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Lewis Acid-Catalyzed [3+2]-Cycloaddition Reactions of Allyl(cyclopentadienyl)iron(II) Dicarbonyl With Carbonyl Compounds

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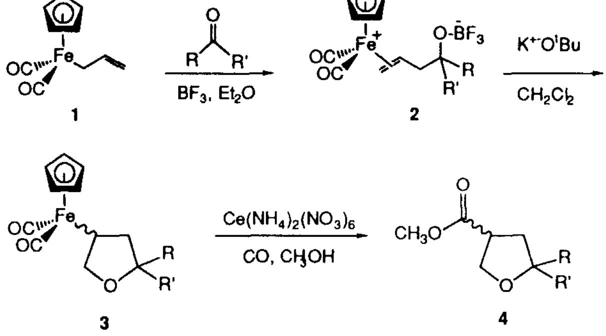
Key Words: Lewis acid catalysis; [3+2]-cycloadditions, allyl(cyclopentadienyl)iron(II) dicarbonyl; tetrahydrofuran synthesis; carbonyl compounds

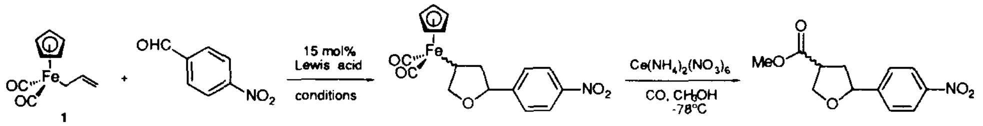
Abstract: *$ZnCl_2$ catalyzes the [3+2]-cycloaddition of allyl(cyclopentadienyl)iron(II) dicarbonyl to carbonyl compounds to give tetrahydrofuran adducts.*

The [3+2]-cycloaddition reaction between an allylmetallic reagent and carbonyl compounds offers a conceptually attractive and expedient approach to furans and related ring systems, which are common substructures of many natural products and pharmaceutical agents.[1] Recently we described a procedure[2] for the synthesis of tetrahydrofuran esters based on the BF_3-promoted reaction of allyl(cyclopentadienyl)iron(II) dicarbonyl (**1**)[3] and carbonyl compounds.[4,5] In this process, allyliron complex **1** reacts with aldehydes[6] or ketones[7] in the presence of BF_3-etherate to afford zwitterionic π-complexes **2** (**eq 1**). Upon treatment of **2** with potassium t-butoxide in methylene chloride, a transient homoallylic alkoxide is generated which spontaneously adds to the iron-alkene π-complex to give iron furan **3**. Without isolation, **3** can be converted to furan esters **4** using methanolic ceric ammonium nitrate under a CO atmosphere. In this Communication, we report that this [3+2]-cycloaddition process can be improved by performing the allylation-cyclization steps in a single operation using Lewis acid catalysis.



(1)

To synthesize iron furan **3** from allyliron complex **1** using our previously reported procedure, an excess amount of the carbonyl compound is required for the initial allylation step (**1** to **2**) to minimize the formation of an allyliron-BF_3 co-adduct, which otherwise interferes with the subsequent cyclization step and is difficult to separate from π-complex **2**. We suspected that this problem could be avoided by carrying out the allylation-cyclization procedure (**1** to **2** to **3**) under Lewis acid *catalysis*. To investigate this possibility, we first studied the reaction of 4-nitrobenzaldehyde with allyliron reagent **1** under a variety of Lewis acid conditions using 15 mol% catalyst (**eq 2**). The reactions were conducted by adding a freshly prepared solution of **1** (2.5 mmol) in CH_2Cl_2 to a stirred mixture of the aldehyde (1 mmol) and Lewis acid (15 mol%) in CH_2Cl_2 at room temperature. After stirring for 15 hours, the reaction mixture is added slowly to a methanolic solution of ceric ammonium nitrate under an atmosphere of CO. Evaporation and purification by flash chromatography gives the tetrahydrofuran ester as a mixture of diastereomers.[8] The isolated yields and diastereomeric ratios of furan esters are given in **Table 1**. Of the Lewis acids examined, $ZnCl_2$ provides the highest yield and stereoselectivity, while BF_3-etherate is the least effective catalyst.



1

(2)

Table 1. Survey of Lewis Acids (@ CH_2Cl_2, 22°C)

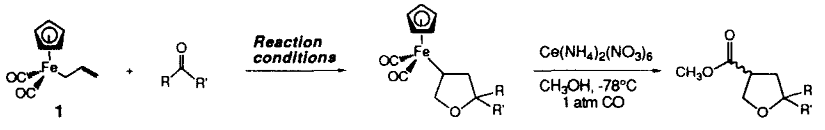
Lewis acid	*Time*	*Isolated yield*[a]*, ratio*[b]
$ZnCl_2$	14 h	71%, 3.1:1
$MgBr_2$	14 h	61%, 1.6:1
$SnCl_4$	15h	58%, 1.8:1
$TiCl_4$	14 h	55%, 2.0:1
$AlBr_3$	12 h	45%, 1.5:1
$Ti(OPr)_4$	15 h	33%, 1.9:1
BBr_3	27h	29%, 1.6:1
BF_3	28 h	18%, 1.9:1

[a] Isolated yields after flash chromatography on silica gel.
[b] Ratios determined by integration of non-overlapping signals in the ^1H NMR spectrum.

