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The Synthesis of Multisubstituted Pyrroles via a Copper-Catalyzed Tandem Three-Component Reaction

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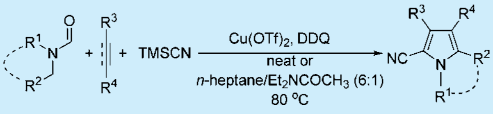
Supporting Information

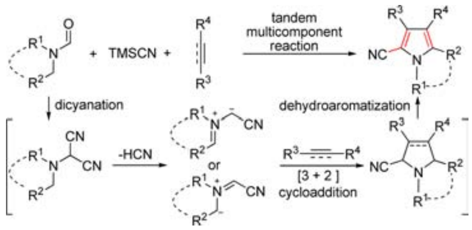


ABSTRACT: An unprecedented nucleophilic addition/cyclization/aromatization cascade of basic chemicals, i.e., aromatic alkenes/alkynes, trimethylsilyl cyanide and *N,N*-disubstituted formamide, has been developed to give a series of multisubstituted pyrroles in moderate to good yields with high regioselectivities. This reaction not only reveals a new reaction mode for α-aminonitriles, but also provides a new and efficient cyclization pattern for the synthesis of multisubstituted pyrroles as well as their derivatives, which might facilitate related biological studies.

Pyrrole,[1] as one of the most important heterocycles, broadly exists in natural products, bioactive molecules, therapeutic agents, agrochemicals, synthetic intermediates, and functional materials.[2] Therefore, since its first isolation from the products of bone pyrolysis in 1857, pyrrole has become one of the most prevalent structural moieties used by chemists for new functional molecule development, stimulating chemists' continuous efforts to develop synthetic methodologies toward the construction of such a structural unit. Except for the classical methods such as Hantzsch pyrrole synthesis and Knorr pyrrole synthesis, a number of efficient synthetic methodologies have been documented in recent years under the promotion of transition metal catalysis.[3,4] Moreover, tremendous multicomponent tandem synthesis methods for pyrrole derivatives have been developed for the pursuit of "ideal synthesis".[5,6] Strategically, most of the reported methods fall into reaction modes such as [4 + 1] cyclization, [3 + 2] cyclization, and self-cyclization of amine derivatives. Despite the above achievements, it is also true that there is a lack of related methods using very basic chemicals,[7] which would very likely be more atom-economical and environmentally benign. Therefore, it is still highly desirable to further explore this topic.

α-Aminonitriles are a special class of versatile synthetic intermediates that can lead to different reaction intermediates under proper conditions.[8] According to the structural features of these compounds and our interest in the construction of the pyrrole skeleton,[9] we envisaged that if a dehydrocyanation of this type of intermediate generated in situ could occur, a subsequent [3 + 2] cycloaddition of the resulting azomethine ylide[10] with a proper dipolarophile followed by an oxidation might be possible to afford multisubstituted pyrroles with a cyano group at the 2-position (Scheme 1). Accordingly, such a tandem process, once feasible, would not only provide a new reaction mode of α-aminonitriles but also lead to a new and efficient cyclization pattern for the synthesis of corresponding pyrrole compounds, whose key structural unit widely exists in many bioactive molecules (Figure 1).[11] Herein we present our results on the copper-catalyzed tandem multicomponent reaction of aromatic alkenes/alkynes with TMSCN and *N,N*-disubstituted formamide for the synthesis of multisubstituted pyrroles.

Scheme 1. Proposed Tandem Process To Afford Multisubstituted Pyrroles



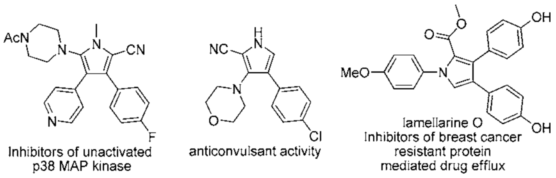


Figure 1. Selected bioactive multisubstituted pyrrole compounds.

