A Lewis Acid-Catalyzed Formal [3 + 3] Cycloaddition of α , β -Unsaturated Aldehydes with 4-Hydroxy-2-Pyrone, Diketones, and Vinylogous Esters

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ABSTRACT



Mg(OTf)₂, CuCl, ZnBr₂, Zn(OTf)₂, In(OTf)₃

A Lewis acid-catalyzed formal cycloaddition of α , β -unsaturated aldehydes with 6-methyl-4-hydroxy-2-pyrone, 1,3-diketones, and vinylogous silyl esters is described here.

Recently, we have been developing a formal cycloaddition or annulation reaction involving α , β -unsaturated aldehydes and 1,3-dicarbonyls,¹⁻³ and have employed this strategy in the synthesis of natural products.^{4–8} The tandem nature⁹ of this annulation involves an initial condensation of **3** with

iminium ions **2** followed by 6π -electron electrocyclic ringclosure of 1-oxatrienes **6**^{10,11} [Scheme 1]. It has become increasingly evident from the literature^{12–14} that this bioinspired strategy is both useful and practical for constructing

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2*H*-pyrans **7** from rather simple and cost-effective starting materials.

There remain two significant problems with this reaction: (1) high temperatures are required [80–150 °C] and (2) in many cases pregeneration of iminium intermediates 2 is necessary prior to the addition of 3 to control the regio-chemistry and enhance the overall yield.¹⁵

This led us to explore if this annulation can be catalyzed or promoted by a Lewis acid^{16,17} and proceed under a milder reaction temperature. We report here a Lewis acid-catalyzed formal [3 + 3] cycloaddition reaction.

A preliminary screening reveals that a range of Lewis acids could be used to promote this formal cycloaddition as summarized in Tables 1 and 2 with use of pyrone 8 and diketone 11, respectively. Notable features are the following: (1) Usage of Lewis acids did not alter the chemistry and provide the same 2H-pyran as when using iminium salts; 2) Lewis acids could be employed at substoichiometric

Table 1. Screening of Lewis Acids for the Reaction of 8

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но в	$\begin{array}{c} \textbf{LA} \\ O \\ \hline CH_2Cl_2 \\ 4 \text{ Å MS} \end{array}$	9				
entry	LA^a	equiv	concn [M] ^c	temp [°C]	time [h]	yield [%] ^b
1	BF ₃ -Et ₂ O	1.00	0.11	rt	24	69
2	BF ₃ -Et ₂ O	0.50	0.12	\mathbf{rt}	16	68
3	BF_3 - Et_2O	0.10	0.09	\mathbf{rt}	24	11
4	BF_3 - Et_2O	0.05	0.09	\mathbf{rt}	24	5
5	TiCl ₄	0.10	0.09	\mathbf{rt}	22	80
6	$SnCl_4$	0.10	0.09	\mathbf{rt}	24	38
7	AlCl ₃	0.10	0.09	\mathbf{rt}	48	8
8	In(OTf) ₃	0.10	0.09	\mathbf{rt}	48	3
9	ZnBr_2	0.10	0.09	\mathbf{rt}	24	48

^{*a*} All reactions were carried out with 186 mg/mmol of 4 Å MS. ^{*b*} Isolated yields. ^{*c*} Concentrations are based on aldehyde **9**.

Table 2. Screening of Lewis Acids for the Reaction of 11

Labic 2.	Screening of	Lewis / telus	for the Re-		1 11
0 L		LA [equiv], a Conc. = 0.13	0 L		
9 H	но 11	4 Å MS [80		0 12	
entry	LA	equiv	temp [°C]	time [h]	yield [%] ^a
1	BE ₂ -Et ₂ O	0.50	rt	16	94
2	BF ₂ -Et ₂ O	0.50	0	16	86
3	BF2-Et2O	0.50	-10	24	$[50]^{b}$
4	BF ₂ -Et ₂ O	0.10	rt	16	80
5	BF_3 -Et ₂ O	0.05	rt	16	65
6	TiCl ₄	0.10	rt	16	95
7	TiCl ₄	0.01	rt	24	70
8	Ti(<i>i</i> -PrO) ₃ Cl	0.10	\mathbf{rt}	16	35
9	$SnCl_4$	0.10	rt	16	81
10	$Sn(OTf)_2$	0.10	rt	16	83
11	AlCl ₃	0.10	rt	16	79
12	$FeCl_3$	0.10	rt	16	77
13	Mg(OTf) ₂	0.10	rt	48	65
14	CuCl	0.10	rt	48	74
15	ZnBr_2	0.10	rt	48	72
16	ZnBr_2	0.01	\mathbf{rt}	48	48
17	$Zn(OTf)_2$	0.10	\mathbf{rt}	24	71
18	In(OTf) ₃	0.10	rt	48	95

