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LETTERS

Studies of the Asymmetric [2+2] Cycloaddition of Silylketenes and Aldehydes Employing Ti-TADDOL Catalysts

Hong Woon Yang and Daniel Romo*

Department of Chemistry, Texas A&M University, College Station, TX 77843-3255

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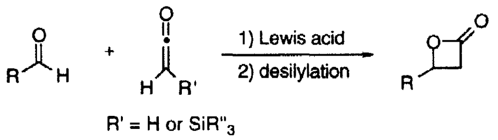
Abstract: Ti-TADDOL catalysts provide good reactivity and moderate enantioselectivity in the asymmetric [2+2] cycloaddition of silyl ketenes and aldehydes. The effects of potential bidentate chelation of benzyloxy substituted aldehydes and of the steric size of the ketene silyl group were studied.

β-Lactones (2-oxetanones) can be viewed as "activated aldol products" since they possess the ability to undergo reaction with nucleophiles involving either β-C-O bond cleavage or acyl C-O cleavage.[1] In addition to being found in many natural products, β-lactones are also quite versatile synthetic intermediates but their use in synthesis has been limited by the lack of direct and general routes for their preparation in optically pure form.[2] Although many preparative methods for the synthesis of β-lactones have been developed, the [2+2] cycloaddition of ketenes and aldehydes is the most efficient and concise route.



In 1911, Staudinger reported the first [2+2] cycloaddition of diphenylketene and carbonyl compounds and the Lewis acid catalyzed version, required for the parent ketene, was described subsequently.[3] More recently, Zaitseva made the important discovery that silylketenes can also undergo Lewis acid mediated [2+2] cycloadditions using catalytic amounts of $BF_3 \bullet OEt_2$.[4] Silylketenes are much more stable than ketene and thus can be prepared and stored for extended periods.[5] As part of a program directed toward the development of general routes for the asymmetric synthesis of β-lactones, we have been interested in the development of a catalytic, asymmetric [2+2] cycloaddition of aldehydes and ketenes. Miyano reported the first attempts at this method using ketene and various aldehydes with 10 mol% of Corey's aluminum based bis-sulfonamide catalyst.[2d] Enantioselectivities ranging from 14-74 %ee and yields varying from 11-82 % were obtained for β-substituted-β-lactones. While our work was in progress, Kocienski and Pons reported the use of trimethylsilylketene in [2+2] cycloadditions using similar conditions and catalysts employed by Miyano. They obtained enantioselectivities ranging from 36-82 %ee and yields from 43-82 % for α-trimethylsilyl-β-alkyl-β-lactones using 30-50 mol% of chiral Lewis acid.[2i] In this Letter, we describe our preliminary studies in this area employing silyl ketenes and Seebach's and Narasaka's dichlorotitanium-TADDOL catalysts[6] which exhibit good

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reactivity and moderate enantioselectivity for this cycloaddition. In addition, studies to probe steric and chelation effects on this reaction are described.

Although we screened several known Lewis acids, the tartrate derived dichlorotitanium-TADDOL catalysts **A** and **B** provided the best results. The ligands were prepared in two steps from (+)-dimethyl-(R,R)-L-tartrate by reported procedures.[6b] Catalysts were prepared immediately prior to use by the procedure of Corey using $Ti(OiPr)_4$ and $SiCl_4$.[7] Various aldehydes and trimethylsilylketene were studied for this reaction (Table 1). In the reaction sequence, the intermediate α-silylated β-lactones **1** were typically not isolated.[8] After determination of the diastereoselectivity based on ^1H NMR of the crude reaction, the mixture of cis and trans isomers was directly treated with $KF\bullet2H_2O$ or TBAF and the enantiomeric purities of β-lactones **2** were determined by chiral GC or HPLC.[9]

