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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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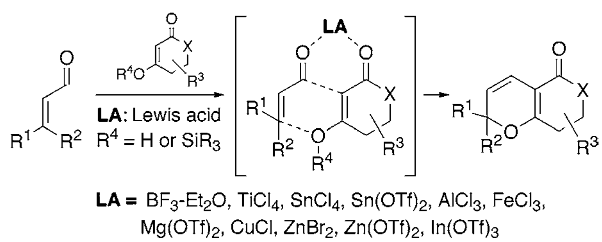
ABSTRACT



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 nature[9] of this annulation involves an initial condensation of **3** with iminium ions **2** followed by 6π-electron electrocyclic ring-closure of 1-oxatrienes **6**[10,11] [Scheme 1]. It has become increasingly evident from the literature[12−14] that this bio-inspired strategy is both useful and practical for constructing

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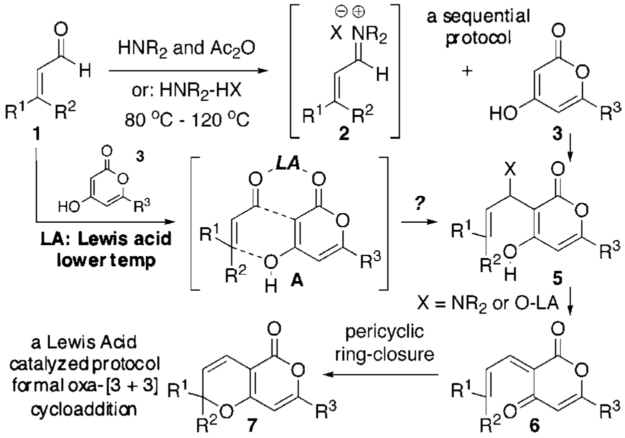
Scheme 1. A Formal *oxa*-[3 + 3] Annulation



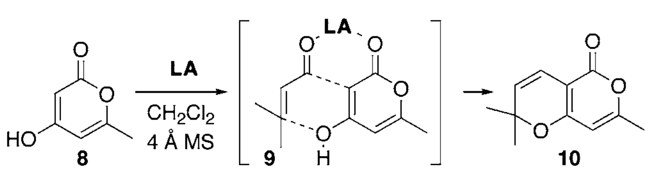
2*H*-pyrans **7** from rather simple and cost-effective starting materials.

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 regiochemistry 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 2*H*-pyran as when using iminium salts; 2) Lewis acids could be employed at substoichiometric

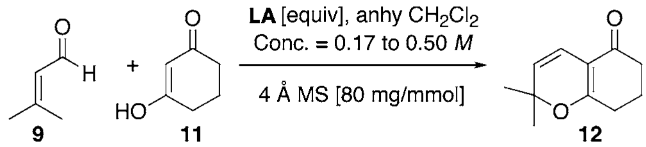
Table 1. Screening of Lewis Acids for the Reaction of **8**



entry	LA[a]	equiv	concn [M][c]	temp [°C]	time [h]	yield [%][b]
1	BF_3-Et_2O	1.00	0.11	rt	24	69
2	**BF_3-Et_2O**	**0.50**	0.12	rt	16	**68**
3	BF_3-Et_2O	0.10	0.09	rt	24	11
4	BF_3-Et_2O	0.05	0.09	rt	24	5
5	**$TiCl_4$**	**0.10**	0.09	rt	22	**80**
6	$SnCl_4$	0.10	0.09	rt	24	38
7	$AlCl_3$	0.10	0.09	rt	48	8
8	In(OTf)$_3$	0.10	0.09	rt	48	3
9	$ZnBr_2$	0.10	0.09	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**



entry	LA	equiv	temp [°C]	time [h]	yield [%][a]
1	**BF_3-Et_2O**	0.50	rt	16	**94**
2	BF_3-Et_2O	0.50	0	16	86
3	BF_3-Et_2O	0.50	−10	24	[50][b]
4	**BF_3-Et_2O**	0.10	rt	16	**80**
5	BF_3-Et_2O	0.05	rt	16	65
6	**$TiCl_4$**	0.10	rt	16	**95**
7	**$TiCl_4$**	0.01	rt	24	**70**
8	Ti(*i*-PrO)$_3$Cl	0.10	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	rt	48	48
17	Zn(OTf)$_2$	0.10	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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(15) This two-step protocol is necessary for many reactions to control the regiochemistry as well as provide consistency in yields, although by using appropriate amine salts, this reaction can be feasible as a one-step protocol. See: References 3 and 13c, and also: Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, 49.

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(19) Details of procedures and characterizations can be found in the Supporting Information.

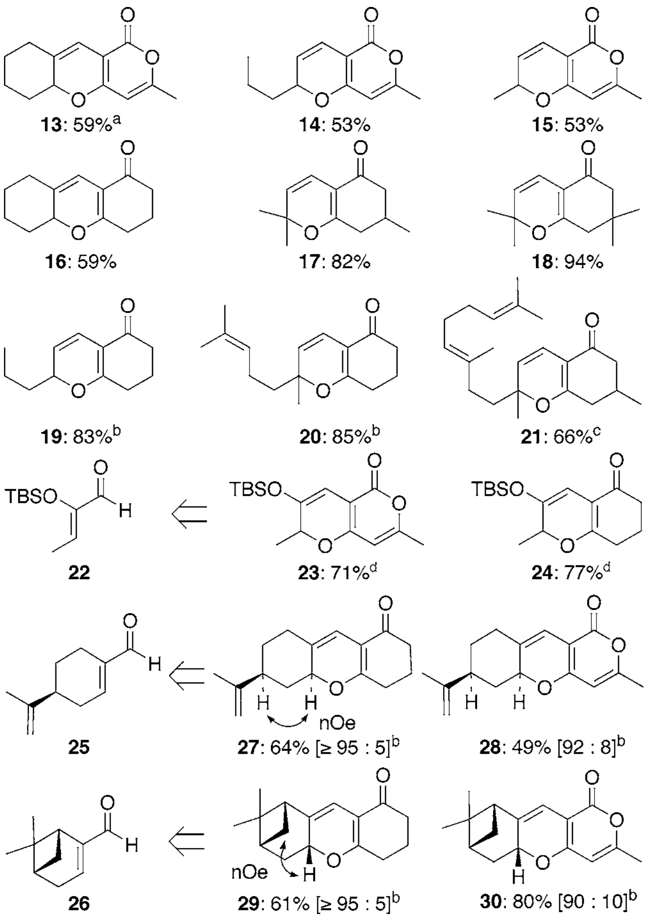


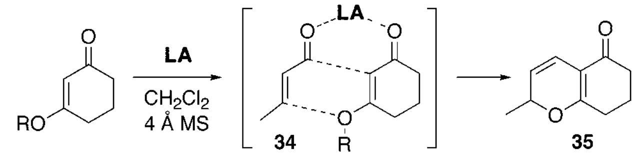
Figure 1. The Scope of Lewis acid-catalyzed [3 + 3] annulation.

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

(20) The major diastereomers in all cases appear to be the more stable isomer with Δ*E* ranging from 0.40 to 1.11 kcal mol^{-1}.

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



entry	R	SM	Lewis acid[a]	equiv	temp [°C]	time [h]	yield [%][b]
1	Me	**31**	BF_3-Et_2O	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**	$TiCl_4$	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 $TiCl_4$ 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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