RSC Advances

PAPER

View Article Online
View Journal | View Issue

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

Received 27th October 2018
Accepted 2nd January 2019

DOI: 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†

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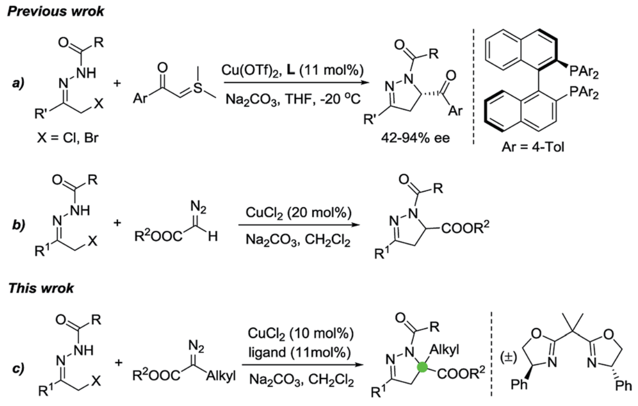
A Cu(II)/bisoxazoline ligand-promoted formal [4 + 1] cycloaddition of diazo esters with azoalkenes formed *in situ* has been developed. This strategy provides a potential protocol for the construction of dihydropyrazoles containing a quaternary center with good to excellent yields.

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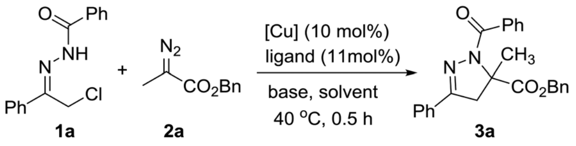
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal structures of **3h**. CCDC 1840892. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra08909d

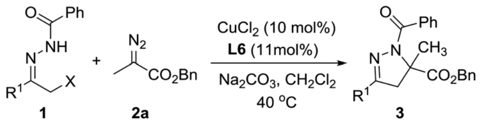
Table 1 Optimization of reaction conditions[a]



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.

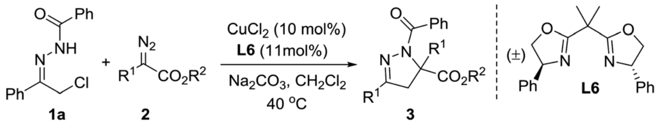
Table 2 Substrate scope for hydrazones[a]



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.

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.

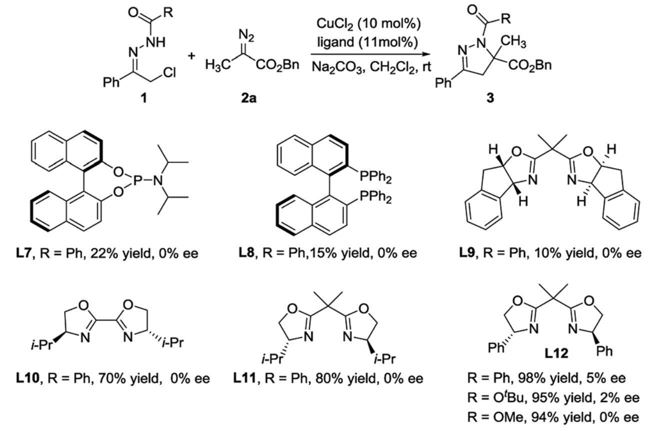
With the optimized conditions in hand, we next explored the substrate scope of the heterodienes. A series of hydrazones **1a–l** bearing electron-neutral, -deficient or -rich aromatic substituents were smoothly reacted with diazo ester **2a** to give the corresponding dihydropyrazoles **3a–l** in 76–98% 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).

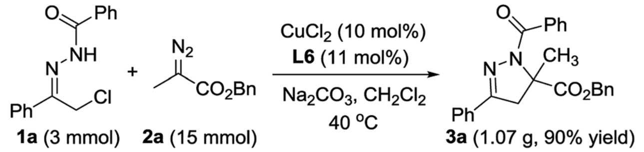
We next attempted to investigate asymmetric variant of this Cu(II)-catalyzed formal [4 + 1] cycloaddition reaction of diazo esters with azoalkenes formed *in situ* (Scheme 2). An extensive screening of chiral phosphine ligands (**L7**, **L8**), bisoxazoline ligands (**L9–12**) and different reaction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

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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