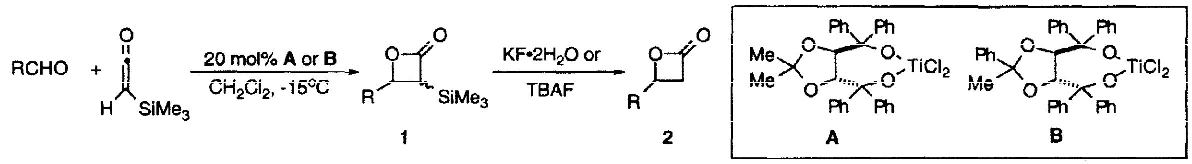


Table 1. Catalytic, Asymmetric [2+2] Cycloadditions of Various Aldehydes and TMS-Ketene

entry	R	Lewis acid	cis/trans (**1**)[a]	% yield (**2**)[b]	rxn time (h)[c]	% ee (**2**)[d]
1	n-Bu	A	34:1	49	24	41
2	$PhCH_2$	A	9:1	58	24	9
3	c-C_6H_{11}	A	>19:1[e]	66	24	80
4	4-NO_2Ph	A	>19:1[e]	71	48	21
5	$PhCH_2CH_2$	A	>19:1[e]	78	73	41[f] 34[g]
6		B	>19:1[e]	78	72	27
7	$BnOCH_2CH_2CH_2CH_2$	A	19:1	76	76	45[f], 28[h]
8		B	>19:1[e]	66	64	43

[a] Ratios determined on the crude reaction mixtures by ^1H NMR (200 or 300 MHz). [b] Yield is for 2 steps. [c] Reaction time is for the [2+2] cycloaddition. [d] % ee's determined by chiral HPLC (Chiralcel OD) or chiral GC (TBS-cyclodextrin, ref. 10). [e] The minor trans diastereomer could not be detected by ^1H NMR (200 or 300 MHz). [f] From pure cis-silylated-β-lactones **1**. [g] From a mixture of β-lactones **1** (cis/trans = 1:1.2). [h] From a mixture of β-lactones **1** (cis/trans = 1.6:1).

The cis isomers of the α-silylated-β-lactones were formed almost exclusively with the exception of phenylacetaldehyde (entry 2, Table 1). Moderate to good yields for the two step reaction sequence were obtained dependent on the reaction time for the cycloaddition. In general, reaction times of 48-76 h led to consistent yields of 66-78%. Although we were unable to obtain the pure trans-β-lactones in most cases, it appears that the enantioselectivity is highest for the cis-β-lactones (entries 5 and 7, Table 1).

To gain some mechanistic understanding of the [2+2] cycloaddition, we examined steric effects of the ketene silyl group. Cossio recently studied the preference for the formation of cis-β-lactones from the [2+2] cycloaddition catalyzed by Lewis acids using *ab initio* calculations.[11] According to his proposed transition state (**C**, Figure), the catalyst coordinates anti to the aldehyde R^2 group as expected[12] and a staggered conformation around the C(3)-C(4) bond is preferred. This nicely rationalizes the stereochemical results of Yamamoto who showed that bulky catalysts lead to increased cis diastereoselectivity.[13] Similar to Yamamoto's results, we observed high cis diastereoselection but a decrease in diastereo-selectivity with increasing size of the ketene silyl group (R^1) (Table 2). This is presumably a result of the increased importance of the gauche R^1/R^2 interaction in transition state arrangement **C** relative to the R^1/catalyst interaction in transition state arrangement **D** (Figure). In addition, there is negligible effect of the silyl group (R^1) on the enantioselectivity.

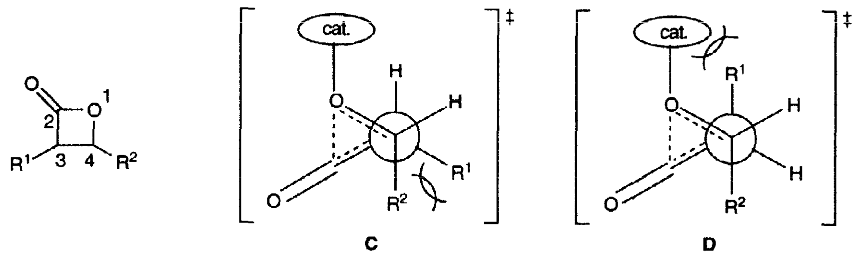
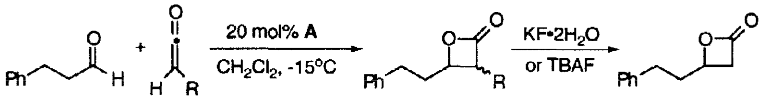


Figure. (a) β-lactone numbering (b) Cossio's Model (ref. 11a) (c) severe steric interaction between R^1 and the catalyst



3 4

Table 2. Effect of Changing the Silyl Group of the Ketene in the [2+2] Cycloaddition

entry	R	cis/trans (**3**)[a]	rxn time (h)[b]	% yield (**4**)[c]	% ee (**4**)[d,e]
1	TMS	>19:1[f]	73	78	41[g], 34[h]
2	TES	13:1	48	74	26
3	TBS	14:1	48	75	31
4	DMPS	14:1	48	75	26