^a Isolated yields unless otherwise indicated. ^b Conversion.

amounts; (3) reaction temperatures could be lowered to room temperature; (4) molecular sieves were needed to ensure the efficiency; (5) reactions of pyrone **8** were more sluggish given its lower solubility in CH_2Cl_2 at room temperature, and thus, diketone **11** worked better for a wider range of Lewis acids; and (6) BF_3 - Et_2O and $TiCl_4$ became the Lewis acids of choice because their respective reactions were faster than those employing weaker Lewis acids such as zinc, copper halides, and In(OTf)₃.

This protocol proved to be general in the preparation of pyrans 13-21, 23, 24, and 27-30 as shown in Figure 1. Particularly, we were able to effectively carry out the reaction of Funk's enal 22^{18} with pyrone 8 and diketone 11 to give the desired pyrans 23 and 24^{19} in 71% and 77% yields, respectively. Although the reaction temperature was quite

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Figure 1. The Scope of Lewis acid-catalyzed [3 + 3] annulation.

high here, it has been very difficult using α -oxygenated enals in this annulation reaction under the iminium salt conditions despite the potential of **23** and **24** in synthetic applications. In addition, by using chiral enals **25** [(*S*)-(-)-perillaldehyde] and **26** [(*R*)-(-)-myrtenal], Lewis acid-promoted formal cycloadditions with pyrone **8** and **11** gave the respective pyrans **27** and **28**, and **29** and **30** in good yields as well as high diastereoselectivity.²⁰

A major advantage in employing Lewis acids would be the success in promoting cycloadditions of vinylogous esters

Table 3. Lewis Acid-Catalyzed [3 + 3] Cycloaddition of Vinylogous Esters

RO	0	LA CH ₂ Cl ₂ 4 Å MS]		0 0 85
entry	R	SM	Lewis acid ^a	equiv	temp [°C]	time [h]	yield [%] ^b
1	Me	31	BF ₃ -Et ₂ O	1.00	0-rt	120	15
2	TMS	32	BF_3 - Et_2O	1.00	0	48	48
3	TIPS	33	$ZnBr_2$	1.00	rt	24	10
4	TIPS	33	BF_3 - Et_2O	0.50	rt	16	45
5	TIPS	33	${ m TiCl_4}$	1.00	rt	24	95

 a All reactions were carried out with 80 mg/mmol of 4 Å MS. b Isolated yields.

such as 31-33. As shown in Table 3, TIPS vinylogous ester 33 appears to work the best, leading to pyran 35 in 95% yield, although 1.0 equiv of TiCl₄ was preferred, or the reaction was rather slow [entry 5]. The reaction of methyl vinylogous ester 31 was very slow [entry 1], whereas TMS vinylogous ester 32 is feasible. This finding is significant because it allows one to protect diketones as vinylogous esters while carrying out other transformations, and subsequently pursue the formal cycloaddition without the concern of having to hydrolyze vinylogous esters back to diketones.⁴

We have described here a Lewis acid-catalyzed formal oxa-[3 + 3] cycloaddition of α , β -unsaturated aldehydes with 6-methyl-4-hydroxy-2-pyrone, 1,3-diketones, and vinylogous silyl esters. Given the recent interest, this report should have an impact on applications of this method in the natural product synthesis.

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Supporting Information Available: Experimental and ¹H NMR spectral and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²⁰⁾ The major diastereomers in all cases appear to be the more stable isomer with ΔE ranging from 0.40 to 1.11 kcal mol⁻¹.