Following the initial hypothesis, we first investigated the feasibility of the multicomponent reaction with styrene, TMSCN, and DMF as the model substrates in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1 equiv) and $Cu(OTf)_2$ (0.1 equiv) at 80 °C, but no desired product **3a** was detected (Table 1, entry 1). In contrast, **3a** could be obtained as the sole product in a yield of 26% simply by reducing the amount of DDQ to 0.2 equiv (entry 2). On the basis of the above results, adding DDQ through a batchwise mode (0.1 equiv/h for 10 times) was attempted, which afforded

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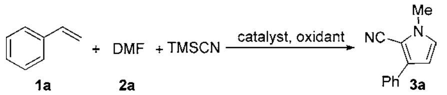
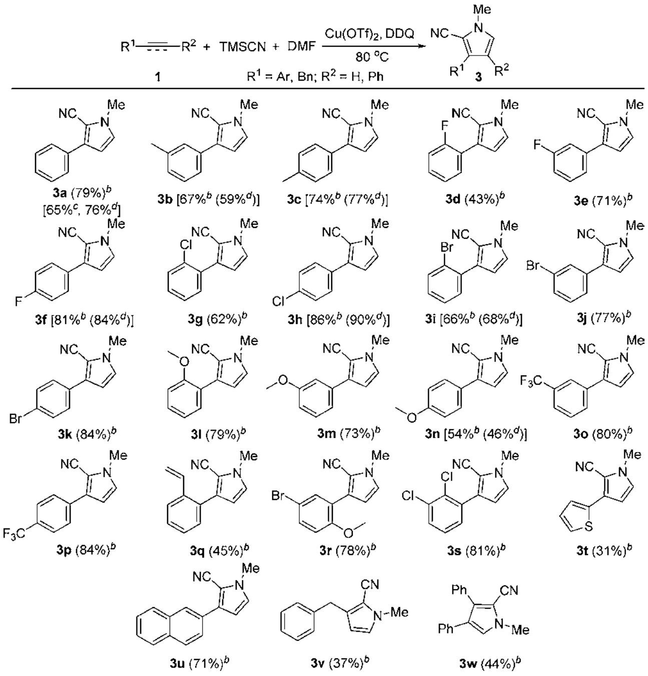
Table 1. Optimization of the Tandem Reaction Conditions[a]



entry	oxidant (equiv)	catalyst (mol %)	T (°C)	t (h)	yield[b] (%)
1	DDQ (1)	Cu(OTf)$_2$ (10)	80	24	n.d.[c]
2	DDQ (0.2)	Cu(OTf)$_2$ (10)	80	24	26
3	DDQ (1)[d]	Cu(OTf)$_2$ (10)	80	24	54
4	DDQ (2)[e]	Cu(OTf)$_2$ (10)	80	24	72
5	DDQ (2)[f]	Cu(OTf)$_2$ (10)	80	24	72
6	DDQ (2)[f]	Cu(OTf)$_2$ (15)	80	24	74
7	DDQ (2)[f]	Cu(OTf)$_2$ (20)	80	24	79
8	air	Cu(OTf)$_2$ (20)	80	24	8

[a] Reaction conditions: styrene (0.5 mmol), TMSCN (5 equiv), DMF (15 equiv), catalyst, and oxidant under Ar, unless otherwise noted. [b] Isolated yields. [c] n.d. = not detected. [d] DDQ was added at 0.1 equiv/h for 10 times. [e] DDQ was added at 0.2 equiv/2 h for 10 times. [f] The first equivalent of oxidant was added at 0.2 equiv/2 h for five times, and the second equivalent of oxidant was then added all at once.

Scheme 2. Evaluation of the Substrate Scope with Different Alkenes[a]



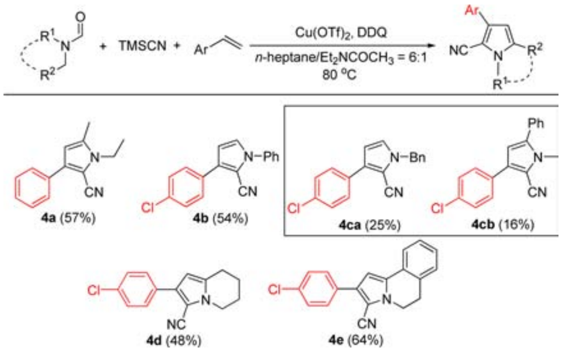
[a] Reaction conditions: aromatic olefin/alkyne (0.5 mmol), TMSCN (5 equiv), Cu(OTf)$_2$ (0.2 equiv), DDQ (2 equiv), and DMF (15 equiv) at 80 °C under Ar for 24 h. [b] Yield of the corresponding alkene. [c] 10 mmol of styrene was used. [d] Yield with the corresponding alkyne.