[a]Ratios determined on the crude reaction mixtures by ^{1}H NMR (200 MHz). [b]Reaction time is for the [2+2] cycloaddition. [c]Yield is for 2 steps. [d]% ee's determined by chiral HPLC (Chiralcel OD). [e]Enantiomeric excess was determined after desilylation of the cis/trans mixture **3**. [f]The minor trans diastereomer could not be detected by ^{1}H NMR (200 MHz). [g]From pure cis silylated-β-lactone **3**. [h]From a mixture of β-lactone **3** (cis/trans = 1:1.2).

We also probed for potential bidentate chelation of aldehydes bearing benzylethers with different tether lengths. As the tether length of benzyloxyaldehydes was decreased, reversed diastereoselectivities and decreased enantioselectivities were observed (Table 3). Based on these results, it appears that existence of different geometrical isomers of the active catalyst as a consequence of participation of the pendant benzylether in coordination to titanium affects both the diastereo- and enantioselectivity of the cycloaddition. It has previously been demonstrated by elegant studies of DiMare using VT-NMR experiments that three adducts of dichloro titanium TADDOL catalyst **A** and an associated bidentate oxazolidinone exist in solution.[14] In the case of the 8-membered chelate (entry 4, Table 3), it is possible that bidentate chelation does not occur for entropic reasons

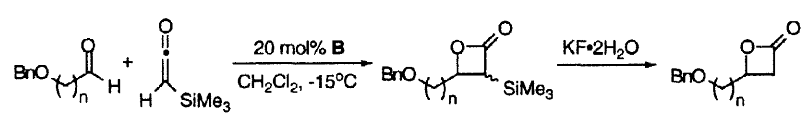


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Table 3. Effect of Changing the Tether Length of Benzyloxy Substituted Aldehydes on the [2+2] Cycloaddition

entry	n	cis/trans (**5**)[a]	% yield (**6**)[b]	rxn time (h)[c]	% ee (**6**)[d]
1	1	35:65	39	53	0
2	2	23:77	79	53	20
3	3	91:9	53	69	35
4	4	>95:5[e]	66	64	43

[a]Ratios determined on the crude reaction mixtures by ^{1}H NMR (200 MHz). [b]Yield is for 2 steps. [c]Reaction time is for the [2+2] cycloaddition. [d]% ee's determined by chiral HPLC (Chiralcel OD). [e]The minor trans diastereomer could not be detected by ^{1}H NMR (200 MHz).

since the enantiomeric excess observed is similar to that observed with the monodentate substrate hydrocinnamaldehyde (compare entries 5 and 7, Table 1).

Investigations of novel, chiral Lewis acids for this [2+2] cycloaddition in addition to further mechanistic studies of this useful reaction are currently underway.

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8. ***Representative procedure for the [2+2] cycloaddition and desilylation as described for the synthesis of β-lactone 2 (R = cyclohexyl).*** The chiral Lewis acid A was prepared as a stock solution (0.40 M) in CH_2Cl_2 immediately prior to use by the procedure of Corey.[7] To a solution of cyclohexanecarboxaldehyde (101.7 mg, 0.89 mmol) and TMS-ketene (204.8 mg, 1.79 mmol) in CH_2Cl_2 (1 ml) was added 0.44 ml of the stock solution (0.18 mmol) of chiral Lewis acid A at -20 °C. The resulting reaction mixture was kept in a freezer (-15 °C) for 24 hrs. After addition of pH 7 buffer (1 ml) at -20 °C, the reaction mixture was warmed to room temperature and filtered through Celite. The solution was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford a pasty colorless solid which was roughly purified using flash chromatography (EtOAc:Hex = 1:9) to remove polar impurities. The purified α-silylated-β-lactone was treated with 0.98 ml of TBAF (1M in THF, 0.98 mmol) at -78 °C. After stirring for 30 min, the reaction mixture was quenched with pH 7 buffer, extracted with ether, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash chromatography (EtOAc:Hex = 1:10) to afford the β-lactone 2 (R = cyclohexyl) (90.5 mg, 66% yield) which exhibited spectral data that matched previously reported data.[15] The ee was determined to be 80 %ee by chiral GC analysis (bis-TBS cyclodextrin[10]).
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