

Cite this: *RSC Adv.*, 2019, **9**, 1487Received 27th October 2018
Accepted 2nd January 2019DOI: 10.1039/c8ra08909d
rsc.li/rsc-advances

Formal [4 + 1] cycloaddition of *in situ* generated 1,2-diaza-1,3-dienes with diazo esters: facile approaches to dihydropyrazoles containing a quaternary center[†]

Bo Chen, Wen-Dao Chu * and Quan-Zhong Liu^{*}

A Cu(II)/bisoxazoline ligand-promoted formal [4 + 1] cycloaddition of diazo esters with azoalkenes formed *in situ* has been developed. This strategy provides a potential protocol for the construction of dihydropyrazoles containing a quaternary center with good to excellent yields.

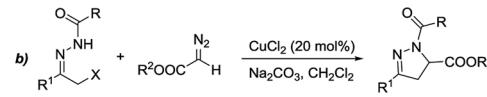
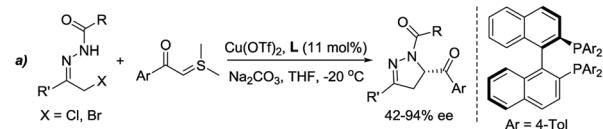
The efficient construction of quaternary carbon centers has remained a crucial issue in organic synthesis.¹ Quaternary carbon centers are ubiquitous in various natural products, and pharmaceutically relevant compounds.² Although significant efforts have been devoted to the effective construction of quaternary centers in recent years,¹ new methodologies that could be advantageous in terms of functional-group tolerance, operational simplicity, and the use of easily obtained starting materials are still highly desired.

On the other hand, dihydropyrazoles represent a class of important heterocycles that occur in biologically active natural products and pharmaceuticals such as anti-amoebic, hypotensive, analgesic, anti-bacterial, anti-cancer, anti-depressant and nonsteroidal anti-inflammatory agents.³ Accordingly, great research efforts have been devoted toward their synthesis, and remarkable advances have been achieved in the construction of these nitrogen heterocycles. Representative synthetic strategies include formal [3 + 2] cycloaddition,⁴ [4 + 1] cycloaddition,⁵ catalytic asymmetric Fischer's pyrazoline synthesis *via* a sequential aza-Michael addition/cyclocondensation process,⁶ and photocatalytic radical cyclization.^{7,8} In comparison with the more ubiquitous family of [3 + 2] cycloadditions, [4 + 1] cycloannulations are relatively underutilized in these target-directed five-membered azaheterocycles construction.⁵ In 2012, Bolm and coworkers reported the first example of asymmetric synthesis of dihydropyrazoles by formal [4 + 1] cycloaddition of *in situ* derived azoalkenes and sulfur ylides (Scheme 1a).^{5a} Recently, diazo

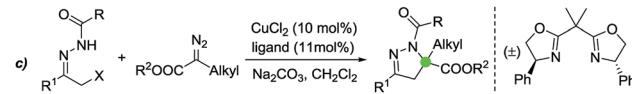
esters as 1,1-dipolar C1 synthons had also been utilized by the group of Favi to synthesize racemic dihydropyrazoles in a similar manner (Scheme 1b).^{5b} However, none of these investigations has explored the possibility of accessing dihydropyrazoles containing a quaternary center. Herein, we present a Cu(II)/bisoxazoline ligand-promoted formal [4 + 1] cycloaddition of diazo esters with azoalkenes formed *in situ*, affording dihydropyrazoles containing a quaternary center with good to excellent yields (Scheme 1c).

At the outset of this investigation, we employed hydrazone **1a** and diazo ester **2a** as the substrates (Table 1). Preliminary screening showed that the ligand has a remarkable effect on the reaction. For instance, the reaction with phosphine ligands gave the desired dihydropyrazole **3a** in low yields (Table 1, entry 2–4). It was found that the reaction proceeded efficiently when bisoxazoline **L6** was employed as ligand, leading to the desired product **3a** in 98% yield (Table 1, entry 7). Subsequently, different bases and solvents were then explored (Table 1, entries 7–16), Na₂CO₃ and CH₂Cl₂ was the best choice.