the product **3a** in a better yield of 54% (entry 3). Furthermore, the yield of **3a** could be improved to 72% with the use of 2 equiv of DDQ (0.2 equiv/2 h for 10 times), and a similar yield was obtained with a simpler adding mode, that is, the second equivalent of DDQ was introduced all at once after the first equivalent (0.2 equiv/2 h) was added (entries 4 and 5). Much lower yields were observed in the presence of other Lewis acid catalysts and oxidants under the same conditions.[12] The reaction was also performed with different amounts of catalyst, and it was found that increasing the amount of Cu(OTf)$_2$ to 0.2 equiv gave compound **3a** in the highest yield (79%; entry 7). Next, the influence of the reaction temperature, reaction time, and amount of DMF were evaluated,[12] but none of the other conditions gave a better yield than those of entry 7, which were used as the optimal reaction conditions. It should be noted that although the reaction could be conducted under air without oxidant, a much lower yield of 8% was obtained (entry 8).

With the optimized reaction conditions in hand (Table 1, entry 7), we subsequently investigated the generality of this tandem reaction. As shown in Scheme 2, a series of vinylbenzenes with electron-donating, -neutral, or -withdrawing groups were subjected to this transformation with TMSCN and DMF, and they all reacted smoothly to give the corresponding products in moderate to good yields, with 1-chloro-4-vinylbenzene giving the product 1-methyl-2-cyano-3-(4-chlorophenyl)pyrrole (**3h**) in the highest yield of 86%. In particular, all of the halogen substituents of the related substrates were untouched, which might provide additional sites for further derivatization. Additionally, subjection of 1,2-divinylbenzene to this transformation selectively afforded the product **3q**, in which one vinyl group was intact. This might also endow **3q** with the possibility for further transformation. Among the monosubstituted vinylbenzenes tested, when the substituent was an electron-neutral or -withdrawing group, the position of the substituent obviously affected the yield of the corresponding product. In general, substrates with a substituent at the *meta* or *para* position always gave higher yields than those with a substituent at the *ortho* position. In the case of the methoxy substituent, totally different results were observed, that is, the presence of methoxy group at the *ortho* position afforded a higher yield than the other two substrates (**3l** vs **3m** and **3n**). Additionally, the reaction was also well applicable to disubstituted vinylbenzenes. For example, 4-bromo-1-methoxy-2-vinylbenzene and 1,2-dichloro-3-vinylbenzene gave products **3r** and **3s** in 78% and 81% yield, respectively. Other than the styrene-type substrates above, some other aryl alkenes were also subjected to this reaction. Among them, 2-vinylthiophene and 2-vinylnaphthalene gave the desired products **3t** and **3u** in 31% and 71% yield, respectively, and allylbenzene was also amenable to the tandem reaction, affording the desired product **3v** in 37% yield. Since the rapid construction of more diverse polysubstituted pyrroles with such a transformation is highly desirable, one 1,2-disubstituted aromatic olefin, (*E*)-1,2-diphenylethene, was tested for this reaction. Fortunately, the desired product **3w** was obtained successfully in a yield of 44%. In order to demonstrate the practicality of this tandem reaction, a gram-scale reaction of styrene was carried out, affording the product **3a** in a yield of 65%, and the derivatization of product **3h** was also attempted.[12] Encouraged by the above results, we next tested the feasibility of applying aromatic alkynes in this transformation. When ethynylbenzene was subjected to this reaction under the optimized conditions, the expected product **3a** was obtained in a yield of 76%. To show its generality, six typical monosubstituted ethynylbenzenes were tested with this reaction. They all went through this tandem transformation well to afford the desired products in similar yields and reaction rates as those with the corresponding vinylbenzenes. However, it should be noted that the use of 2-vinylpyridine, 2-vinylfuran, 1-hexene, 1*H*-indene, 1,2-dihydronaphthalene, (*E*)-4-styrylbenzonitrile, (*E*)-1-methoxy-4-styrylbenzene, and 1,2-diphenylethyne did not afford the expected products.

