Reaction Rate Acceleration Enabled by Tethered Lewis Acid–Lewis Base Bifunctional Catalysis: A Catalytic, Enantioselective [2+2] Ketene Aldehyde Cycloaddition Reaction

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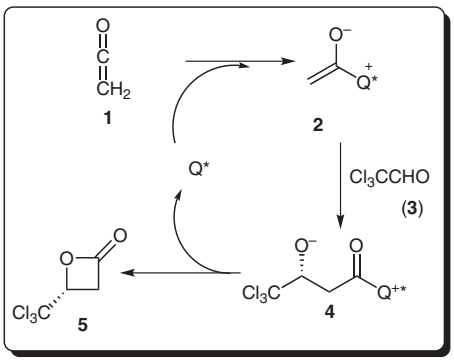
This paper is dedicated to Professor Marvin J. Miller of the University of Notre Dame on the occasion of his 60th birthday.

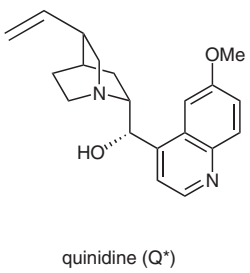
Abstract: A tethered Lewis acid–Lewis base (LA*–LB*) bifunctional catalyst promotes the asymmetric [2+2] cycloaddition reaction between ketene and aldehydes rapidly. The LA*–LB* bifunctional catalyst, a quinine tethered Co(III)–salen complex (5 mol%) catalyzes the [2+2] cycloaddition reaction to produce the C4-substituted β-lactones in uniformly >99% ee and high isolated yields (71–97%). The dramatic rate acceleration, the hallmark of cooperative intramolecular bifunctional catalysis, is achieved for the catalytic, enantioselective [2+2] cycloaddition reaction between aldehydes and *unsubstituted* ketene.

Key words: Lewis acids, Lewis bases, bifunctional catalysts, rate acceleration, enantioselectivity

Enantiomerically pure β-lactones are valuable small molecules that can be converted into a variety of chiral synthons for asymmetric synthesis.[1] Because the [2+2] cycloaddition reaction between ketene and aldehydes affords β-lactones in one step, developing new catalytic methods for synthesizing β-lactones from ketene and aldehydes attracts much attention.[1,2] In 1982, Wynberg reported an enantioselective synthesis of β-lactone **5** from ketene **1** and chloral **3**, catalyzed by quinidine (Q*, Scheme 1).[3] This formal [2+2] reaction entails a tandem aldol–lactonization process (from **2** to **4** to **5**) to produce the β-lactone **5** in excellent ee, but limited only to activated substrates.[3] Significant research effort has been devoted to expanding the substrate scope of the [2+2] reaction. In addition to Romo's early strategy for synthesizing bicyclic β-lactones from aldehyde acids,[4] Nelson and Calter independently developed new catalytic methods to synthesize chiral β-lactones from aldehydes and substituted ketenes.[5] Chiral Lewis bases (LB*) and chiral Lewis acids (LA*) were developed by Fu[6a] and Corey,[6b] respectively, to synthesize β-lactones from pure ketenes. Most recently, new catalytic systems developed for the [2+2] cycloaddition reaction between aldehydes and substituted ketenes were reported by Peters[6c,d] and Ye,[6e] respectively. However, no catalytic methods that rapidly produce *enantiomerically pure* (i.e. >99% ee) C4-alkyl or aryl β-lactones are currently available for the [2+2] cycloaddition reaction between aldehydes and unsubstituted ketene.

Employing the [2+2] cycloaddition reaction as a test reaction, we recently reported the discovery of an active Lewis acid–Lewis base (LA*–LB*) bifunctional catalyst **6** (Figure 1).[7,8] We synthesized the (±)-Co(II)–LB* bifunctional catalyst **6** from the (±)-diaminopropionic acid, and demonstrated the LB*-dependent asymmetric induction concept.[7,9] We have also developed an empirical model for predicting the *R*/*S* absolute stereochemistry of the LA*–LB* catalyzed reactions.[9] Herein, we report a highly enantioselective [2+2] reaction catalyzed by a Co(III)-based LA*–LB* bifunctional catalyst that displays remarkable rate acceleration. The tethered LA*–LB* bifunctional catalyst promotes the formation of enantio-





Scheme 1 The catalytic cycle of the Wynberg reaction

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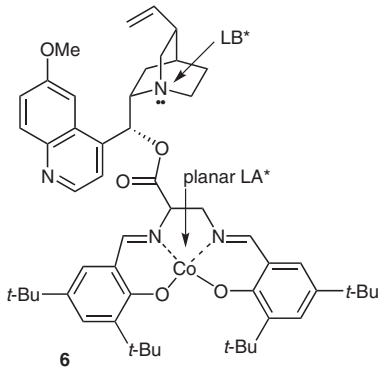
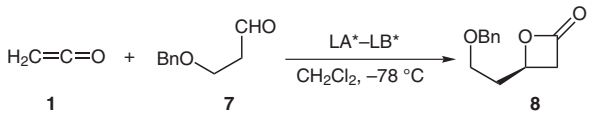


