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Enantioselective β-Lactone Formation from Ketene and Aldehydes Catalyzed by a Chiral Oxazaborolidine

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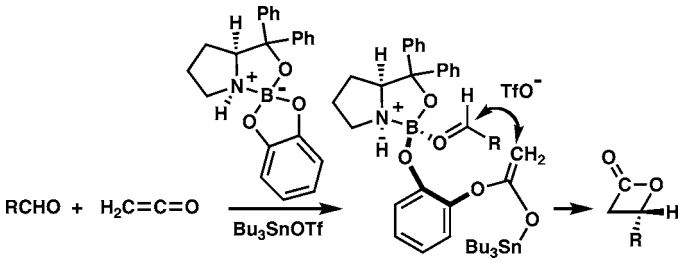
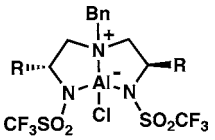
ABSTRACT



A novel catalytic system has been developed for the enantioselective synthesis of β-lactones from ketene and aldehydes.

The enantioselective synthesis of β-lactones from ketenes and aldehydes has progressed slowly since the pioneering discovery by Wynberg of the effectiveness of cinchona alkaloids as nucleophilic catalysts for the reaction of chloral with ketene.[1,2] The Wynberg reaction has been considerably extended by the studies of Romo, Nelson, and co-workers.[3]



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Nelson and co-workers have also developed the novel catalyst **1** for effecting β-lactone formation from aldehydes of the type RCH_2CHO with ketene generated in situ from acetyl bromide and i-Pr_2NEt.[4] Nelson's method with **1** as catalyst has been used with a range of ketenes and aldehydes having an α-methylene group. The mechanistic basis for enantioselectivity is unclear. Finally, the very specific case of β-lactone formation from trimethylsilylketene and α-keto esters using Cu(II)-BOX complexes has been described by Evans and Janey.[5] The work presented herein started from the hypothesis that a useful and mechanistically clear enantioselective route to chiral β-lactones might be possible using the same chiral oxazaborolidines (**2**) that have been applied so successfully for the borane-mediated enantioselective reduction (CBS reduction) of ketones.[6] The pathway that was envisaged for catalytic enantioselective β-lactone

(1) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168.

(2) For reviews, see: (a) Schneider, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 744−746. (b) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434.

(3) (a) Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197−1199. (b) Tennyson, R. L.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248−7252. (c) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945−7946. (d) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352−5353.

(4) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. (b) Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883−1886. (c) Nelson, S. G.; Spencer, K. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1323−1325. (d) Nelson, S. G.; Kim, B.-K.; Peelen, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 9318−9319. (e) Nelson, S. G.; Peelen, T. J.; Wan, Z. *Tetrahedron Lett.* **1999**, *40*, 6541−6543. (f) Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14−15.

(5) Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125−2128.

(6) (a) Corey, E. J.; Bakshi, R.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Corey, E. J.; Bakshi, R.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

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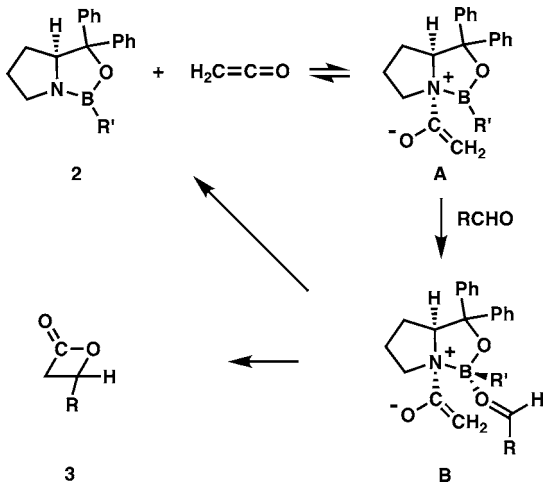
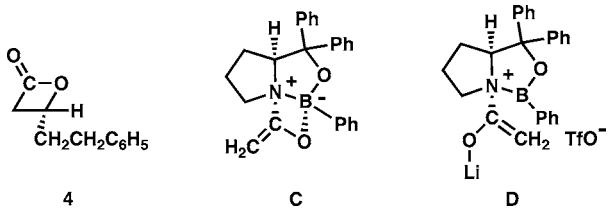
formation from catalyst **2**, an aldehyde, and ketene is outlined in Scheme 1.