To further test the generality of this tandem reaction, a series of *N*,*N*-disubstituted formamides were also investigated (Scheme 3). Different from the above results using relatively

Scheme 3. Evaluation of the Substrate Scope with Different *N*,*N*-Disubstituted Formamides[a]

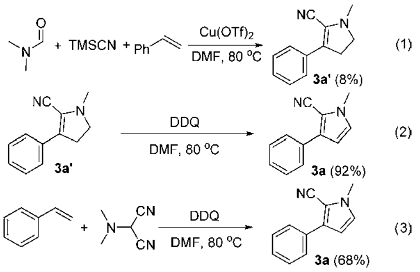


[a] Reaction conditions: aromatic olefin (0.5 mmol), *N*,*N*-disubstituted formamide (3 equiv), TMSCN (6 equiv), Cu(OTf)$_2$ (0.2 equiv), and DDQ (2 equiv) in *n*-heptane/Et$_2$NCOCH$_3$ (6:1 v/v) (1 mL) at 80 °C under Ar for 24 h.

inexpensive DMF as the substrate, screening of an appropriate solvent system was necessary for these transformations. On the basis of the previous results,[13] a combination of *n*-heptane and *N*,*N*-diethylacetamide (6:1 v/v) (1 mL) was selected as the optimal choice for the subsequent investigation.[12] As shown in Scheme 3, a series of *N*,*N*-disubstituted acyclic/cyclic formamides were subjected to the reaction with TMSCN and styrene or 1-chloro-4-vinylbenzene under the optimized conditions, and all of them afforded the expected products in moderate yields, which is acceptable as there might be more than three transformations involved in the tandem process. In the case of acyclic substrates, i.e., *N*,*N*-diethylformamide and *N*-methyl-*N*-phenylformamide, the desired products **4a** and **4b** were obtained in 57% and 54% yield, respectively. Since there are two possible reaction sites with *N*-benzyl-*N*-methylformamide, the corresponding reaction afforded two products, **4ca** and **4cb**, in 25% and 16% yield, respectively. The presence of a benzyl group in **4ca** could allow subsequent modification at the pyrrole nitrogen atom. With respect to cyclic formamides, piperidine-1-carbaldehyde and 3,4-dihydroisoquinoline-2(1*H*)-carbaldehyde both reacted smoothly to give the desired products **4d** and **4e** in moderate yields, which may simplify the synthesis of fused pyrroles. Furthermore, the structure of **4e** was unambiguously confirmed by X-ray diffraction crystal structure analysis (CCDC 1471974).[12] It should be pointed out that some other amides, including *N*-methylformamide, formamide, and *N*,*N*-dimethylacetamide, which have been proved to be inefficient during the dicyanation process,[13] could not afford the expected products,[12] indicating that the dicyanation step is a prerequisite for this tandem reaction.

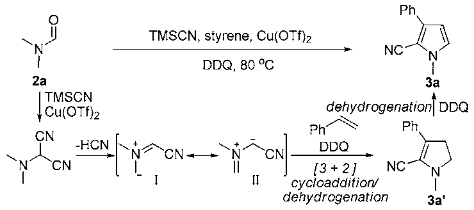
In order to better understand the tandem reaction process, some control experiments were carried out. First, when the reaction was performed in the absence of DDQ at 80 °C for 12 h, intermediate **3a′** was isolated in a yield of 8% (Scheme 4, eq 1). Intermediate **3a′** could be transformed to product **3a** in 92% yield in the presence of DDQ (Scheme 4, eq 2). Furthermore, intermediate **3a′** was also observed in the reaction of styrene and 2-(dimethylamino)malononitrile (53% yield from DMF[13]), which also afforded the desired product **3a** in 68% yield (Scheme 4, eq 3). These results support not only that the tandem process likely goes through the intermediate 2-(dimethylamino)malononitrile and dihydropyrrole **3a′** but also our original design of such a reaction mode.

Scheme 4. Preliminary Mechanistic Studies



On the basis of the above experimental results, a plausible pathway is proposed using substrate **2a** as an example (Scheme 5). First, in the presence of Cu(OTf)$_2$, copper-catalyzed dicyanation of DMF could afford 2-(dimethylamino)-malononitrile, which would give the azomethine ylide after release of HCN. Subsequent regioselective [3 + 2] cycloaddition between energetically favorable azomethine ylide **II** and styrene followed by in situ dehydrogenation would afford intermediate **3a′**. Finally, further oxidative aromatization of intermediate **3a′** would give the final product **3a**.

