *33*, 2701. (b) Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuner, P. *Helv. Chim. Acta* **1992**, *75*, 1721. (c) Lehuedu, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, 991. (d) Dong, Y.; Naranjan, N.; Ablaza, S. L.; Yu, S. X.; Bolvig, S.; Forsyth, D. A.; Le Quesne, P. W. *J. Org. Chem.* **1999**, *64*, 2657. (e) Arrowsmith, J.; Jennings, S. A.; Clark, A. S.; Stevens, M. F. G. *J. Med. Chem.* **2002**, *45*, 5458. (f) Haubmann, C.; Huebner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3143. (g) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389. (h) Jones, A. *Pyrroles*; Wiley: New York, **1990**.

(4) (a) Denny, W. A.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1990**, *33*, 814. (b) Toja, E.; Selva, D.; Schiatti, P. *J. Med. Chem.* **1984**, *27*, 610. (c) Demopoulos, V. J.; Rekka, E. *J. Pharm. Sci.* **1995**, *84*, 79. (d) Burli, R. W.; McMinn, D.; Kaizerman, J. A.; Hu, W.; Ge, Y.; Pack, Q.; Jiang, V.; Gross, M.; Garcia, M.; Tanaka, R.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1253. (e) Burli, R. W.; Jones, P.; McMinn, D.; Le, Q.; Duan, J.-X.; Kaizerman, J. A.; Difuntorum, S.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1259. (f) Jonas, R.; Klockow, M.; Lues, I.; Pruecher, H.; Schliep, H. J.; Wurziger, H. *Eur. J. Med. Chem.* **1993**, 129. (g) Von der Saal, W.; Hoelck, J.-P.; Kampe, W.; Mertens, A.; Mueller-Beckmann, B. *J. Med. Chem.* **1989**, *32*, 1481. (h) Del Poeta, M.; Schell, W. A.; Dykstra, C. C.; Jones, S.; Tidwell, R. R.; Czarny, A.; Bajic, M.; Bajic, M.; Kumar, A.; Boykin, D.; Perfect, J. R. *Antimicrob. Agents Chemother.* **1998**, *42*, 2495.

(5) (a) Ferraris, D.; Ficco, R. P.; Dain, D.; Ginski, M.; Lautar, S.; Lee-Wisdom, K.; Liang, S.; Lin, Q.; Lu, M. X.-C.; Morgan, L.; Thomas, B.; Williams, L. R.; Zhang, J.; Zhou, Y.; Kalish, V. J. *Bioorg. Med. Chem.* **2003**, *11*, 3695. (b) DeLaszlo, S. E.; Visco, D.; Agarwal, L.; Chang, L.; Chin, J.; Croft, G.; Forsyth, A.; Fletcher, D.; Frantz, B.; Hacker, C.; Hanlon, W.; Harper, C.; Kostura, M.; Li, B.; Luell, S.; MacCoss, M.; Mantlo, N.; O'Neill, E. A.; Orevillo, C.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Sidler, K.; Widmer, W. R.; OKeefe, S. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2689. (c) Dowell, R. I.; Hales, N. H.; Tucker, H. *Eur. J. Med. Chem.* **1993**, 513. (d) Chesworth, R.; Wessel, M. D.; Heyden, L.; Mangano, F. M.; Zawistoski, M.; Gegnas, L.; Galluzzo, D.; Lefker, B.; Cameron, K. O.; Tickner, J.; Lu, B.; Castleberry, T. A.; Petersen, D. N.; Brault, A.; Perry, P.; Ng, O.; Owen, T. A.; Pan, L.; Ke, H.-Z.; Brown, T. A.; Thompson, D. D.; DaSilva-Jardine, P. *Bioorg. Med. Chem. Lett.* **2005**, *24*, 5562. (e) Bovy, P. R.; Reitz, D. B.; Collins, J. T.; Chamberlain, T. S.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Koepke, J. P.; Smits, G. J.; McGraw, D. E.; Gaw, J. F. *J. Med. Chem.* **1993**, *36*, 101. (f) Renneberg, D.; Dervan, P. B. *J. Am. Chem. Soc.* **2003**, *125*, 5707. (g) Marques, M. A.; Doss, R. M.; Foister, S.; Dervan, P. B. *J. Am. Chem. Soc.* **2004**, *126*, 10339.

(6) (a) Biava, M.; Fioravanti, R.; Porretta, G. C.; Deidda, D.; Maullu, C.; Pompei, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2983. (b) Ragno, R.; Marshall, G. R.; DiSanto, R.; Costi, R.; Massa, S.; Pompei, R.; Artico, M. *Bioorg. Med. Chem.* **2000**, *8*, 1423. (c) Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafi, A.; Manetti, F. *Bioorg. Med. Chem.* **2003**, *11*, 515. (d) Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafi, A.; Manetti, F. *Bioorg. Med. Chem.* **2004**, *12*, 1453. (e) Biava, M.; Porretta, G. C.; Poce, G.; Deidda, D.; Pompei, R.; Tafi, A.; Manetti, F. *Bioorg. Med. Chem.* **2005**, *13*, 1221. (f) Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Molicotti, P.; Manetti, F.; Botta, M. *J. Med. Chem.* **2006**, *49*, 4946. (g) Biava, M.; Porretta, G. C.; Manetti, F. *Mini-Rev. Med. Chem.* **2007**, *7*, 65. (h) Biava, M.; Porretta, G. C.; Poce, G.; Logu, A. D.; Saddi, M.; Meleddu, R.; Manetti, F.; Rossi, E. D.; Botta, M. *J. Med. Chem.* **2008**, *51*, 3644.

