Ring Expansion of Oxetanes to 4-Substituted Furans with NHC-Cu Catalysts

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Abstract: Ring expansion of oxetanes and azetidines was rarely reported. However, this could be a very effective method for the synthesis of tetrahydrofurans. The ring expansion of oxetanes with diazo compounds was reported, but the substrate scope was quite limited. We successfully developed a new NHC ligand combined with copper could successfully accomplish this reaction with high yield.

1. Introduction

Typical utility of carbene and carbenoid reactions is the carbon-carbon bond forming reaction which provides a number of convenient and direct tools for molecular construction by manipulating divalent and ambiphilic, particularly electrophilic nature of carbene-type reactive molecules under controlled conditions. There were several methods to form the C-C bond with carbenoid shown as followings: (1) vinylcarbenes in equilibrium with cyclopropenes and their addition reactions, (2) carbenes substituted by hetero atoms, such as O, N, P, and S, (3) electrophilicity of carbenoids and their stereoselective alkylation, (4) mechanism and synthetic application of C-H insertion reactions by carbenes and carbenoids, (5) rhodium-catalyzed reactions of ketocarbenoid with O-H, and N-H bond, (6) novel methods of generating carbenes under neutral and mild conditions.[1-4]
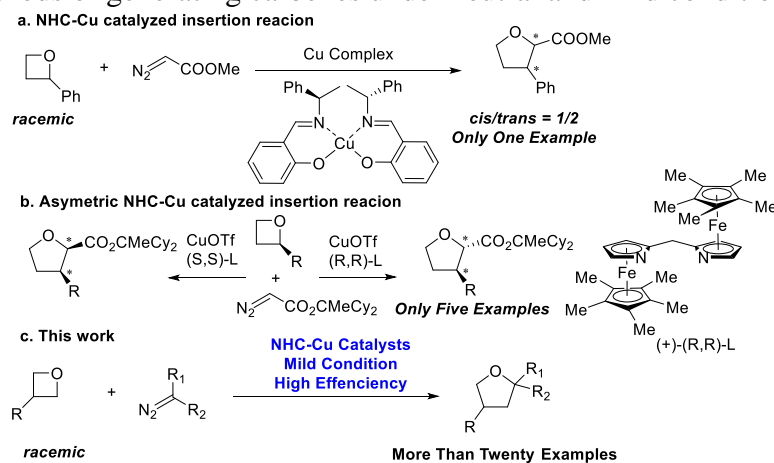

Figure 1. Ring expansion with Cu catalysts and diazo compounds

According to the previous research, the Cu-catalyzed ring expansion of oxetanes and azetidines with diazo compounds was still faced with several important problems, which is: (1) limited substrate scope.[5] See Figure 1. In Fu's report, only five substrates were used, and electron donation group showed great influence on the ring expansion reaction.[6] Both yield and ee value decreased significantly. For azetidines, only one substrate was reported. The limited substrate scope showed great influence on the reaction which could be used in organic synthesis. (2) No asymmetric ring expansion of the azetidine was reported. (3) In Fu's report, only active diazo compound was used which was quite easily decompose in Lewis acid conditions.

2. Optimization of the Ring Expansion Reaction

The ring expansion of 3-phenyl oxetane was firstly discovered with dimethyl diazo malonate and IMesCuCl with 35% yield. Different from the previous report, our initial test for this reaction used the 3-phenyl oxetane.
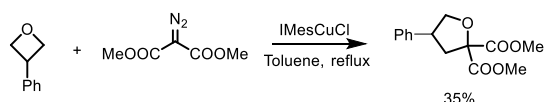

Figure 2. Initial attempt of this reaction

The optimization of this reaction started from the optimization of diazo compounds. This reaction was first reported by Regitz in 1967. [7] See Figure 2. It is a base-promoted transfer of a diazo group from an azide to an active methyl or methylene moiety of a substrate with one or more electron-withdrawing groups. Therefore, it is known as the Regitz diazo transfer.[8] Then, different diazo compounds were also synthesized for further optimization of this reaction. See Figure 3 and Table 1.
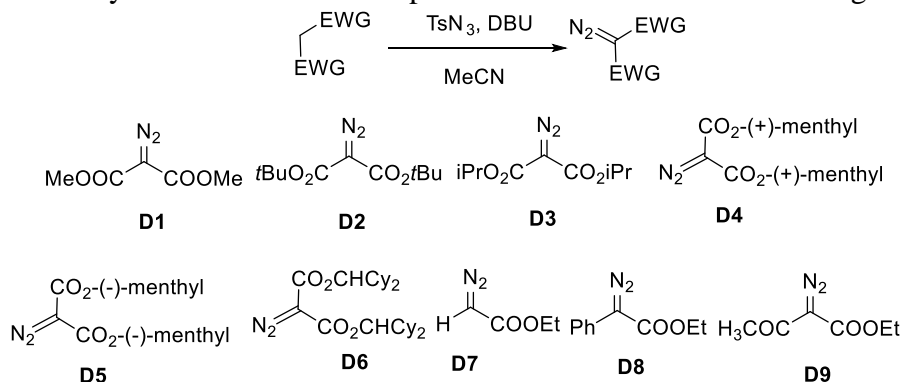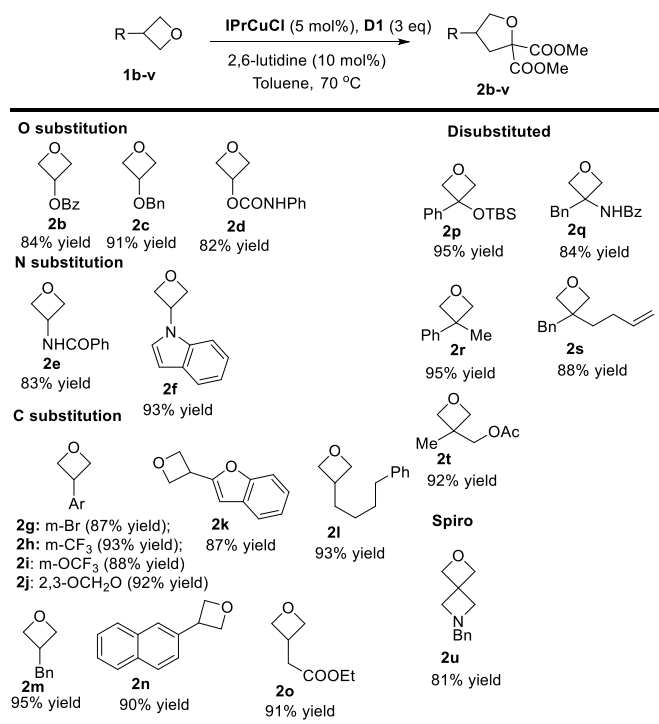