Scheme 5. Plausible Reaction Pathway



In summary, a novel tandem reaction involving copper-catalyzed dicyanation/azomethine formation/1,3-dipolar cycloaddition/dehydrogenative aromatization has been successfully developed.[14] Through the use of this methodology, a series of multisubstituted pyrrole derivatives were obtained from readily accessible starting materials, i.e., *N*,*N*-disubstituted formamides, TMSCN, and aromatic olefins or alkynes, in moderate to good yields. As a beneficial complement to the construction of the pyrrole ring from formamides,[15] this method features much simpler starting formamides and reaction procedure. The method might provide a rapid and versatile route for the synthesis of polysubstituted pyrroles with a high degree of chemical and structural complexity and diversity, which would facilitate the screening of potential active compounds in related studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01883.

Full experimental details (PDF)
Crystallographic data for **4e** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (b) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, *2007*, 3095. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264.

(2) (a) Gossauer, A. In *Houben-Weyl—Methods of Organic Chemistry*; Thieme: Stuttgart, Germany, 1994; p 556. (b) Tamao, K.; Ohno, S.; Yamaguchi, S. *Chem. Commun.* **1996**, 1873. (c) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (d) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (e) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587. (f) Sayah, B.; Pelloux-Léon, N.; Vallée, Y. *J. Org. Chem.* **2000**, *65*, 2824. (g) Domingo, V. M.; Alemán, C.; Brillas, E.; Juliá, L. *J. Org. Chem.* **2001**, *66*, 4058. (h) Wang, X.; Ma, Z.; Wang, X.; De, S.; Ma, Y.; Chen, C. *Chem. Commun.* **2014**, *50*, 8628. (i) Gholap, S. S. *Eur. J. Med. Chem.* **2016**, *110*, 13.

(3) Selected reviews after 2012: (a) Broere, D. L. J.; Ruijter, E. *Synthesis* **2012**, *44*, 2639. (b) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (c) Deng, Y.; Persson, A. K. Å.; Bäckvall, J.-E. *Chem. - Eur. J.* **2012**, *18*, 11498. (d) Heravi, M. M.; Hashemi, E. *Monatsh. Chem.* **2012**, *143*, 861. (e) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884. (f) Shintani, R. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 931. (g) Tanaka, K.; Tajima, Y. *Eur. J. Org. Chem.* **2012**, *2012*, 3715. (h) Yamamoto, Y. *Chem. Rev.* **2012**, *112*, 4736. (i) Joshi, S. D.; More, U. A.; Kulkarni, V. H.; Aminabhavi, T. M. *Curr. Org. Chem.* **2013**, *17*, 2279. (j) Obradors, C.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16. (k) Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989. (l) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. *RSC Adv.* **2015**, *5*, 15233.

(4) Selected papers after 2014: (a) Chen, G.-Q.; Zhang, X.-N.; Wei, Y.; Tang, X.-Y.; Shi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8492. (b) Debrouwer, W.; Heugebaert, T. S. A.; Stevens, C. V. *J. Org. Chem.* **2014**, *79*, 4322. (c) Xuan, J.; Xia, X.-D.; Zeng, T.-T.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5653. (d) Zhang, Z.; Zhang, W.; Li, J.; Liu, Q.; Liu, T.; Zhang, G. *J. Org. Chem.* **2014**, *79*, 11226. (e) Zhou, N.; Xie, T.; Liu, L.; Xie, Z. *J. Org. Chem.* **2014**, *79*, 6061. (f) Kim, D.-S.; Seo, Y.-S.; Jun, C.-H. *Org. Lett.* **2015**, *17*, 3842. (g) Xiao, P.; Yuan, H.; Liu, J.; Zheng, Y.; Bi, X.; Zhang, J. *ACS Catal.* **2015**, *5*, 6177. (h) Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30. (i) Li, K.; You, J. *J. Org. Chem.* **2016**, *81*, 2327.

(5) Selected reviews: (a) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (b) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633.

