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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

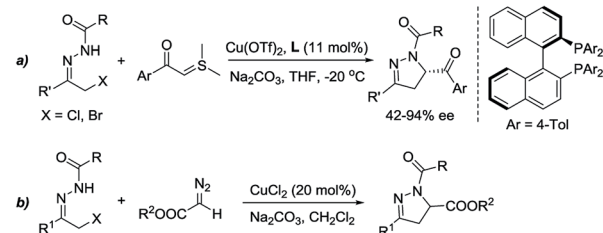
esters as 1,1-dipolar C1 synthons had also been utilized by the group of Favi to synthesize racemic dihydropyrazoles in a similar manner (Scheme 1b).^{5b} However, none of these investigations has explored the possibility of accessing dihydropyrazoles containing a quaternary center. Herein, we present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

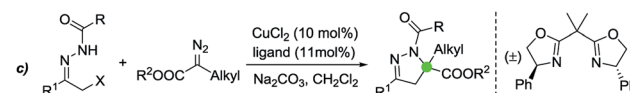
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Previous work

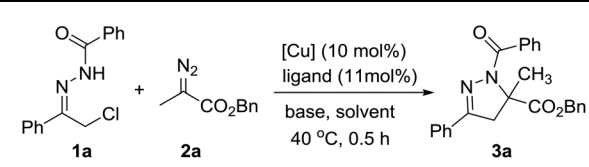


This work



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

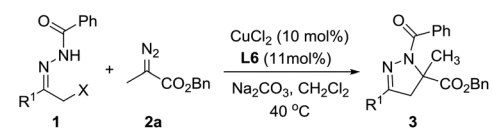
^a Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2a** (0.5 mmol), base (0.5 mmol), Cu cat. (10 mol%), and ligand (11 mol%) in anhydrous solvent (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. ^b Yields refer to isolated products.

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).

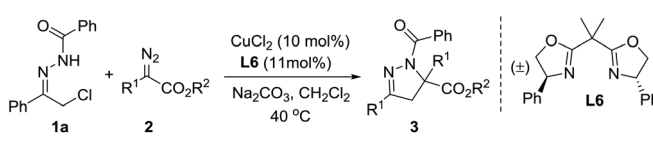
We next attempted to investigate asymmetric variant of this Cu(II)-catalyzed formal [4 + 1] cycloaddition reaction of diazo esters with azoalkenes formed *in situ* (Scheme 2). An extensive screening of chiral phosphine ligands (**L7**, **L8**), bisoxazoline ligands (**L9–12**) and different reaction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


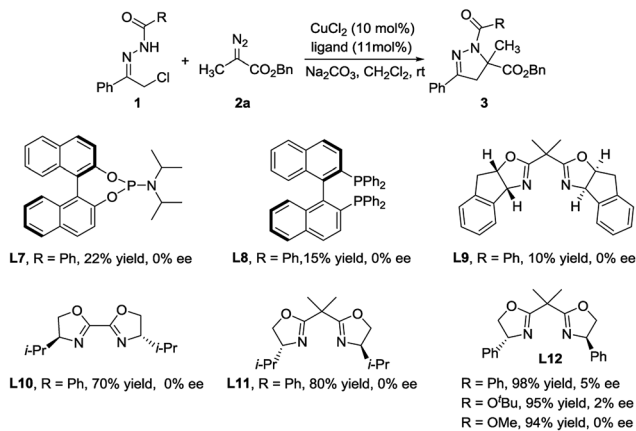
Entry	2	R ¹	R ²	Yield ^b of 3 (%)
1	2a	Me	Bn	3a , 98
2	2b	Me	Et	3p , 98
3	2c	Et	Et	3q , 92
4	2d	Bn	Bn	3r , trace
5	2e	Ph	Et	3s , trace

^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.

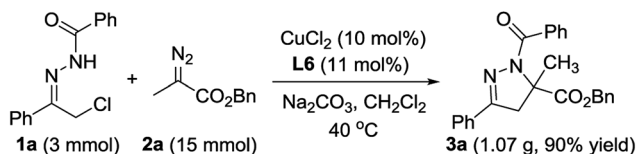
proceeded smoothly with 5 equiv. of **2a**, affording 1.07 g of **3a** (90% yield).

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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