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

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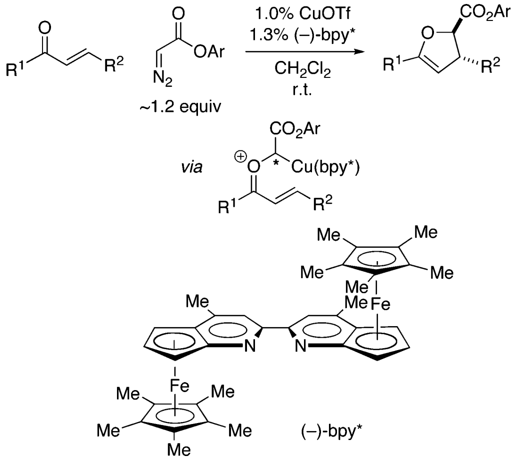
2,3-Dihydrofurans are subunits of a range of biologically active compounds (e.g., aflatoxin B_1 and clerodin);[1] furthermore, they serve as extremely useful synthetic intermediates, since they can be transformed with good stereoselectivity into an array of highly functionalized tetrahydrofurans.[2] 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 $CuSO_4$ 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]

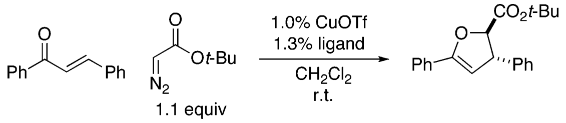


(1)

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).

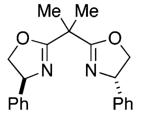
To improve upon our preliminary lead (Table 1, entry 4), we investigated the dependence of these Cu/bpy*-catalyzed asymmetric [4+1] cycloadditions on the steric demand of the diazoester (Table 2). Use of a small alkyl or aryl group led to lower ee (entries 2 and 3 versus entry 1). On the other hand, 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).

Table 1. Copper-Catalyzed Asymmetric [4+1] Cycloadditions: Survey of Ligands[a]



entry	ligand	yield (%)[b]	dr	ee (%)
1	bis(oxazoline) **1**	12	>20:1	−20[c]
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		

[a] All data are the average of two runs. [b] Isolated yield of the trans diastereomer. [c] The opposite enantiomer is produced.



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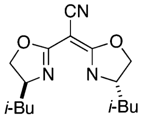

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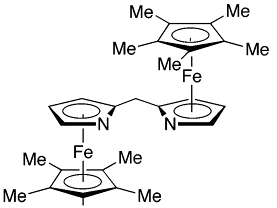

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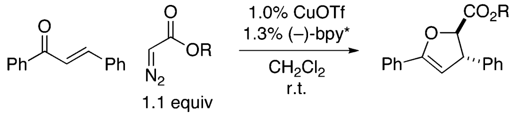
Table 2. Copper-Catalyzed Asymmetric [4+1] Cycloadditions: Impact of the Structure of the Diazoester[a]



entry	R	yield (%)[b]	dr	ee (%)
1	*t*-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-*t*-butyl−4-methylphenyl	47	16:1	85

[a] All data are the average of two runs. [b] Isolated yield of the trans diastereomer.

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 R^1 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

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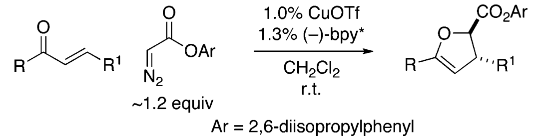
Table 3. Copper-Catalyzed Asymmetric [4+1] Cycloadditions: Scope[a]



entry	R	R^1	yield (%)^b	dr	ee (%)
1	Ph	Ph	79	13:1	85
2	4-(F_3C)C_6H_4	Ph	59	19:1	76
3	4-ClC_6H_4	Ph	77	19:1	88
4^c	4-(MeO)C_6H_4	Ph	84	>20:1	92
5	Ph	4-ClC_6H_4	81	>20:1	88
6	Ph	4-(MeO)C_6H_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	*n*-Bu	92	>20:1	78
11	*n*-Hex	Ph	69	13:1	75
12	*n*-Hex	Me	80	>20:1	71

[a] All data are the average of two runs. [b] Isolated yield of the trans diastereomer. [c] The product was hydrolyzed and then acetylated prior to isolation.

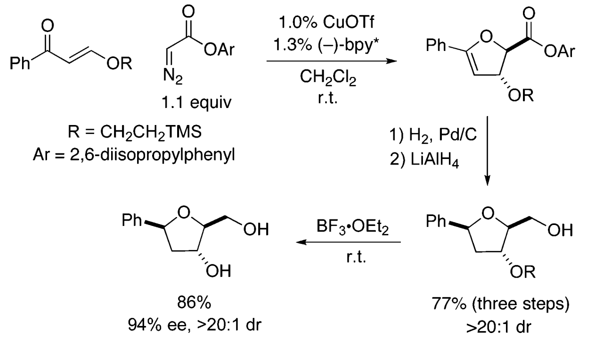
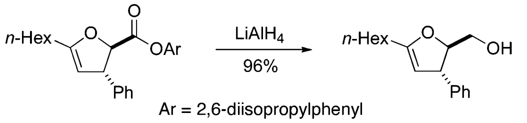


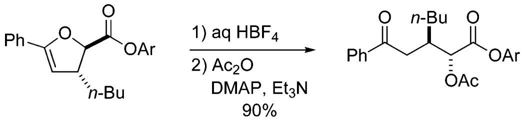
Figure 1. Catalytic asymmetric synthesis of deoxy-C-nucleosides.

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).



(2)



(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 because of 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 (94% 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.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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