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Copper-Catalyzed Asymmetric [4+1] Cycloadditions of Enones with Diazo Compounds to Form Dihydrofurans

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2,3-Dihydrofurans are subunits of a range of biologically active compounds (e.g., aflatoxin B₁ and clerodin);¹ furthermore, they serve as extremely useful synthetic intermediates, since they can be transformed with good stereoselectivity into an array of highly functionalized tetrahydrofurans.² Although many strategies for the synthesis of 2,3-dihydrofurans have been described, virtually no catalytic asymmetric processes have been developed.³

In 1967, Spencer reported that CuSO₄ catalyzes the [4+1] cycloaddition of β -methoxy- α,β -unsaturated ketones with ethyl diazoacetate, leading to furans upon elimination of methanol from the presumed 2,3-dihydrofuran intermediate.⁴ Since this pioneering work, there have been several other studies of copper-catalyzed reactions of enones with diazo compounds, but none of these investigations has explored the possibility of accessing 2,3-dihydrofurans with control of relative or absolute stereochemistry.⁵

We recently decided to address this challenge, and in this report we describe our progress to date. Specifically, we have established that, through the use of planar-chiral bipyridine ligand bpy*,⁶ copper-catalyzed [4+1] cycloadditions of α,β -unsaturated ketones with diazoacetates can produce highly substituted 2,3-dihydrofurans in good yield, dr, and ee (eq 1).^{7,8}

(1)

In initial studies, we explored cycloadditions of enones with diazo compounds in the presence of a variety of chiral ligands that have proved useful in other copper-catalyzed processes. Unfortunately, for the reaction of chalcone with *t*-butyl diazoacetate, a bis(oxazoline),⁹ a semicorrin,¹⁰ and a bis(azaferrocene)¹¹ were not effective (Table 1, entries 1-3). On the other hand, a planar-chiral 2,2'-bipyridine (bpy*)¹² provided promising yield, dr, and ee (entry 4).

In order to improve upon our preliminary lead (Table 1, entry 4), we investigated the dependence of these Cu/bpy*-catalyzed asymmetric [4+1] cycloadditions on the steric demand of the diazoester (Table 2). Use of a small alkyl or aryl group led to lower ee (entries 2 and 3 versus entry 1). On the other hand, hindered aryl esters furnished higher enantioselectivities (entries 4-6), with the 2,6-diisopropylphenyl ester providing the best combination of yield, dr, and ee (entry 5).

We have examined the scope of this copper-catalyzed asymmetric synthesis of 2,3-dihydrofurans (Table 3). The enantiomeric excesses are highest when the enone substituents are unsaturated. Thus, regardless of whether R or R¹ is an electron-poor or an electron-rich aromatic group, good ee is typically observed (entries 2-6). Furthermore, the reaction proceeds with useful enantioselectivity when a heteroaromatic substituent is present (entries 7 and 8). Finally, an enone that bears an alkenyl group undergoes cycloaddition with high efficiency (entry 9).

This Cu/bpy*-catalyzed method for the synthesis of 2,3-dihydrofurans may also be applied to alkyl-substituted enones, although such cycloadditions proceed with more modest enantiomeric excess than those that bear only unsaturated groups. Nevertheless, the desired dihydrofurans are generally produced in good yield and with excellent diastereoselectivity (Table 3, entries 10-12).¹³

The 2,3-dihydrofuran products can be converted into a variety of other useful families of compounds without an erosion in dr or ee. Thus, a primary alcohol can be generated via

treatment of the cycloaddition adduct with LiAlH_4 (eq 2). Furthermore, hydrolysis and then acetylation affords an acyclic ester that bears an α and a β stereocenter (eq 3).

Deoxy-C-nucleosides are of interest in medicinal chemistry as mimics of naturally occurring nucleosides.¹⁴ We have established that our Cu/bpy*-catalyzed [4+1] cycloaddition can be applied to the expeditious catalytic asymmetric synthesis of this class of compounds (Figure 1). Cycloaddition of an α -diazoacetate to the illustrated vinylogous ester furnishes a 2,3-dihydrofuran, which is not isolated due to its sensitivity. Hydrogenation of the olefin and then reduction of the ester affords the desired tetrahydrofuran in good yield and diastereoselectivity (77% yield for three steps; >20:1 dr). Deprotection of the trimethylsilylethyl group then provides the deoxy-C-nucleoside (93% ee).^{15,16}

In conclusion, we have described the first examples of diastereo- and enantioselective copper-catalyzed [4+1] cycloadditions of enones with diazo compounds. This new method furnishes synthetically useful, highly substituted 2,3-dihydrofuran derivatives with good efficiency and stereoselection. Additional studies of asymmetric copper-catalyzed reactions of diazo compounds are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Catalytic asymmetric synthesis of deoxy-C-nucleosides.

Table 1

Copper-catalyzed asymmetric [4+1] cycloadditions: Survey of ligands

entry	ligand	yield (%) ^a	dr	ee (%)
1	bis(oxazoline) 1	12	>20:1	-20 ^b
2	semicorrin 2	<2	-	-
3	bis(azaferrocene) 3	6	>20:1	34
4	(-)-bpy*	45	>20:1	60
5	no ligand	10	>20:1	-
6	no CuOTf, no ligand	<2	-	-

All data are the average of two runs.

^a Isolated yield of the trans diastereomer.^b The opposite enantiomer is produced.

Table 2

Copper-catalyzed asymmetric [4+1] cycloadditions: Impact of the structure of the diazoester

entry	R	yield (%) ^a	dr	ee (%)
1	<i>t</i> -Bu	45	>20:1	60
2	Et	43	>20:1	37
3	Ph	44	>20:1	37
4	2,6-dimethylphenyl	63	7:1	83
5	2,6-diisopropylphenyl	79	13:1	85
6	2,6-di- <i>t</i> -butyl-4-methylphenyl	47	16:1	85

All data are the average of two runs.

^a Isolated yield of the trans diastereomer.

Table 3

Copper-catalyzed asymmetric [4+1] cycloadditions: Scope

entry	R	R ¹	~1.2 equiv	1.0% CuOTf 1.3% (-)-bpy [*]	CH ₂ Cl ₂ r.t.	Ar = 2,6-diisopropylphenyl	yield (%) ^a	dr	ee (%)
1	Ph	Ph					79	13:1	85
2	4-(F ₃ C)C ₆ H ₄	Ph					59	19:1	76
3	4-ClC ₆ H ₄	Ph					77	19:1	88
4 ^b	4-(MeO)C ₆ H ₄	Ph					84	19:1	92
5	Ph	4-ClC ₆ H ₄					81	>20:1	88
6	Ph	4-(MeO)C ₆ H ₄					84	9:1	93
7	N-Boc-2-pyrrolyl	Ph					68	>20:1	93
8	Ph	3-furyl					63	6:1	87
9	Ph	CH=CHPh					76	7:1	93
10	Ph	<i>n</i> -Bu					92	>20:1	78
11	<i>n</i> -Hex	Ph					69	13:1	75
12	<i>n</i> -Hex	Me					80	>20:1	71

All data are the average of two runs.

^a Isolated yield of the trans diastereomer.

^b The product was hydrolyzed and then acetylated, prior to isolation.