Previous work



This work



Chemical Synthesis and Pollution Control, Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, No. 1, Shida Road, Nanchong 637002, P. R. China. E-mail: chuwendaonpo@126.com; quanzhongliu@cwnu.edu.cn

† Electronic supplementary information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal structures of **3h**. CCDC 1840892. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra08909d

Scheme 1 Synthesis of dihydropyrazoles by formal [4 + 1] cycloaddition.

Table 1 Optimization of reaction conditions^a

Entry	[Cu]	Ligand	Base	Solvent	Yield ^b (%)	Reaction Conditions	
						[Cu] (10 mol%)	ligand (11 mol%)
1	CuCl ₂	None	Na ₂ CO ₃	CH ₂ Cl ₂	None		
2	CuCl ₂	L1	Na ₂ CO ₃	CH ₂ Cl ₂	18		
3	CuCl ₂	L2	Na ₂ CO ₃	CH ₂ Cl ₂	6		
4	CuCl ₂	L3	Na ₂ CO ₃	CH ₂ Cl ₂	22		
5	CuCl ₂	L4	Na ₂ CO ₃	CH ₂ Cl ₂	5		
6	CuCl ₂	L5	Na ₂ CO ₃	CH ₂ Cl ₂	6		
7	CuCl ₂	L6	Na ₂ CO ₃	CH ₂ Cl ₂	98		
8	CuCl ₂	L6	K ₂ CO ₃	CH ₂ Cl ₂	15		
9	CuCl ₂	L6	Cs ₂ CO ₃	CH ₂ Cl ₂	26		
10	CuCl ₂	L6	NaOH	CH ₂ Cl ₂	Trace		
11	CuCl ₂	L6	KOtBu	CH ₂ Cl ₂	Trace		
12	CuCl ₂	L6	Et ₃ N	CH ₂ Cl ₂	Trace		
13	CuCl ₂	L6	Na ₂ CO ₃	THF	83		
14	CuCl ₂	L6	Na ₂ CO ₃	Toluene	Trace		
15	CuCl ₂	L6	Na ₂ CO ₃	CH ₃ CN	5		
16	CuCl ₂	L6	Na ₂ CO ₃	Hexane	12		

^a Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2a** (0.5 mmol), base (0.5 mmol), Cu cat. (10 mol%), and ligand (11 mol%) in anhydrous solvent (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. ^b Yields refer to isolated products.

With the optimized conditions in hand, we next explored the substrate scope of the heterodienes. A series of hydrazones **1a–l** bearing electron-neutral, -deficient or -rich aromatic substituents were smoothly reacted with diazo ester **2a** to give the corresponding dihydropyrazoles **3a–l** in 76–98% yield (Table 2, entry 1–12). Also α -bromo *N*-benzoyl hydrazone **1o** reacted well, and 88% yield were achieved (Table 2, entry 15). In contrast, 2-naphthyl-substituted hydrazone **1m** and aliphatic hydrazone **1n** only gave a small quantity of product **3m** and **3n** (Table 2, entry 13–14).

Next, the scope of the reaction was extended by conducting the reaction with various diazo esters (Table 3). Variation of the ester R² group (entries 1 and 2) had little influence on the yield of product **3**. The significant steric effect of R¹ has been observed. Methyl and ethyl groups gave excellent results (entries 2–3), while the more bulky groups gave only a trace of products (entries 4–5).

