

# Base-Promoted Synthesis of N–H Free Pyrroles *via* net [3 + 2]-Cycloaddition

Huimin Jin,<sup>+a, c, d</sup> Fan Zhou,<sup>+a, c, d</sup> Zhenhua Xiang,<sup>a, c, d</sup> Lingfeng Chen,<sup>a</sup>  
Guang Liang,<sup>a,\*</sup> Patrick J. Walsh,<sup>b,\*</sup> and Jie Li<sup>a, b, c, d,\*</sup>

<sup>a</sup> School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang 311399, People's Republic of China  
E-mail: cui.liang1234@163.com; lijie@hzcu.edu.cn

<sup>b</sup> Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, USA  
E-mail: p.walsh@sas.upenn.edu

<sup>c</sup> Department of Pharmacy, School of Medicine, Hangzhou City University, No. 48, Huzhou Road, Hangzhou 310015, People's Republic of China

<sup>d</sup> College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, People's Republic of China

<sup>+</sup> These two authors contributed equally.

Manuscript received: September 18, 2023; Revised manuscript received: October 22, 2023;

Version of record online: ■■, ■■

*Dedicated to Prof. Miquel Pericas for his amazing leadership at ICIQ and his remarkable scientific achievements.*



Supporting information for this article is available on the WWW under <https://doi.org/10.1002/adsc.202301053>

**Abstract:** A base-promoted net-[3 + 2] cycloaddition of nitriles and 1-arylpropynes for the synthesis of pyrroles is described. The developed method provides convenient access to various 2,5-disubstituted or 2,4,5-trisubstituted pyrroles in 40% to 96% yields (32 examples). Among methods for the synthesis of pyrroles, the protocol presented here stands out for its convenience and atom-economy.

**Keywords:** heterocycles, pyrroles; nitriles; 1-arylpropyne

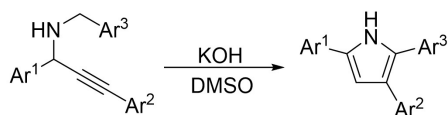
## Introduction

Pyrroles represent one of the most prominent classes of heterocycles. They are present in numerous natural products<sup>[1]</sup> and as key structural units in various pharmaceuticals.<sup>[2]</sup> They are also valuable motifs that exhibit a variety of bioactivities such as antitumor,<sup>[3]</sup> antiviral,<sup>[4]</sup> antifungal,<sup>[5]</sup> and antihyperlipidemic activities.<sup>[6]</sup> Additionally, these privileged heterocycles are core substructures in agrochemicals<sup>[7]</sup> and functional materials.<sup>[8]</sup> In this regard, significant efforts have been dedicated to the synthesis of pyrroles.<sup>[9]</sup> Traditionally, access to pyrrole rings are based on Knorr,<sup>[10]</sup> Hantzsch,<sup>[11]</sup> and Paal-Knorr reactions.<sup>[12]</sup> Recently, many efficient methods, including transition metal-catalyzed processes<sup>[13]</sup> and multicomponent reactions,<sup>[14]</sup> among others,<sup>[15]</sup> have been developed to construct functionalized pyrroles. Despite noteworthy advances, there remains room for improvement. The strict stand-

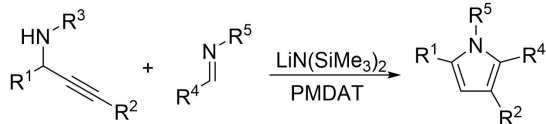
ards for trace metal contaminants in active pharmaceutical agents favor the development of transition metal-free processes.<sup>[16]</sup> Furthermore, highly functionalized starting materials and intermediates reduce practicality. Consequently, there is a demand for modular, efficient, direct and atom-economical approaches for the synthesis of functionalized pyrroles.