Table 2. Effect of Solvent and Temperature on $ZnCl_2$-Catalyzed Reaction

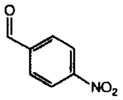
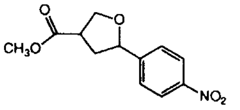
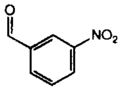
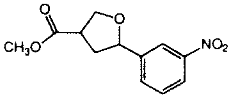
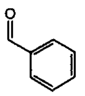
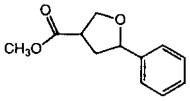
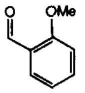
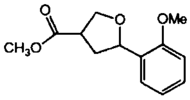
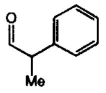
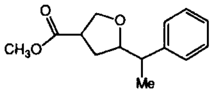
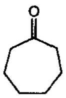
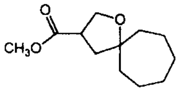
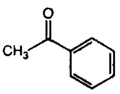
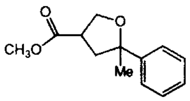
Solvent	*Temperature*	*Time*	*Isolated yield*[a]*, ratio*[b]
CH_2Cl_2	22°C	14 h	71%, 3.1:1
	-20°C	24 h	41%, 3.5:1
	-78°C	37 h	25%, 3.4:1
THF	22°C	14 h	40%, 2.5:1
	-20°C	22 h	2%, 1.9:1
hexane	22°C	14 h	34%, 1.8:1
	-20°C	21 h	21%, 2.3:1
Et_2O	22°C	13 h	29%, 2.0:1
	-20°C	20 h	8%, 1.9:1
benzene	22°C	14 h	22%, 2.0:1
toluene	-20°C	23 h	3%, 1.5:1

The effect of solvent and temperature on the [3+2]-reaction was also studied, using 15 mol% $ZnCl_2$ as catalyst (**Table 2**). From the list of solvents examined, methylene chloride gives the best results in terms of both the product yield and stereoselectivity. We also found that reactions conducted at room temperature proceed in higher yield than those at -20°C, although the diastereoselectivity appears to be slightly better at lower temperature. Thus, these experiments suggest that the best conditions for the [3+2]-cycloaddition include the use of catalytic $ZnCl_2$ in CH_2Cl_2 solution at room temperature.



(3)

Table 3. [3+2]-Cycloaddition Reactions of Iron Complex **1** and Carbonyl Compounds

Carbonyl Compound	***Product***	***Reaction conditions***	***% yield[a], ratio[b]***
		$ZnCl_2$ (15 mol%), CH_2Cl_2, RT $ZnCl_2$ (100 mol%), CH_2Cl_2, RT no Lewis acid, CH_2Cl_2, RT	71% (3.1:1) 50% (1.1:1) 60% (1.9:1)
		$ZnCl_2$ (15 mol%), CH_2Cl_2, RT no Lewis acid, CH_2Cl_2, RT	62% (2.7:1) 45% (1.9:1)
		$ZnCl_2$ (15 mol%), CH_2Cl_2, RT $ZnCl_2$ (100 mol%), CH_2Cl_2, RT no Lewis acid, CH_2Cl_2, RT	36% (2.1:1) 40% (1.1:1) 8% (1.8:1)
		$ZnCl_2$ (15 mol%), CH_2Cl_2, RT $ZnCl_2$ (100 mol%), CH_2Cl_2, RT	31% (2.0:1) 28% (1.2:1)
		$ZnCl_2$ (100 mol%), CH_2Cl_2, RT $TiCl_4$ (200 mol%), CH_2Cl_2, -78°C	16% [c] 15% [c]
		$ZnCl_2$ (100 mol%), CH_2Cl_2, RT $TiCl_4$ (200 mol%), CH_2Cl_2, -78°C	0% 37%
		$ZnCl_2$ (100 mol%), CH_2Cl_2, RT $TiCl_4$ (200 mol%), CH_2Cl_2, -78°C	0% 15% (1.0:1)

[a] Isolated yields after flash chromatography on silica gel.

[b] Ratios determined by integration of non-overlapping signals in the ^1H NMR spectrum.

[c] Ratios not determined due to overlapping signals in the ^1H NMR spectrum.

To expand upon the scope of this [3+2]-cycloaddition methodology, a variety of aldehydes and ketones were surveyed in Lewis acid catalyzed reactions with **1** (**eq 3**). We have summarized the results of these experiments in **Table 3**. For aromatic aldehydes, the best yields and stereoselectivity are consistently obtained using 15 mol% of $ZnCl_2$ in CH_2Cl_2. Attempts to use larger amounts of catalyst (100 mol%) tends to give lower yields and stereoselectivity. Ketones also participate in these cycloadditions, provided that two molar equivalents of $TiCl_4$ is used in place of $ZnCl_2$. In certain cases, the cycloadditions take place at room temperature in the absence of Lewis acid, however, these uncatalyzed reactions seem to be limited to activated aldehydes (eg., 3-nitrobenzaldehyde, 4-nitrobenzaldehyde).

In conclusion, we have found that the [3+2]-cycloaddition reaction of allyl(cyclopentadienyl)iron(II) dicarbonyl with aldehydes and ketones proceeds in the presence of Lewis acid catalysts. This methodology offers advantages over the procedure reported earlier in that excess amounts of the carbonyl compound are not required, and the overall yields and (in most cases) diastereoselectivity of the cycloadducts are noticeably improved. We are currently extending this methodology to the synthesis of other classes of heterocycles and to intramolecular cycloaddition processes for the construction of multicyclic ring systems.

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(8) All furan esters gave satisfactory ^1H NMR, ^{13}C NMR, infrared, and high resolution mass spectral analysis.

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