We next attempted to investigate asymmetric variant of this Cu(II)-catalyzed formal [4 + 1] cycloaddition reaction of diazo esters with azoalkenes formed *in situ* (Scheme 2). An extensive screening of chiral phosphine ligands (**L7**, **L8**), bisoxazoline ligands (**L9–12**) and different reaction conditions had been implemented. Unfortunately, only up to 5% ee was obtained when **L12** was employed as chiral ligand, albeit with excellent yield (98%).

To show the synthetic potential of this strategy, we have carried out a gram scale synthesis of **3a** (Scheme 3). Under the optimized reaction conditions, the reaction with 3 mmol of **1a**

Table 2 Substrate scope for hydrazones^a

Entry	1	X	R ¹	Yield ^b of 3 (%)
1	1a	Cl	Ph	3a , 98
2	1b	Cl	2-Br-Ph	3b , 82
3	1c	Cl	2-F-Ph	3c , 78
4	1d	Cl	2-CH ₃ -Ph	3d , 76
5	1e	Cl	3-Cl-Ph	3e , 93
6	1f	Cl	3-OCH ₃ -Ph	3f , 92
7	1g	Cl	3-CH ₃ -Ph	3g , 89
8	1h	Cl	4-Cl-Ph	3h , 98
9	1i	Cl	4-F-Ph	3i , 94
10	1j	Cl	4-OCH ₃ -Ph	3j , 98
11	1k	Cl	4-NO ₂ -Ph	3k , 92
12	1l	Cl	4-CH ₃ -Ph	3l , 98
13	1m	Cl	2-Naphthyl	3m , trace
14	1n	Cl	n-Bu	3n , trace
15	1o	Br	Ph	3o , 88

^a Reaction was run under the following conditions: a solution of **1** (0.1 mmol), **2a** (0.5 mmol), Na₂CO₃ (0.5 mmol), CuCl₂ (10 mol%), and **L6** (11 mol%) in anhydrous CH₂Cl₂ (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. ^b Yields refer to isolated products.

Table 3 Substrate scope for diazo esters^a

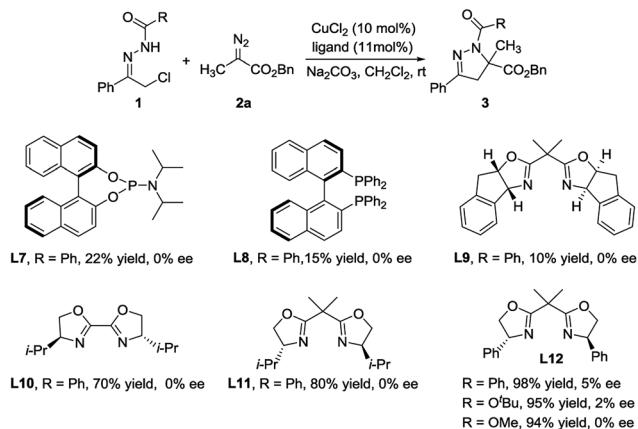
Entry	2	R ¹	R ²	Yield ^b of 3 (%)
1	2a	Me	Bn	3a , 98
2	2b	Me	Et	3p , 98
3	2c	Et	Et	3q , 92
4	2d	Bn	Bn	3r , trace
5	2e	Ph	Et	3s , trace

^a Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2** (0.5 mmol), Na₂CO₃ (0.5 mmol), CuCl₂ (10 mol%), and **L6** (11 mol%) in anhydrous CH₂Cl₂ (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. ^b Yields refer to isolated products.

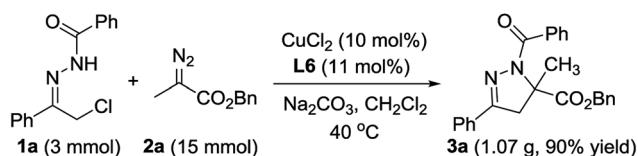
proceeded smoothly with 5 equiv. of **2a**, affording 1.07 g of **3a** (90% yield).