In line with our long-standing interest in the functionalization of carbanions derived from weakly acidic pronucleophiles,<sup>[17]</sup> we wondered if the reaction of nitriles with 1-arylpropyne under basic conditions could lead to pyrroles via a net-[3 + 2] cycloaddition reaction. In accordance with our supposition, a variety of 2,5-disubstituted or 2,4,5-trisubstituted pyrroles are accessible in the presence of silylamide bases. Compared to base-promoted strategies developed by Verma,<sup>[18]</sup> Wan,<sup>[19]</sup> and Cui<sup>[20]</sup> (Scheme 1) our method avoids the use of preformed substrates such as function-

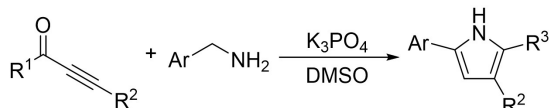
(a) Verma's work



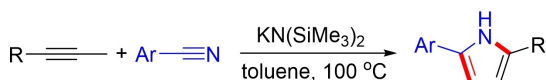
(b) Wan's work



(c) Cui's work



(d) this work

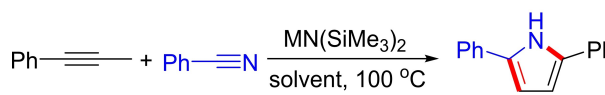
**Scheme 1.** Base-promoted synthesis of functionalized pyrroles.

alized propargyl amines, imines, and ynones. Moreover, the present work also stands out for its atom-economy.

## Results and Discussion

Initially, we optimized the [3+2] cycloaddition reaction with 1-phenylpropyne **1a** and benzonitrile **2a** as the model substrates using THF as solvent at 100 °C for 12 h (Table 1). Among the three silylamide bases tested [KN(SiMe<sub>3</sub>)<sub>2</sub>, NaN(SiMe<sub>3</sub>)<sub>2</sub>, LiN(SiMe<sub>3</sub>)<sub>2</sub>], KN(SiMe<sub>3</sub>)<sub>2</sub> and NaN(SiMe<sub>3</sub>)<sub>2</sub> were suitable (entries 1 and 2) with KN(SiMe<sub>3</sub>)<sub>2</sub> the most promising (67% yield). LiN(SiMe<sub>3</sub>)<sub>2</sub> only led to trace amounts of pyrrole **3aa** (entry 3). These results provide yet another example of the dramatic impact, but often mysterious role of main group metal cations on reactivity in organic transformations.<sup>[21]</sup> Further screening of different solvents, including CPME (cyclopentyl methyl ether), 1,4-dioxane, DME, and toluene indicated that toluene was the best choice, providing the product in 88% yield (entry 7 vs entries 4–6). Notably, excess base was critical for this reaction. Only 60% and 38% yield of cycloadduct was observed when 2 equiv. and 1 equiv. of KN(SiMe<sub>3</sub>)<sub>2</sub> were employed, respectively (entries 8, 9). Similarly, a temperature of 100 °C was essential to maintain high conversion. Lowering the reaction temperature to 80 °C gave only 37% yield of pyrrole product (entry 10), while no product was obtained when the reaction was conducted at 60 °C (entry 11). Interestingly, slightly increasing the amount of benzonitrile **2a** to 1.2 equiv. resulted in better yield of **3aa** (entries 7 vs. 12, from 88% to 95%). Therefore, the optimized conditions employed 1.2 equiv. of benzonitrile **2a**,

**Table 1.** Reaction Optimization Studies.<sup>[a]</sup>



Entry	Solvent	Base	1 a:2 a	Yield <sup>[b]</sup> (%)
1	THF	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	67
2	THF	NaN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	63
3	THF	LiN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	trace
4	CPME	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	73
5	1,4-Dioxane	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	49
6	DME	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	72
7	Toluene	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	88
8 <sup>[c]</sup>	Toluene	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	60
9 <sup>[d]</sup>	Toluene	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	38
10 <sup>[e]</sup>	Toluene	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	37
11 <sup>[f]</sup>	Toluene	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1	—
12	Toluene	KN(SiMe <sub>3</sub> ) <sub>2</sub>	1:1.2	95

<sup>[a]</sup> Reactions were conducted with **1a** (0.1 mmol), **2a** (0.1–0.12 mmol), base (0.3 mmol), solvent (1 mL), 12 h.

<sup>[b]</sup> Isolated yields.

