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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†

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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 aza-heterocycles 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

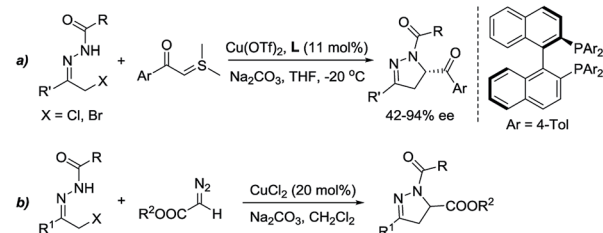
esters as 1,1-dipolar C1 synthons had also been utilized by the group of Favi to synthesize racemic dihydropyrazoles in a similar manner (Scheme 1b).^{5b} However, none of these investigations has explored the possibility of accessing dihydropyrazoles containing a quaternary center. Herein, we present 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.

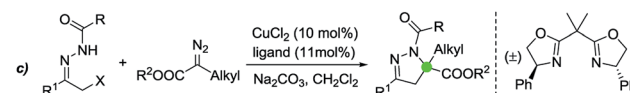
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Previous work

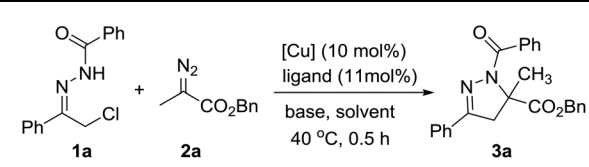


This work



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



Table 1 Optimization of reaction conditions^a


Entry	[Cu]	Ligand	Base	Solvent	Yield ^b (%)
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

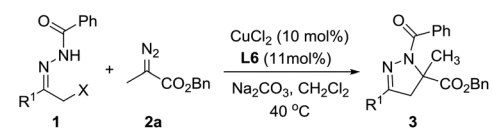
^a Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2a** (0.5 mmol), base (0.5 mmol), Cu cat. (10 mol%), and ligand (11 mol%) in anhydrous solvent (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. ^b Yields refer to isolated products.

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).

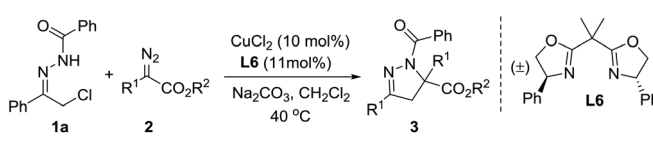
We next attempted to investigate asymmetric variant of this Cu(II)-catalyzed formal [4 + 1] cycloaddition reaction of diazo esters with azoalkenes formed *in situ* (Scheme 2). An extensive screening of chiral phosphine ligands (**L7**, **L8**), bisoxazoline ligands (**L9–12**) and different reaction 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	<i>n</i> -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


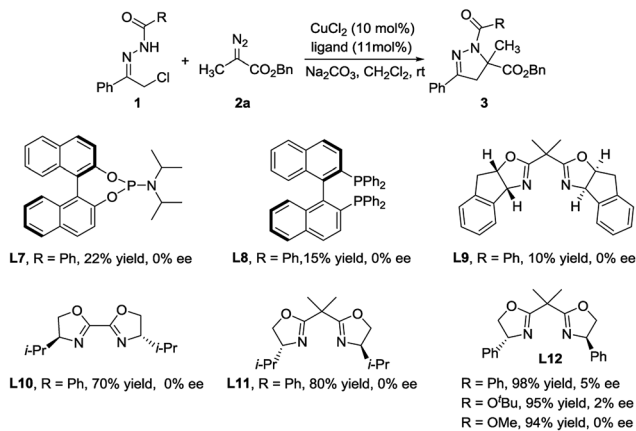
Entry	2	R ¹	R ²	Yield ^b of 3 (%)
1	2a	Me	Bn	3a , 98
2	2b	Me	Et	3p , 98
3	2c	Et	Et	3q , 92
4	2d	Bn	Bn	3r , trace
5	2e	Ph	Et	3s , trace

^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.

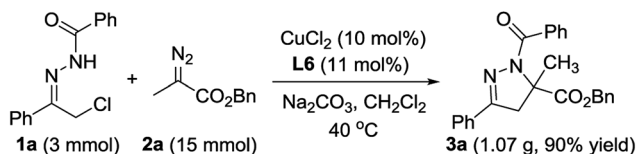
proceeded smoothly with 5 equiv. of **2a**, affording 1.07 g of **3a** (90% yield).

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

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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. Takehi 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. Küçük 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. Küçük, 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.