In summary, we have developed a Cu(II)/bisoxazoline ligand-promoted formal [4 + 1] cycloaddition of diazo esters with azoalkenes formed *in situ*, affording dihydropyrazoles containing a quaternary center with good to excellent yields. The reaction involves the use of stable, readily available starting materials and is operationally simple.





Scheme 2 The investigation on asymmetric [4 + 1] annulation reaction.



Scheme 3 Reaction on the gram scale.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financial supported by the National Natural Science Foundation of China (No. 21572183 and 21801208).

Notes and references

- For selected reviews, see: (a) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037–2066; (b) J. C. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363–5367; (c) J. Christoffers and A. Baro, *Quaternary Stereocenters-Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, 2005; (d) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369–396; (e) M. Shimizu, *Angew. Chem., Int. Ed.*, 2011, **50**, 5998–6000; (f) B. M. Wang and Y. Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207–1222; (g) J. P. Das and I. Marek, *Chem. Commun.*, 2011, **47**, 4593–4623; (h) M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal and L. E. Overman, *Angew. Chem., Int. Ed.*, 2016, **55**, 4156–4186.
- (a) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, **75**, 311–335; (b) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629–661 and references within; (c) Y. Tu, C. Jeffries, H. Ruan, C. Nelson, D. Smithson, A. A. Shelat, K. M. Brown, X.-C. Li, J. P. Hester, T. Smillie, I. A. Khan, L. Walker, K. Guy and B. Yan, *J. Nat. Prod.*, 2010, **73**, 751–754.
- (a) M. Kissane and A. R. Maguire, *Chem. Soc. Rev.*, 2010, **39**, 845–883; (b) C.-H. Küchenthal and W. Maison, *Synthesis*, 2010, 719–740; (c) A. Sahoo, S. Yabanoglu, B. N. Sinha, G. Ucar, A. Basu and V. Jayaprakash, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 132–136; (d) M. Johnson, B. Younglove, L. Lee, R. LeBlanc, H. Holt Jr, P. Hills, H. Mackay, T. Brown, S. L. Mooberry and M. Lee, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5897–5901; (e) M. A. Ali and M. Shaharyar, *Bioorg. Med. Chem.*, 2007, **15**, 1896–1902; (f) J. H. M. Lange and C. G. Kruse, *Curr. Opin. Drug Discovery Dev.*, 2004, **7**, 498.
- (a) S. Kanemasa and T. Kanai, *J. Am. Chem. Soc.*, 2000, **122**, 10710–10711; (b) R. Shintani and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 10778–10779; (c) M. P. Sibi, L. M. Stanley and C. P. Jasperse, *J. Am. Chem. Soc.*, 2005, **127**, 8276–8277; (d) A. Suárez, C. W. Downey and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 11244–11245; (e) T. Kano, T. Hashimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 2174–2175; (f) M. P. Sibi, L. M. Stanley and T. Soeta, *Adv. Synth. Catal.*, 2006, **348**, 2371–2375; (g) M. P. Sibi, L. M. Stanley and T. Soeta, *Org. Lett.*, 2007, **9**, 1553–1556; (h) L. Gao, G. S. Hwang, M. Y. Lee and D. H. Ryu, *Chem. Commun.*, 2009, 5460–5462; (i) H. Suga, Y. Furihata, A. Sakamoto, K. Itoh, Y. Okumura, T. Tsuchida, A. Kakehi and T. Baba, *J. Org. Chem.*, 2011, **76**, 7377–7387; (j) T. Arai and Y. Ogino, *Molecules*, 2012, **17**, 6170–6178; (k) T. Imaizumi, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2012, **134**, 20049–20052; (l) M. Rueping, M. S. Maji, H. B. Kücük and I. Atodiresei, *Angew. Chem., Int. Ed.*, 2012, **51**, 12864–12868; (m) G. Wang, X. Liu, T. Huang, Y. Kuang, L. Lin and X. Feng, *Org. Lett.*, 2013, **15**, 76–79; (n) A. L. Gerten, M. C. Slade, K. M. Pugh and L. M. Stanley, *Org. Biomol. Chem.*, 2013, **11**, 7834–7837; (o) T. Arai, Y. Ogino and T. Sato, *Chem. Commun.*, 2013, **49**, 7776–7778; (p) T. Hashimoto, Y. Takiguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2013, **135**, 11473–11476; (q) M. Hori, A. Sakakura and K. Ishihara, *J. Am. Chem. Soc.*, 2014, **136**, 13198–13201; (r) X. Hong, H. B. Kücük, M. S. Maji, Y.-F. Yang, M. Rueping and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 13769–13780; (s) X. Wang, Y.-m. Pan, X.-c. Huang, Z.-y. Mao and H.-s. Wang, *Org. Biomol. Chem.*, 2014, **12**, 2028–2032; (t) D.-Y. Zhang, L. Shao, J. Xu and X.-P. Hu, *ACS Catal.*, 2015, **5**, 5026–5030.
- (a) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres and C. Bolm, *J. Am. Chem. Soc.*, 2012, **134**, 6924–6927; (b) O. A. Attanasi, L. D. Crescentini, G. Favi, F. Mantellini, S. Mantenuto and S. Nicolini, *J. Org. Chem.*, 2014, **79**, 8331–8338; (c) Z. Wang, Y. Yang, F. Gao, Z. Wang, Q. Luo and L. Fang, *Org. Lett.*, 2018, **20**, 934–937.
- (a) H. Yanagita and S. Kanemasa, *Heterocycles*, 2007, **71**, 699–709; (b) S. Müller and B. List, *Angew. Chem., Int. Ed.*, 2009, **48**, 9975–9978; (c) S. Müller and B. List, *Synthesis*, 2010, **2010**, 2171–2178; (d) O. Mahé, I. Dez, V. Levacher and J.-F. Brière, *Angew. Chem., Int. Ed.*, 2010, **49**, 7072–7075; (e) N. R. Campbell, B. Sun, R. P. Singh and L. Deng, *Adv. Synth. Catal.*, 2011, **353**, 3123–3128; (f) M. Fernández, E. Reyes, J. L. Vicario, D. Badía and L. Carrillo, *Adv. Synth. Catal.*,