<sup>[c]</sup> 2 Equiv. of KN(SiMe<sub>3</sub>)<sub>2</sub>.

<sup>[d]</sup> 1 Equiv. of KN(SiMe<sub>3</sub>)<sub>2</sub>.

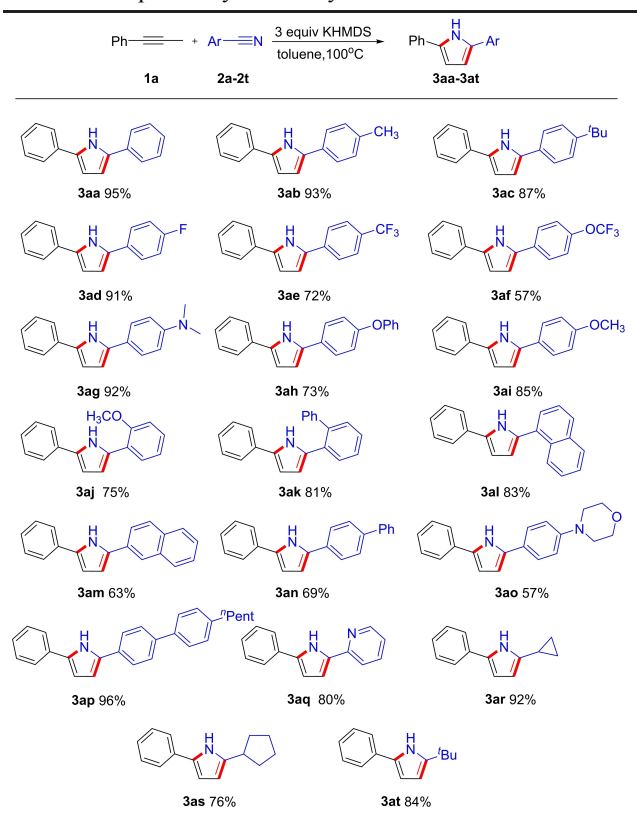
<sup>[e]</sup> 80 °C.

<sup>[f]</sup> 60 °C.

1 equiv. of 1-phenylpropyne **1a**, and 3 equiv. of KN(SiMe<sub>3</sub>)<sub>2</sub> in toluene at 100 °C for 12 h (entry 12 in Table 1).

With the optimized reaction conditions in hand, we examined the scope of the net [3+2] cycloaddition reaction beginning with the nitrile partner. As depicted in Table 2, benzonitriles possessing alkyl groups (4-Me and 4-<sup>t</sup>Bu) were well tolerated to afford products **3ab** and **3ac** in 93% and 87% yield, respectively. In addition, aryl nitriles bearing electronically diverse substituents, including electronegative and electron withdrawing groups (4-F, 4-CF<sub>3</sub>, 4-OCF<sub>3</sub>) gave the annulated products (**3ad**, **3ae**, **3af**) in 57–91% yields. Substrates **1g–1i** with electron-donating substituents at the *para* position (–NMe<sub>2</sub>, –OPh, –OMe) afforded 2,5-disubstituted pyrroles **3ag–3ai** in 73–92% yields. Notably, sterically hindered aryl nitriles bearing 2-OMe and 2-Ph groups were also applicable in this protocol, giving the pyrrole products **3aj–3ak** in 75–81% yields. 1-Naphthonitrile and 2-naphthonitrile gave **3al** and **3am** in 83 and 63% yields, respectively. Benzonitriles containing 4-phenyl, 4-morpholino, and 4-(4'-pentylphenyl) groups provided **3an–3ap** in 57–96% yields.