Figure 3. Synthesis of diazo compounds

The reaction condition was optimized with large amounts of conditions. Original optimization was tested with substrate 1a and different NHC-Cu catalysts. D1 was found to be the best diazo compound with excellent yield (entry 5-12). D2 and D3 replaced the methyl group with tBu or iPr in D1, which were more steric hindered. The increasing steric hinder effect might be the possible explanation for the decreasing reaction yield. For diazo compound D4, D5 and D6, the reaction yield decreased significantly. Even after 48 h, remaining substrate could be detected in the crude NMR, which might be cause by the too bulky substitution groups was quite hard to exist as substitution groups on the same carbon on THF ring. Besides that, other unactive diazo compound with two different substitution group also showed poor diastereoselectivity of the products. At last, different additives were used and found that adding 10 mol% 2, 6-lutidine could give the product with 96% yield. The final best condition was 5 mol% IPrCuCl catalyst, 3 eq D1, and 10 mol% 2, 6-lutidine in Toluene at 70°C for 48h (Table 1).

Table 1. Optimization of reaction conditions.[a]

Entry	Catalyst	Diazo	Additive	Temp (°C)	Yield (%)[a]
1	IMesCuCl	D1	-	110	35
2	SIMesCuCl	D1	-	110	36
3	IPrCuCl	D1	-	110	42
4	SIPrCuCl	D1	-	110	31
5	IPrCuCl	D2	-	110	40
6	IPrCuCl	D3	-	110	20
7	IPrCuCl	D4	-	110	n.d.
8	IPrCuCl	D5	-	110	n.d.
9	IPrCuCl	D6	-	110	n.d.
10	IPrCuCl	D7	-	110	n.d.
11	IPrCuCl	D8	-	110	n.d.
12	IPrCuCl	D9	-	110	12
13	IPrCuCl	D1	-	90	53
14	IPrCuCl	D1	-	70	75
15	IPrCuCl	D1	-	50	n.d.
16	IPrCuCl	D1	DMAP (10 mol%)	70	61
17	IPrCuCl	D1	2,6-lutidine (10 mol%)	70	65
18	IPrCuCl	D1	2,6-di-tBu-pyridine (10mol%)	70	96
19	IPrCuCl	D1	pyridine (10 mol%)	70	85

Note: [a]Yields were determined by isolation, n.d. stands for not detected.

3. Substrate scope of this reaction

Figure 4. Substrate scope of this reaction

After the best reaction condition was achieved, numbers of substrate were screened to test the reaction tolerance to function groups. Different substitution patterns of 3-substituted oxetane were tested: O-substitution, N-substitution, C-substitution and disubstituted. For 3-O-substituted oxetanes, different substitutions (ester, ether and amide) were included. Only benzoyl group showed moderate yield. Amine or indole substituted oxetanes were quite reactive and the enantioselectivity was excellent. For single C-Substitution on C3 of the oxetanes, aryl and alkyl groups were tested. Among them, benzyl group showed the best reaction yield (90% yield). The disubstituted oxetanes reacted in excellent yield. Particularly, cyclopropane side product was not observed in the ring expansion of oxetane with alkene substitution, which showed excellent reaction selectivity of this ring expansion reaction. At last, spiro-oxetanes were also tested, and the ring expansion only happened on the oxetane ring compared with the N-heterocycle. See Figure 4.

4. Experimental

Ring expansion of oxetanes:

To a solution of NHC-Cu catalyst (5 mol%) oxetane substrates (0.1 mmol), diazo compound (3 eq, 0.3 mmol, 48 mg), 2,6-lutidine (10 mol%, 1uL) and toluene (1.5 mL) were added. After 48 h reaction, the reaction was quenched with NH4Cl. The organic layer was collected and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired product.

5. Conclusions

In summary, new chiral NHC ligands were synthesized successfully and they were employed as efficient catalysts of the ring expansion of 3-substituted oxetanes with diazo compounds. According to our results, only diazo compounds with two same substitution groups could be used in this reaction. Different substitution pattern of oxetanes were tested for the ring expansion reaction. Reactivity of disubstituted oxetanes showed better reactivity than monosubstituted substrates. Finally, the reaction mechanism was not proposed, and further study of this reaction is undergoing in our lab.

Acknowledgements

Conflict of Interest

The authors declare that they have no conflicts of interest.

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