Scheme 1

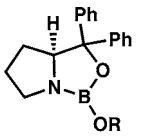


In the case of the catalyzed reduction of ketones by borane and **2**, borane coordinates with the nitrogen of **2** to form a cis-fused oxazaborolidine−BH_3 complex (at N) which then binds the ketone because of the enhanced Lewis acidity of the ring boron.[6] As a result, the coordinated BH_3 and carbonyl groups are both activated and brought into proximity for face-selective hydride transfer from BH_3 to C═O. We hypothesized that ketene might coordinate to the nitrogen of **2** in a similar way to form intermediate **A** in Scheme 1. Attachment of an aldehyde at the ring boron of **A** might then lead to the ternary complex **B**, which could then undergo C−C coupling and elimination of a *β*-lactone **3** with regeneration of catalyst **2**. We were encouraged to find that treatment of 3-phenylpropionaldehyde and 10 mol % of **2**, R′ = C_6H_5, in CH_2Cl_2 solution at −40 °C with a solution of ketene[7] in CH_2Cl_2 (at −40 °C) for 7 h did produce dextrorotatory (*R*)-*β*-lactone **4**.[8] However, both the yield (20%) and enantioselectivity (7:3) were unsatisfactory. The absolute configuration of the major enantiomer was determined to be *R* as expected for the pathway outlined in Scheme 1. A possible reason for the slowness of the reaction (poor conversion to *β*-lactone after 7 h reaction time) was determined from quenching of the reaction mixture with water and identification of one of the species present as the *N*-acetyl derivative of (*S*)-α,α-diphenyl-2-pyrrolidinomethanol. This result led us to suppose that the reaction of ketone with **2** produces the bidentate coordination product **C** rather than **B** of Scheme 1. The formation of this more stabilized



intermediate serves to explain both the low level of catalytic activity of catalyst **2** and the low enantioselection. Clearly, the reaction of aldehyde with **C** via an open (i.e., noncyclic) transition state might not be very face selective. It was hoped that the addition of lithium triflate to the reaction mixture might result in the conversion of **C** into a more reactive intermediate **D** and lead to more useful results. Unfortunately, although lithium triflate produced some rate enhancement (52% yield after 7 h at −40 °C in CH_2Cl_2), the 7:3 enantioselectivity was not significantly improved.

We then explored the use of two new catalysts, **5** and **6**. These oxazaborolidines were readily made from (*S*)-(−)-α,α-diphenyl-2-pyrrolidinomethanol by heating with the corresponding borate esters. When these catalysts (10 mol %) were used in the test reaction of 3-phenylpropionaldehyde and ketene in CH_2Cl_2 at −40 °C, the (*R*)-*β*-lactone predominated, but the yield and enantioselectivity of the reaction was if anything slightly lower than with **2**, R′ = Ph, as catalyst.