**Table 2.** Scope of Aryl and Alkyl Nitriles.<sup>[a,b]</sup>



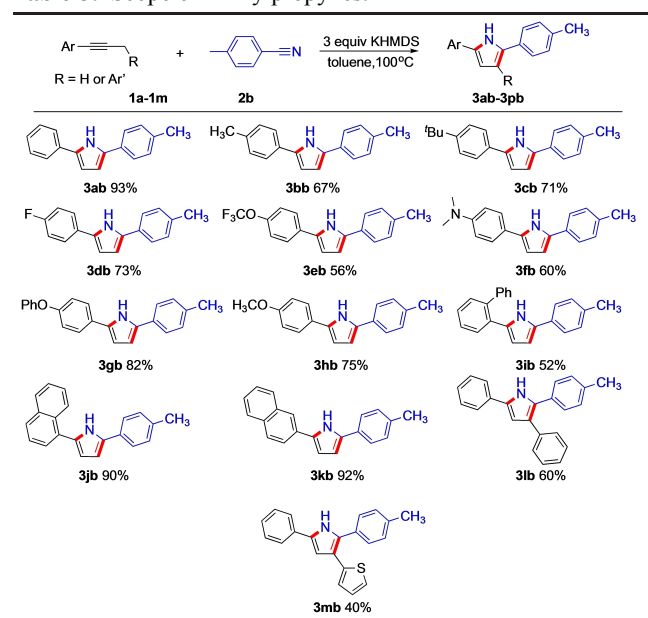
<sup>[a]</sup> Reaction conditions: **1a** (0.1 mmol), aryl nitrile (0.12 mmol), KN(SiMe<sub>3</sub>)<sub>2</sub> (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), toluene (0.1 M), 100 °C, 12 h.

<sup>[b]</sup> Isolated yield.

Heterocyclic 2-pyridyl nitrile was also a suitable substrate in this transformation, furnishing the corresponding product **3aq** in 80% yield. We were interested to determine if aliphatic nitriles were applicable to this method. Such substrates can be deprotonated in the presence of silyl amide bases (Et–CN has a pK<sub>a</sub> value of 32.5 in DMSO), raising concerns.<sup>[22]</sup> Of note, aliphatic nitriles, such as cyclopropanecarbonitrile, cyclopentanecarbonitrile, and the sterically congested pivalonitrile, were all suitable in this protocol, affording the desired products **3ar–3at** in 76–92% yields. To examine the scalability of this transformation, 6 mmol of **1a** was combined with 1.2 equiv. of cyclopropanecarbonitrile (**2r**) under optimal reaction conditions and the pyrrole product **3ar** was isolated in 87% yield (0.955 g).

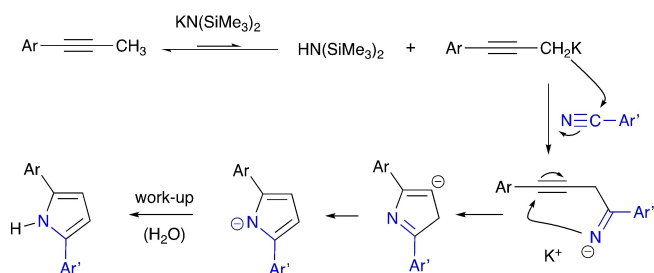
The scope of 1-arylpropynes was next examined with *p*-tolonitrile (**2b**) as outlined in Table 3. 1-Phenylpropynes possessing methyl and *tert*-butyl groups at the *para* position afforded **3bb–3cb** in 67–71% yields. Additionally, 1-arylpropynes bearing electronically-diverse substituents (4-F, 4-OCF<sub>3</sub>, 4-NMe<sub>2</sub>, 4-OPh, 4-OMe) provided the desired products (**3db**, **3eb**, **3fb**, **3gb**, **3hb**) in 56–82% yields. A sterically hindered substrate bearing a 2-Ph group on the phenyl group of 1-phenylpropyne gave the annulated product **3ib** in 52% yield. Arylpropynes with extended  $\pi$ -systems, such as 1-(prop-1-ynyl)naphthalene (**1j**) and 2-(prop-1-ynyl)naphthalene (**1k**) were both excellent substrates and produced products **1jb** and **1kb** in 90% and 92% yield.

**Table 3.** Scope of 1-Arylpropynes.<sup>[a,b]</sup>



<sup>[a]</sup> Reaction conditions: 1-arylpropyne (0.1 mmol), **2b** (0.12 mmol), KN(SiMe<sub>3</sub>)<sub>2</sub> (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), toluene (0.1 M), 100 °C, 12 h.