(6) Selected papers: (a) Soleimani, E.; Zainali, M. *J. Org. Chem.* **2011**, *76*, 10306. (b) Thompson, B. B.; Montgomery, J. *Org. Lett.* **2011**, *13*, 3289. (c) Feng, X.; Wang, Q.; Lin, W.; Dou, G.-L.; Huang, Z.-B.; Shi, D.-Q. *Org. Lett.* **2013**, *15*, 2542. (d) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (e) Dawande, S. G.; Kanchupalli, V.; Lad, B. S.; Rai, J.; Katukojvala, S. *Org. Lett.* **2014**, *16*, 3700. (f) Kim, J. H.; Choi, S. Y.; Bouffard, J.; Lee, S.-g. *J. Org. Chem.* **2014**, *79*, 9253.

(7) (a) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (b) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (c) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6958. (d) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (e) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (f) Forberg, D.; Obenauf, J.; Friedrich, M.; Huhne, S.-M.; Mader, W.; Motz, G.; Kempe, R. *Catal. Sci. Technol.* **2014**, *4*, 4188.

(8) (a) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. (b) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, *1998*, 63. (c) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.

(9) (a) Zhang, Y.-Q.; Zhu, D.-Y.; Li, B.-S.; Tu, Y.-Q.; Liu, J.-X.; Lu, Y.; Wang, S.-H. *J. Org. Chem.* **2012**, *77*, 4167. (b) Mou, X.-Q.; Xu, Z.-L.; Wang, S.-H.; Zhu, D.-Y.; Wang, J.; Bao, W.; Zhou, S.-J.; Yang, C.; Zhang, D. *Chem. Commun.* **2015**, *51*, 12064.

(10) Selected papers: (a) Tsuge, O.; Kanemasa, S.; Yorozu, K.; Ueno, K. *Chem. Lett.* **1985**, *14*, 1601. (b) Fang, J.; Yan, C.-G. *Mol. Diversity* **2014**, *18*, 91. (c) Robles-Machín, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem. - Eur. J.* **2010**, *16*, 5286. (d) Li, J.; Zhao, H.; Jiang, X.; Wang, X.; Hu, H.; Yu, L.; Zhang, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 6306.

(11) Selected papers: (a) Unverferth, K.; Engel, J.; Höfgen, N.; Rostock, A.; Günther, R.; Lankau, H.-J.; Menzer, M.; Rolfs, A.; Liebscher, J.; Müller, B.; Hofmann, H.-J. *J. Med. Chem.* **1998**, *41*, 63–73. (b) Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479. (c) Bullington, J.; Argentieri, D.; Averill, K.; Carter, D.; Cavender, D.; Fahmy, B.; Fan, X.; Hall, D.; Heintzelman, G.; Jackson, P.; Leung, W.-P.; Li, X.; Ling, P.; Olini, G.; Razler, T.; Reuman, M.; Rupert, K.; Russell, R.; Siekierka, J.; Wadsworth, S.; Wolff, R.; Xiang, B.; Zhang, Y.-M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6102. (d) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2011**, *13*, 312. (e) Zhou, H.; Chen, J.; Meagher, J. L.; Yang, C.-Y.; Aguilar, A.; Liu, L.; Bai, L.; Cong, X.; Cai, Q.; Fang, X.; Stuckey, J. A.; Wang, S. *J. Med. Chem.* **2012**, *55*, 4664. (f) Huang, X.-C.; Xiao, X.; Zhang, Y.-K.; Talele, T.; Salim, A.; Chen, Z.-S.; Capon, R. *Mar. Drugs* **2014**, *12*, 3818.

(12) For details, see the Supporting Information.

(13) Mou, X.-Q.; Xu, L.; Wang, S.-H.; Yang, C. *Tetrahedron Lett.* **2015**, *56*, 2820.

(14) Wang, S.-H.; Mou, X.-Q.; Peng, R. A Three-Component Reaction for the Synthesis of Multisubstituted Pyrroles. Chinese Patent Application 201610416844.3, June 14, 2016.

(15) Selected examples: (a) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Abdon, R. L., II; Trost, B. M. *Tetrahedron* **1994**, *50*, 93. (b) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Paixão, J. A.; Beja, A. M.; Silva, M. R. *J. Org. Chem.* **2005**, *70*, 6629. (c) Sugimoto, K.; Miyakawa, Y.; Tokuyama, H. *Tetrahedron* **2015**, *71*, 3619.