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 for m a l[3+2]c y c l o a d d i t i o n ,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 azaheterocycles 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).3e 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).3e 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.
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 10 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 phosphate 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.
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