<sup>[b]</sup> Isolated yield.



**Scheme 2.** Possible reaction path.

yield, respectively. Importantly, the reaction was also applicable to 1,3-diarylpropynes, including 1,3-diphenylpropyne and 1-phenyl-3-(2'-thienyl)-propyne, to furnish the 2,3,5-trisubstituted pyrroles (**31b** and **31b**), albeit with somewhat diminished yields (40–60%). Overall, a wide range of functionalized pyrroles were synthesized *via* a net-[3+2] annulation of readily available aryl nitriles with 1-arylpropyne or 1,3-diarylpropynes.

Based on our past efforts with deprotonation of weakly acidic pro-nucleophiles,<sup>[17]</sup> we favor a mechanism that involves reversible deprotonation of the 1-arylpropyne (Scheme 2). Addition of the resulting propargylic anion to the nitrile generates a metalated imine. Attack of the metalated imine on the alkyne leads to a carbanion that is protonated, perhaps by the liberated  $\text{HN}(\text{SiMe}_3)_2$ . The  $\text{KN}(\text{SiMe}_3)_2$  can then deprotonate and aromatize the pyrrolide. The pyrrolide is protonated upon workup to furnish the pyrrole. We cannot, however, rule out the possibility of a concerted [3+2] cycloaddition reaction.

## Conclusion

In summary, a transition metal-, ligand-, and additive-free method is presented for the rapid synthesis of pyrroles. The reaction involves the condensation of 1-arylpropynes and aryl nitriles mediated by  $\text{KN}(\text{SiMe}_3)_2$  leading to valuable functionalized pyrroles. The availability of the starting materials, as well as atom-economy make this net [3+2] cycloaddition process particularly attractive. A wide range of 2,5-diaryl-1H-pyrroles, including 2,3,5-triaryl-1H-pyrroles, were prepared in 40% to 96% yields (32 examples). Due to its ability to access desirable N–H free pyrrole building blocks in one step *via* tandem C–C and N–C bond-formations, we envision that this protocol will find wide application in the chemical sciences. Further studies to activate arylpropyne for the synthesis of useful building blocks are underway in our laboratories.

## Experimental Section

### General Procedure A

An oven-dried 10 mL vial equipped with a stir bar was charged with 1-arylpropyne (0.1 mmol, 1.0 equiv.) under a nitrogen atmosphere in a glovebox. The aryl nitrile (0.12 mmol, 1.2 equiv.), dissolved in 1 mL of dry toluene, was added to the reaction vial followed by addition of  $\text{KN}(\text{SiMe}_3)_2$  (1.0 mol/L in THF, 0.3 mL, 0.3 mmol, 3.0 equiv.) by syringe at room temperature to give a homogeneous, clear solution. Upon addition of the base, the color of the reaction mixture turned to brown. The vial was capped, removed from the glovebox, placed in an oil bath at 100 °C and stirred for 12 h. After that time, the vial was removed from the bath, cooled to room temperature and the reaction mixture was quenched with three drops of saturated  $\text{NH}_4\text{Cl}$  solution and the vial was opened to the air. The resulting solution was passed through a short pad of silica gel and eluted with ethyl acetate (1 mL×3). The combined organic solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

### Acknowledgements

LJ thanks Zhejiang Provincial Natural Science Foundation of China (LY20C020003) and National Natural Science Foundation of China (31670357). PJW thanks the US National Science Foundation (CHE-2154593).

### Conflict of Interest

Part of this study was used to apply for a patent (CN 115872914) by the authors LJ, JHM, and ZF. There are no other conflicts to declare.