(7) (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474. (b) van Beelen, D. C.; Wolters, J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 437. (c) Trautwein, A. W.; SuSmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381. (d) FerreiraV, F.; DeSouza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2002**, *33*, 411.

(8) (a) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635. (b) Kleinspehn, G. G. *J. Am. Chem. Soc.* **1955**, *77*, 1546. (c) Fabiano, E.; Golding, B. T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3371. (d) Hamby, J. M.; Hodges, J. C. *Heterocycles* **1993**, *35*, 843. (e) Alberola, A.; Ortega, A. G.; Sadaba, M. L.; Sanudo, C. *Tetrahedron* **1999**, *55*, 6555. (f) Elghamry, I. *Synth. Commun.* **2002**, *32*, 897.

(9) (a) Paal, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367. (b) Jones, R. A.; Been, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, **1977**, Chap. 3. (c) Chiu, P. K.; Lui, K. H.; Maini, P. N.; Sammes, M. P. *J. Chem. Soc., Chem. Commun.* **1987**, 109. (d) Chiu, P. K.; Sammes, M. P. *Tetrahedron* **1990**, *46*, 3439.

(10) (a) Yu, S. X.; Quesne, P. W. L. *Tetrahedron Lett.* **1995**, *36*, 6205. (b) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 5873. (c) Braun, R. U.; Zeitler, K.; Mueller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (d) Curini, M.; Montanari, F.; Rosati, O.; Lioy, E.; Margarita, R. *Tetrahedron Lett.* **2003**, *44*, 3923. (e) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213. (f) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. (g) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (h) Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. *Synlett* **2000**, 391. (i) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389. (j) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (k) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. *Tetrahedron Lett.* **2005**, *46*, 2643. (l) Raghavan, S.; Anuradha, K. *Synlett* **2003**, 711. (m) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, Z. *Synlett* **2003**, 75. (n) Wang, B.; Kang, Y. R.; Yang, T.; Yang, L. M. *Synth. Commun.* **2005**, *35*, 1051. (o) Wang, B.; Gu, Y. L.; Luo, C.; Yang, T.; Yang, L. M.; Suo, J. S. *Tetrahedron Lett.* **2004**, *45*, 3417; and references therein.

(11) (a) Lu, Y. D.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 1. (b) Cho, S. H.; Chang, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 2836. (c) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Divyavani, C.; Basha, S. J.; Sarma Akella, V. S. *J. Org. Chem.* **2008**, *73*, 3252. (d) St, C. y. r. D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (e) Scheidt, K. A.; Galliford, C. V. *J. Org. Chem.* **2007**, *72*, 1811. (f) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. (g) Scheidt, K. A.; Bharadwaj, A. R. *Org. Lett.* **2004**, *14*, 2465. (h) Arndtsen, B. A.; Dhawan, R. *J. Am. Chem. Soc.* **2004**, *126*, 468. (i) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427.

(12) (a) Buchwald, S. L.; Martin, R.; Larsen, C. H.; Cuenca, A. *Org. Lett.* **2007**, *9*, 3379. (b) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (c) Liu, R. S.; Li, C. W.; Shen, H. C. *Tetrahedron Lett.* **2004**, *45*, 9245. (d) Odom, A. L.; Armstrong, D.; Keith, A. J.; Ramanathan, B. *Org. Lett.* **2004**, *17*, 2957. (e) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (f) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1399. (g) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873.

(13) (a) Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 396. (b) Liu, B.; Liu, J.; Jia, X.; Huang, L.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 1124. (c) Liu, B.; Huang, L.; Liu, J.; Zhong, Y.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 2901.

(14) The CCDC number: 706290.

(15) Humptman, H.; Mader, M. *Synthesis* **1978**, 307.

(16) **General Procedure for the Preparation of Imines**

To a round-bottomed flask containing the amine (10 mmol) in toluene (20 mL) was added anhyd Na_2SO_4 (50 mmol). The mixture was stirred, and then ethyl glyoxalate (12 mmol) was added slowly. After the reaction was completed (about 1 h, monitored by TLC), Na_2SO_4 was removed by filtration, and toluene was distilled under reduced pressure to yield the crude imine (95% yield), which was used for the next step without purification.

General Procedure for the Preparation of Pyrrole Derivatives

To a flask containing phenylacetylene (6 mmol), a 1.2 M solution of Me_2Zn in toluene (6 mmol) was added at r.t. The resulting solution was stirred for 1 h, and then the imine (1 mmol) in toluene (1 mL) was added at the same temperature. The reaction mixture was stirred for 5 h. After the reaction was completed (monitored by TLC), it was quenched by addition of H_2O (5 mL). The mixture was diluted with Et_2O, stirred for 5 min, and then filtered through Celite. The collected filtrate was separated, and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (eluent: EtOAc–PE, 1:50) to afford the desired pyrrole products.

2-Methyl-5-phenyl-3-(phenylethynyl)-1-*p*-tolyl-1*H*-pyrrole (1a)

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.43 (s, 3 H), 6.60 (s, 1 H), 7.07–7.10 (d, 2 H), 7.16–7.19 (m, 7 H), 7.32–7.41 (m, 3 H), 7.57–7.60 (d, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.75, 21.63, 85.48, 90.72, 103.35, 111.27, 124.78, 126.47, 127.56, 128.28, 128.50, 130.02, 131.47, 132.93, 134.07, 136.40, 136.51, 137.97. HRMS: *m/z* calcd for $C_{26}H_{21}N$ [M^+]: 347.1679; found: 347.1680.