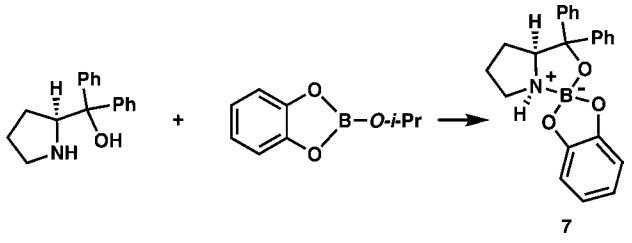
5, R = 3-pentyl
6, R = Ph

A different type of oxazaborolidine, the zwitterion **7**, could be prepared cleanly by reaction of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinomethanol with catechol isopropyl borate in CH_2Cl_2 at 23 °C for 3 h followed by removal of volatile components in vacuo.[9] Although this compound was not an active catalyst, it could be transformed into one by reaction with tri-*n*-butyltin triflate (1 equiv) in CH_2Cl_2 at −78 °C for 30 min.[10] When a solution of this activated form of precatalyst **7** in CH_2Cl_2 at −78 °C was treated with various aldehydes and ketene (10 equiv) in CH_2Cl_2 at −78 °C for 24 h, chiral dextrorotatory *β*-lactones were obtained in fair

(7) The preparation of ketene was carried out by thermolysis (1 atm N_2) of commercially available diketene. The ketene was trapped at −78 °C under nitrogen in dichloromethane (ca. 5 M). Diketene was placed in a round-bottom flask attached to one end of a Pyrex glass tube in a thermolysis oven. The other end was attached to a receiving flask containing dry dichloromethane at −78 °C. After the oven had stabilized at 550 °C, diketene was heated to gentle boiling allowing the vapor to pass through the Pyrex glass tube. Ketene condensed as a white fog which was collected in stirred dichloromethane at −78 °C. The ketene solution was stored under N_2 at −78 °C and is stable at that temperature for at least two weeks. Background references for synthesis of ketene: (a) Moore, H. W.; Wilbur, D. S. *J. Org. Chem.* **1980**, *45*, 4483−4491. (b) Andreades, S.; Carlson, H. D. *Org. Synth.* **1965**, *45*, 50−54.

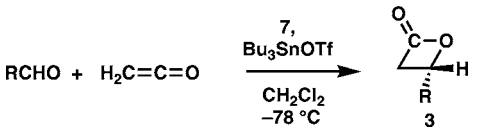
(8) For absolute configuration, see: Nelson, S. G.; Spencer, K. L. *J. Org. Chem.* **2000**, *65*, 1227−1230.

(9) A 100-mL, two-necked, round-bottomed flask equipped with a stir bar was charged with (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol (2.53 g, 10 mmol, from Aldrich or Lancaster) and 40 mL of dichloromethane. The resulting solution was stirred at room temperature for about 10 min. A solution of catechol isopropylborate (1.78 g, 10 mmol) in 10 mL of dichloromethane was added slowly at room temperature over about 10 min. The resulting solution was stirred at room temperature for 3 h. Concentration in vacuo (ca. 0.1 mmHg, 1 h) afforded **7** as clear oil. The solution of **7** can be stored under N_2 at −20 °C as a 0.25 M dichloromethane solution for a long period of time without noticeable decomposition.



yields (60−78% range) and moderately good enantioselectivity (12:1 to 5:1 range). The results with six different aldehydes are summarized in Table 1. In each case, the predominating enantiomer was **3**.[8]

Table 1. Oxazaborolidine-Catalyzed Enantioselective Addition of Ketene to Aldehydes



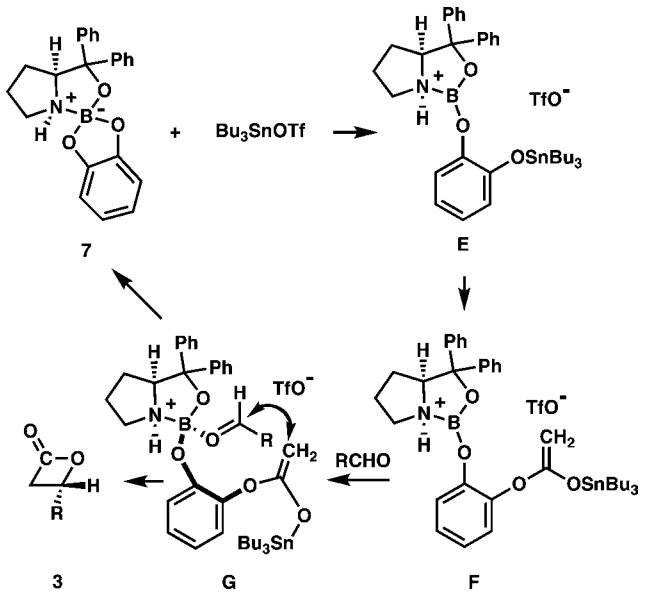
entry	RCHO	% yield (isolated)	% ee, config[a]
1	$PhCH_2CH_2CHO$	73	81, *R*
2	n-$C_5H_{11}CHO$	78	84, *R*
3	$BnOCH_2CH_2CHO$	58	65, *R*
4	*cyclo*-$C_6H_{11}CHO$	78	70, *S*
5	Me_2CHCHO	62	68, *S*
6	Me_2CHCH_2CHO	72	67, *R*