### References

- [1] a) R. Khajuria, S. Dham, K. K. Kapoor, *RSC Adv.* **2016**, *6*, 37039–37066; b) C. T. Walsh, S. Garneau-Tsodikova, A. R. Howard-Jones, *Nat. Prod. Rep.* **2006**, *23*, 517–31; c) A. Furstner, *Angew. Chem. Int. Ed.* **2003**, *42*, 3582–603; d) P. A. Jacobi, L. D. Coutts, J. Guo, S. I. Hauck, S. H. Leung, *J. Org. Chem.* **2000**, *65*, 205–213; e) I. S. Young, P. D. Thornton, A. Thompson, *Nat. Prod. Rep.* **2010**, *27*, 1801–39; f) S. C. Philkhana, F. O. Badmus, I. C. Dos Reis, R. Kartika, *Synthesis* **2021**, *53*, 1531–1555; g) F.-L. Haut, N. J. Feichtinger, I. Plangger, L. A. Wein, M. Müller, T.-N. Streit, K. Wurst, M. Podewitz, T. Magauer, *J. Am. Chem. Soc.* **2021**, *143*, 9002–9008.
- [2] a) G. Li Petri, V. Spano, R. Spatola, R. Holl, M. V. Raimondi, P. Barraja, A. Montalbano, *Eur. J. Med. Chem.* **2020**, *208*, 112783; b) K. H. Van Pee, J. M. Ligon, *Nat. Prod. Rep.* **2000**, *17*, 157–64; c) Y. Arikawa, H. Nishida, O. Kurasawa, A. Hasuoka, K. Hirase, N. Inatomi, Y. Hori, J. Matsukawa, A. Imanishi, M. Kondo, N. Tarui, T. Hamada, T. Takagi, T. Takeuchi, M. Kajino, *J. Med. Chem.* **2012**, *55*, 4446–56; d) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma, *RSC Adv.* **2015**, *5*, 15233–15266.


