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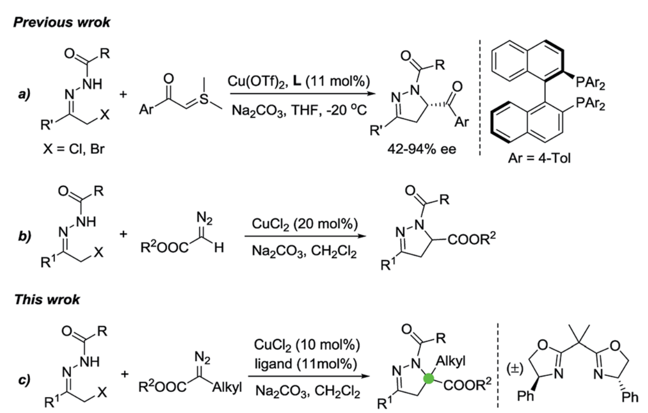
A Cu(II)/bisoxazoline ligand-promoted formal [4 + 1] cycloaddition of diazo esters with azoalkenes formed *in situ* has been developed. This strategy provides a potential protocol for the construction of dihydropyrazoles containing a quaternary center with good to excellent yields.

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), Na_2CO_3 and CH_2Cl_2 was the best choice.



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

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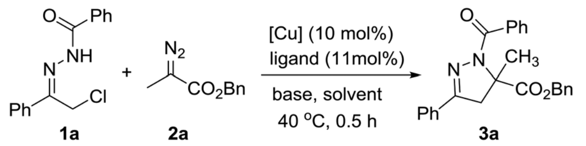
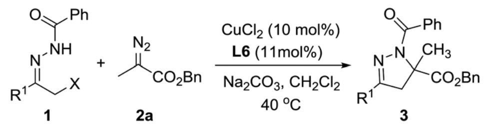
Table 1 Optimization of reaction conditions[a]



Entry	[Cu]	Ligand	Base	Solvent	Yield[b] (%)
1	$CuCl_2$	None	Na_2CO_3	CH_2Cl_2	None
2	$CuCl_2$	**L1**	Na_2CO_3	CH_2Cl_2	18
3	$CuCl_2$	**L2**	Na_2CO_3	CH_2Cl_2	6
4	$CuCl_2$	**L3**	Na_2CO_3	CH_2Cl_2	22
5	$CuCl_2$	**L4**	Na_2CO_3	CH_2Cl_2	5
6	$CuCl_2$	**L5**	Na_2CO_3	CH_2Cl_2	6
7	$CuCl_2$	**L6**	Na_2CO_3	CH_2Cl_2	98
8	$CuCl_2$	**L6**	K_2CO_3	CH_2Cl_2	15
9	$CuCl_2$	**L6**	Cs_2CO_3	CH_2Cl_2	26
10	$CuCl_2$	**L6**	NaOH	CH_2Cl_2	Trace
11	$CuCl_2$	**L6**	KO*t*Bu	CH_2Cl_2	Trace
12	$CuCl_2$	**L6**	Et_3N	CH_2Cl_2	Trace
13	$CuCl_2$	**L6**	Na_2CO_3	THF	83
14	$CuCl_2$	**L6**	Na_2CO_3	Toluene	Trace
15	$CuCl_2$	**L6**	Na_2CO_3	CH_3CN	5
16	$CuCl_2$	**L6**	Na_2CO_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.

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), Na_2CO_3 (0.5 mmol), $CuCl_2$ (10 mol%), and **L6** (11 mol%) in anhydrous CH_2Cl_2 (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. [b] Yields refer to isolated products.

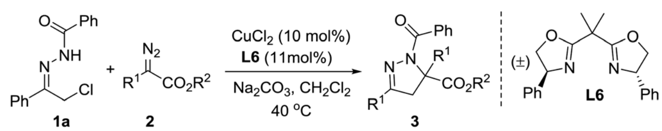
With the optimized conditions in hand, we next explored the substrate scope of the heterodienes. A series of hydrazones **1a–l** bearing electron-neutral, -deficient or -rich aromatic substituents were smoothly reacted with diazo ester **2a** to give the corresponding dihydropyrazoles **3a–l** in 76–98% 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 R^2 group (entries 1 and 2) had little influence on the yield of product **3**. The significant steric effect of R^1 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** proceeded smoothly with 5 equiv. of **2a**, affording 1.07 g of **3a** (90% yield).

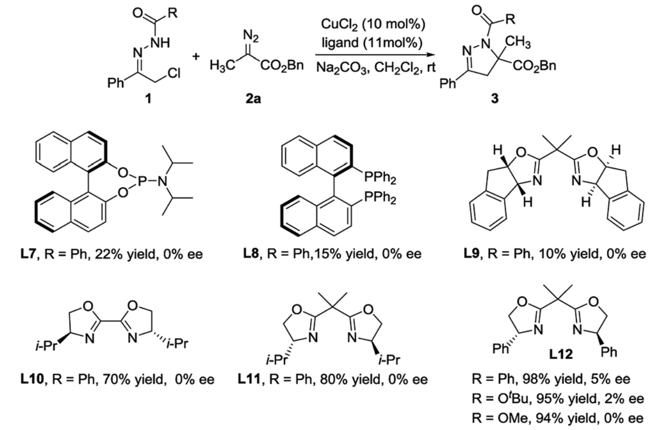
Table 3 Substrate scope for diazo esters[a]



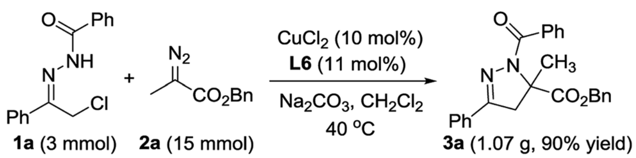
Entry	2	R^1	R^2	Yield[b] of **3** (%)
1	**2a**	Me	Bn	**3a**, 98
2	**2b**	Me	Et	**3p**, 98
3	**2c**	Et	Et	**3q**, 92
4	**2d**	Bn	Bn	**3r**, trace
5	**2e**	Ph	Et	**3s**, trace

[a] Reaction was run under the following conditions: a solution of **1a** (0.1 mmol), **2** (0.5 mmol), Na_2CO_3 (0.5 mmol), $CuCl_2$ (10 mol%), and **L6** (11 mol%) in anhydrous CH_2Cl_2 (1 mL) was stirred at 40 °C under nitrogen atmosphere for 0.5 h. [b] Yields refer to isolated products.

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.

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