2012, **354**, 371–376; (g) O. Mahé, I. Dez, V. Levacher and J.-F. Brière, *Org. Biomol. Chem.*, 2012, **10**, 3946–3954.

7 (a) X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, A. M. Beauchemin and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 12163–12167; (b) Q. Wei, J.-R. Chen, X.-Q. Hu, X.-C. Yang, B. Lu and W.-J. Xiao, *Org. Lett.*, 2015, **17**, 4464–4467; (c) J. Cheng, P. Xu, W. Li, Y. Cheng and C. Zhu, *Chem. Commun.*, 2016, **52**, 11901–11904; (d) Q.-Q. Zhao, J. Chen, D.-M. Yan, J.-R. Chen and W.-J. Xiao, *Org. Lett.*, 2017, **19**, 3620–3623; (e) J.-m. Yu, G.-P. Lu and C. Cai, *Chem. Commun.*, 2017, **53**, 5342–5345.

8 For other methods for synthesis of dihydropyrazoles, see: (a) C. B. Tripathi and S. Mukherjee, *Org. Lett.*, 2014, **16**, 3368–3371; (b) X. Wu, M. Wang, G. Zhang, Y. Zhao, J. Wang and H. Ge, *Chem. Sci.*, 2015, **6**, 5882–5890; (c) M.-N. Yang, D.-M. Yan, Q.-Q. Zhao, J.-R. Chen and W.-J. Xiao, *Org. Lett.*, 2017, **19**, 5208–5211; (d) J. Zhao, M. Jiang and J.-T. Liu, *Org. Chem. Front.*, 2018, **5**, 1155–1159.