- [3] F. Yang, N. G. Nickols, B. C. Li, G. K. Marinov, J. W. Said, P. B. Dervan, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 1863–1868.
- [4] S. Jiang, H. Lu, S. Liu, Q. Zhao, Y. He, A. K. Debnath, *Agents Chemother.* **2004**, *48*, 4349–4359.
- [5] a) M. Z. Wang, H. Xu, T.-W. Liu, Q. Feng, S.-J. Yu, S.-H. Wang, Z.-M. Li, *Eur. J. Med. Chem.* **2011**, *46*, 1463–1472; b) J. D. Oliver, G. E. M. Sibley, N. Beckmann, K. S. Dobb, M. J. Slater, L. McEntee, S. du Pré, J. Livermore, M. J. Bromley, N. P. Wiederhold, W. W. Hope, A. J. Kennedy, D. Law, M. Birch, *Natl. Acad. Sci. Usa.* **2016**, *113*, 12809–12814.
- [6] R. B. Thompson, *FASEB J.* **2001**, *15*, 1671–1676.
- [7] a) T. T. Yao, D. X. Xiao, Z. S. Li, J. L. Cheng, S. W. Fang, Y. J. Du, J. H. Zhao, X. W. Dong, G. N. Zhu, *J. Agric. Food Chem.* **2017**, *65*, 5397–5403; b) A. Speck-Planche, L. Guilarte-Montero, R. Yera-Bueno, J. A. Rojas-Vargas, A. Garcia-López, E. Uriarte, E. Molina-Pérez, *Pest Manage. Sci.* **2011**, *67*, 438–445.
- [8] a) Y. Li, Y. Lei, L. Dong, L. Zhang, J. Zhi, J. Shi, B. Tong, Y. Dong, *Chem. Eur. J.* **2019**, *25*, 573–581; b) A. Loudet, K. Burgess, *Chem. Rev.* **2007**, *107*, 4891–4932; c) A. M. Elnahrawy, A. A. Haroun, I. Hamadneh, A. H. Al-Dujaili, S. Kamel, *Carbohydr. Polym.* **2017**, *168*, 182–190; d) P. Novák, K. Müller, K. S. V. Santhanam, O. Haas, *Chem. Rev.* **1997**, *97*, 207–282; e) Y. Li, C. Y. Gao, X. H. Fan, L. M. Yang, *Chem. Eng. J.* **2022**, *443*, 136536; f) J. Yang, Y. Zhang, X. Wu, W. Dai, D. Chen, J. Shi, B. Tong, Q. Peng, H. Xie, Z. Cai, Y. Dong, X. Zhang, *Nat. Commun.* **2021**, *12*, 4883.
- [9] T. Shi, G. F. Yin, X. D. Wang, Y. X. Xiong, Y. Peng, S. Li, Y. F. Zeng, Z. Wang, *Green Syn. Catal.* **2023**, *4*, 20–34.
- [10] L. Knorr, *Chem. Ber.* **1884**, *17*, 1635–1642.
- [11] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476.
- [12] C. Paal, *Chem. Ber.* **1885**, *18*, 367–371.
- [13] a) B. M. Trost, J. P. Lumb, J. M. Azzarelli, *J. Am. Chem. Soc.* **2011**, *133*, 740–743; b) K. Kawakita, E. P. Beaumier, Y. Kakiuchi, H. Tsurugi, I. A. Tonks, K. Mashima, *J. Am. Chem. Soc.* **2019**, *141*, 4194–4198; c) P. Polák, T. Tobrman, *Org. Lett.* **2017**, *19*, 4608–4611; d) E. Coya, N. Sotomayor, E. Lete, *Adv. Synth. Catal.* **2014**, *356*, 1853–1865; e) J. Bai, N. Xu, H. Wang, X. Luan, *Org. Lett.* **2022**, *24*, 5099–5104; f) J. Roger, A. L. Gottumukala, H. Doucet, *ChemCatChem.* **2010**, *2*, 20–40; g) M. B. Li, E. S. Grape, J. E. Bäckvall, *ACS Catal.* **2019**, *9*, 5184–5190; h) P. F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585–9587; i) C. B. Bheeter, L. Chen, J. F. Soulé, H. Doucet, *Catal. Sci. Technol.* **2016**, *6*, 2005–2049; j) A. Mizuno, H. Kusama, N. Iwasawa, *Angew. Chem. Int. Ed.* **2009**, *48*, 8318–8320; k) M. Yamaguchi, S. Fujiwara, K. Manabe, *Org. Lett.* **2019**, *21*, 6972–6977; l) R. Rossi, F. Bellina, M. Lessi, C. Manzini, L. A. Perego, *Synthesis.* **2014**, *46*, 2833–2883; m) H. Chai, L. Wang, T. Liu, Z. Yu, *Organometallics.* **2017**, *36*, 4936–4942.
- [14] a) I. Azad, F. Hassan, M. Saquib, N. Ahmad, A. Rahman Khan, A. G. Al-Sehemi, M. A. Nasibullah, *Orient. J. Chem.* **2018**, *34*, 1670–1700; b) V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev.* **2015**, *45*, 4633–4657.
