



Cite this: *RSC Adv.*, 2019, 9, 1487

Received 27th October 2018

Accepted 2nd January 2019

DOI: 10.1039/c8ra08909d

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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.<sup>1</sup> Quaternary carbon centers are ubiquitous in various natural products, and pharmaceutically relevant compounds.<sup>2</sup> Although significant efforts have been devoted to the effective construction of quaternary centers in recent years,<sup>1</sup> 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.<sup>3</sup> 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,<sup>4</sup> [4 + 1] cycloaddition,<sup>5</sup> catalytic asymmetric Fischer's pyrazoline synthesis *via* a sequential aza-Michael addition/cyclocondensation process,<sup>6</sup> and photocatalytic radical cyclization.<sup>7,8</sup> 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.<sup>5</sup> 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).<sup>5a</sup> Recently, diazo

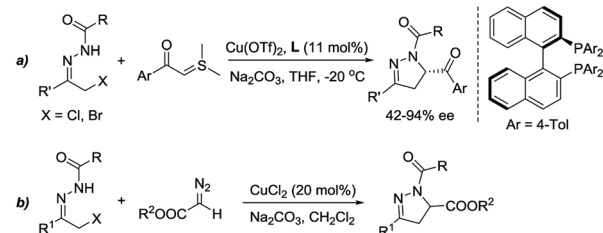
esters as 1,1-dipolar C1 synthons had also been utilized by the group of Favi to synthesize racemic dihydropyrazoles in a similar manner (Scheme 1b).<sup>5b</sup> However, none of these investigations has explored the possibility of accessing dihydropyrazoles containing a quaternary center. Herein, we 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), Na<sub>2</sub>CO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub> was the best choice.

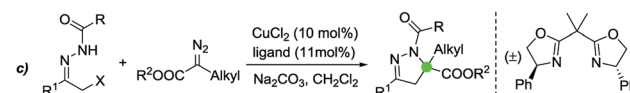
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† Electronic supplementary information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal structures of **3h**. CCDC 1840892. For ESI and crystallographic data in CIF or other electronic format see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

### Previous work

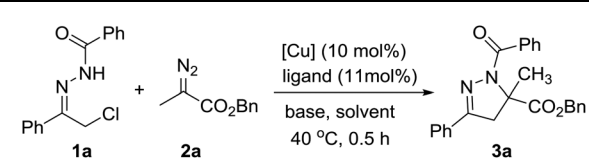


### This work



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



Table 1 Optimization of reaction conditions<sup>a</sup>


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

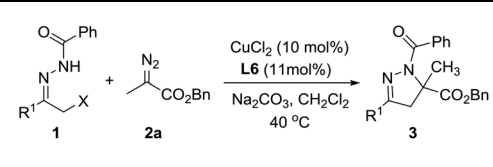
<sup>a</sup> Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2a** (0.5 mmol), base (0.5 mmol), Cu cat. (10 mol%), and ligand (11 mol%) in anhydrous solvent (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. <sup>b</sup> Yields refer to isolated products.

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  $\alpha$ -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 R<sup>2</sup> group (entries 1 and 2) had little influence on the yield of product **3**. The significant steric effect of R<sup>1</sup> 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).

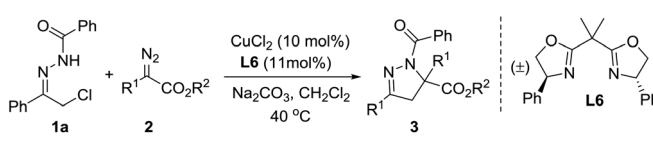
We next attempted to investigate asymmetric variant of this Cu(II)-catalyzed formal [4 + 1] cycloaddition reaction of diazo esters with azoalkenes formed *in situ* (Scheme 2). An extensive screening of chiral phosphine ligands (**L7**, **L8**), bisoxazoline ligands (**L9–12**) and different reaction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


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

<sup>a</sup> Reaction was run under the following conditions: a solution of **1** (0.1 mmol), **2a** (0.5 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.5 mmol), CuCl<sub>2</sub> (10 mol%), and **L6** (11 mol%) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. <sup>b</sup> Yields refer to isolated products.

Table 3 Substrate scope for diazo esters<sup>a</sup>


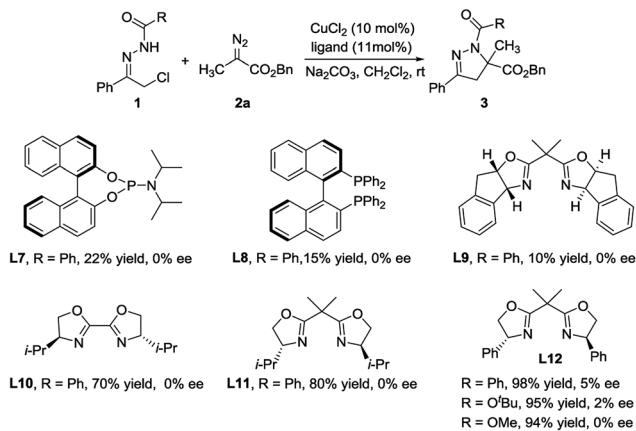
Entry	<b>2</b>	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>b</sup> of <b>3</b> (%)
1	<b>2a</b>	Me	Bn	<b>3a</b> , 98
2	<b>2b</b>	Me	Et	<b>3p</b> , 98
3	<b>2c</b>	Et	Et	<b>3q</b> , 92
4	<b>2d</b>	Bn	Bn	<b>3r</b> , trace
5	<b>2e</b>	Ph	Et	<b>3s</b> , trace

<sup>a</sup> Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2** (0.5 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.5 mmol), CuCl<sub>2</sub> (10 mol%), and **L6** (11 mol%) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. <sup>b</sup> Yields refer to isolated products.

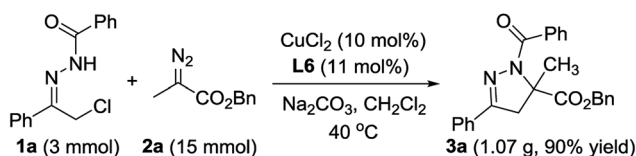
proceeded smoothly with 5 equiv. of **2a**, affording 1.07 g of **3a** (90% yield).

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).

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