[a] For analytical methods, see ref 8.

The mechanistic hypothesis leading to the use of tri-*n*-butyltin triflate to activate **7** for catalysis of the reaction between an aldehyde and ketene is outlined in Scheme 2. Activation of the precatalyst **7** by tri-*n*-butyltin triflate could reasonably be expected to produce the ion pair **E**, which by reaction with ketene should form the intermediate **F**. Intermediate **F** should be a sufficiently strong boron Lewis acid to coordinate with the aldehyde and generate the reactive complex **G** as a transient species. Because **G** contains two mutually reactive units, the nucleophilic CH_2 of the ketene acetal subunit and the electrophilic carbonyl carbon of the

(10) To a solution of **7** (200 μL, 0.05 mmol, 0.25 M in dichloromethane) in dichloromethane (1.0 mL) at −78 °C was added Bu_3SnOTf (200 μL, 0.05 mmol, 0.25 M in dichloromethane). After 30 min, a precooled 5 M solution of ketene in dichloromethane (1 mL, 5 mmol) was added at −78 °C followed by hydrocinnamaldehyde (66 μL, 0.5 mmol). The resulting homogeneous mixture was kept at −78 °C for 24 h and then quenched by addition of saturated aqueous Na_2HCO_3 (0.5 mL) at the same temperature. After being warmed to room temperature, the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (ether/hexane, 3:7) to afford the β-lactone **4** (64 mg, 73%) as a colorless oil. Enantioselectivity (91:9) was determined by HPLC analysis using a Daicel Chiralcel OD-H column, flow rate 1 mL/min, hexane-*i*-PrOH (9:1); retention times 15.9 min (*S*) and 18.1 min (*R*); $[\alpha]^{23}_D$ +5.62 (*c* 0.3, $CHCl_3$).

Scheme 2. Possible Pathway for the Catalyzed Enantioselective Formation of Chiral β-Lactones



coordinated aldehyde, C−C bond formation and extrusion of β-lactone should be a favorable reaction pathway. In accordance with the intermediacy of **G** and the geometry of the coordinated aldehyde that is precedented by many previously observed reactions,[6] the absolute configuration expected for this pathway is that which is actually observed (**3**) for the various entries in Table 1. The sequence shown in Scheme 2 provides a logical, coherent, and satisfying explanation for all our results. It also provides a basis for further development of this enantioselective methodology toward improved yields and enantioselectivities.

The scope of this approach to the catalytic enantioselective synthesis of chiral β-lactones has yet to be fully explored with a broader range of substrates. However, it can be noted that entries 4 and 5 of Table 1 provide the first demonstration of β-lactone formation from α-branched aldehydes and ketene. With regard to the scope of our β-lactone-forming process, another obvious direction for further work is the development of a methodology for the preparation of pure (cold) solutions of higher homologues of ketene in the aldoketene series (i.e., monosubstituted ketenes). We hope to report on this aspect of the methodology in due course.

Acknowledgment. We are grateful to Professor Masakatsu Shibasaki for his encouragement of this research.

Supporting Information Available: Experimental procedures, physical data, and analysis of enantioselectivity for the β-lactones listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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