- [15] a) P. Ryabchuk, T. Leischner, C. Kreyenschulte, A. Spannenberg, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2020**, *59*, 18679–18685; b) M. Li, Y. Sun, Y. Xie, Y. Yu, F. Huang, H. Huang, *Chem. Commun.* **2020**, *56*, 11050–11053; c) D. Andreou, M. G. Kallitsakis, E. Loukopoulos, C. Gabriel, G. E. Kostakis, I. N. Lykakis, *J. Org. Chem.* **2018**, *83*, 2104–2113; d) T. Soeta, A. Matsumoto, Y. Ukaji, *J. Org. Chem.* **2018**, *83*, 4831–4834; e) C. Ye, Y. Jiao, M. F. Chiou, Y. Li, H. Bao, *Chem. Sci.* **2021**, *12*, 9162–9167; f) L. Zhu, Y. Yu, Z. Mao, X. Huang, *Org. Lett.* **2015**, *17*, 30–33; g) M. N. Zhao, Z. H. Ren, D. S. Yang, Z. H. Guan, *Org. Lett.* **2018**, *20*, 1287–1290; h) L. O. Khafizova, M. G. Shaibakova, N. A. Rikhter, T. V. Tyumkina, U. M. Dzhemilev, *Tetrahedron.* **2019**, *75*, 906–911; i) L. Chen, J. Q. Huo, H. L. Si, X. Y. Xu, S. Kou, J. Mao, J.-L. Zhang, *Org. Lett.* **2021**, *23*, 4348–4352; j) J. Cen, Y. Wu, J. Li, L. Huang, W. Wu, Z. Zhu, S. Yang, H. Jiang, *Org. Lett.* **2019**, *21*, 2090–2094; k) Y. Zhou, L. Zhou, L. T. Jesikiewicz, P. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2020**, *142*, 9908–9914; l) X. Xin, D. Wang, X. Li, B. Wan, *Angew. Chem. Int. Ed.* **2012**, *51*, 1693–1697; m) B. S. Karki, L. Devi, A. Pokhriyal, R. Kant, N. Rastogi, *Chem. Asian J.* **2019**, *14*, 4793–4797; n) B. S. Karki, L. Devi, A. Pokhriyal, R. Kant, N. Rastogi, *Chem. Asian J.* **2019**, *14*, 4793–4797.
- [16] Food and Drug Administration, "Q3D(R2)-Guideline for Elemental Impurities; International Council for Harmonisation; Guidance for Industry; Availability", can be found under <https://www.federalregister.gov/documents/2022/09/15/2022-19997/q3dr2-guideline-for-elemental-impurities-international-council-for-harmonisation-guidance-for>; D. Barbaras, J. Brozio, I. Johannsen, T. Allmendinger, *Org. Process Res. Dev.* **2009**, *13*, 1068–1079.
- [17] a) G. Liu, P. J. Walsh, J. Mao, *Org. Lett.* **2019**, *21*, 8514–8518; b) F. Gao, B. S. Kim, P. J. Walsh, *Chem. Sci.* **2016**, *7*, 976–983; c) H. Jiang, S.-C. Sha, S. A. Jeong, B. C. Manor, P. J. Walsh, *Org. Lett.* **2019**, *21*, 1735–1739; d) X. Cao, S.-C. Sha, M. Li, B.-S. Kim, C. Morgan, R. Huang, X. Yang, P. J. Walsh, *Chem. Sci.* **2016**, *7*, 611–618; e) J. Li, C. Wu, B. Zhou, P. J. Walsh, *J. Org. Chem.* **2018**, *83*, 2993–2999; f) J. Zhang, A. Bellomo, N. Trongsiriwat, T. Jia, P. J. Carroll, S. D. Dreher, M. T. Tudge, H. Yin, J. R. Robinson, E. J. Schelter, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 6276–6287; g) J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2012**, *134*, 13765–13772; h) J. Mao, Z. Wang, X. Xu, G. Liu, R. Jiang, H. Guan, Z. Zheng, P. J. Walsh, *Angew. Chem. Int. Ed.* **2019**, *58*, 11033–11038; i) F. Yang, D. Zou, S. Chen, H. Wang, Y. Zhao, L. Zhao, L. Li, J. Li, P. J. Walsh, *Adv. Synth. Catal.* **2020**, *362*, 3423–3430.

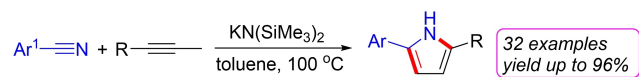
- [18] P. K. Mishra, S. Verma, M. Kumar, A. K. Verma, *Org. Lett.* **2018**, *20*, 7182–7185.
- [19] Y. Hu, C. Wang, D. Wang, F. Wu, B. Wan, *Org. Lett.* **2013**, *15*, 3146–3149.
- [20] J. Shen, G. Cheng, X. Cui, *Chem. Commun.* **2013**, *49*, 10641–10643.
- [21] T. X. Gentner, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2021**, *60*, 9247–9262.
- [22] F. G. Bordwell, M. Van der Puy, N. R. Vanier, *J. Org. Chem.* **1976**, *41*, 1885–1886.
-

## RESEARCH ARTICLE

### Base-Promoted Synthesis of N–H Free Pyrroles *via* net [3+2]-Cycloaddition

*Adv. Synth. Catal.* **2023**, *365*, 1–7

 H. Jin, F. Zhou, Z. Xiang, L. Chen, G. Liang\*, P. J. Walsh\*, J. Li\*



- C-C and C-N bonds formation
- atom-economical process
- operational-simplicity