Figure 1 A salen-Co(II) based LA*–LB* bifunctional catalyst



Scheme 2

Table 1 Initial Reaction Optimization Studies

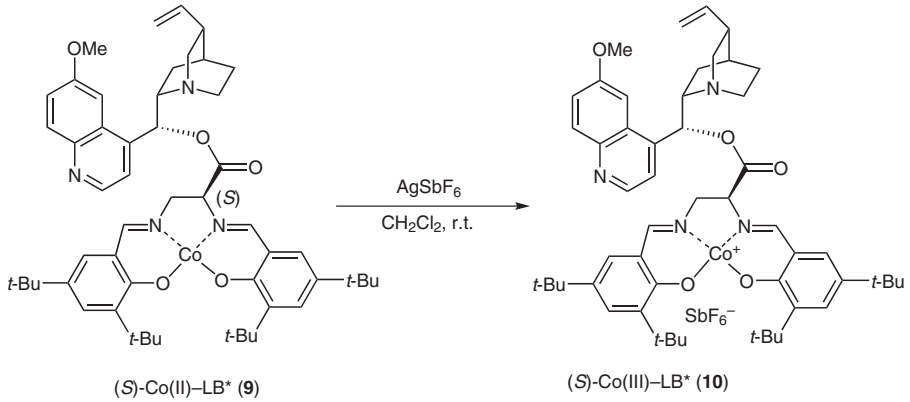
Entry[a]	LA*–LB* catalyst (mol%)	Reaction time (h)	Yield (%)[b]	ee (**8**)[c]
1	**6** (10)	12	6	–
2	**9** (10)	12	5–6	–
3	**10** (5)	12	45	>99%
4	**10** (5)	12	65	>99%
5	**10** (5)	8 min	82	>99%
6	**9** (5)	2	–	–

[a] Reaction concentration [**7**] = 0.1 M; ketene was generated either from acetyl chloride/Hünig's base in situ (entries 1–4) or via pyrolysis of acetone (entries 5 and 6). For entry 3, acetyl chloride was added slowly (3 h) to the reaction and the reaction was stirred at –78 °C for 12 h; For entry 4, acetyl chloride was added very slowly (6 h) to the reaction, which was stirred at –78 °C for 12 h. For entry 5, ketene gas was bubbled into the reaction. See Experimental Section for details.
[b] Isolated yields (entries 3–5), except for entries 1 and 2, where conversion% was estimated by crude ^{1}H NMR.
[c] The ee was determined by chiral HPLC.

merically pure (>99% ee) β-lactones rapidly from aldehydes and ketene, with reaction times ranging from minutes to one hour.

Our initial effort was focused on expanding the substrate scope of the [2+2] cycloaddition reaction catalyzed by the bifunctional catalyst **6**. We employed enolizable 3-benzyloxypropanal (**7**) as the substrate for initial optimization studies (Scheme 2). The Co(II)-based LA*–LB* bifunctional catalyst **6** proved less active for aldehyde **7**, in spite of many attempts. When ketene **1** was generated slowly in situ from acetyl chloride and Hünig's base,[10] catalyst **6** (10 mol%) gave only 6% conversion of the reaction after 12 hours at –78 °C (entry 1, Table 1). The (*S*)-Co(II)–LB* catalyst **9** (LB* = quinine) was subsequently synthesized from the corresponding ligand, which was derived from the (*S*)-diaminopropionic acid linker, and anhydrous $CoCl_2$ as a light-brown powder, using a modified procedure. However, the (*S*)-Co(II)–LB* bifunctional catalyst **9** did not show an improvement in catalytic activity for aldehyde **7**. Employing the (*S*)-Co(II)–LB* catalyst **9** (10 mol%) produced little conversion of the aldehyde (entry 2, Table 1). In the low conversion reactions, competing side reactions dominated to produce the undesired ketene dimers. Taken together, these initial results suggested that a more active bifunctional catalyst is necessary in order to suppress the background reactions.

Inspired by Jacobsen's seminal work on hydrolytic kinetic resolution of epoxides catalyzed by Co–salen complexes,[11] we decided to oxidize the metal in catalyst **9** from Co(II) to Co(III). We reasoned that the Co(III)-based bifunctional catalyst **10** should be more active, because Jacobsen's Co(III)–salen complex displays enhanced Lewis acidity over its Co(II) analog.[11] Indeed, after oxidizing the Co(II) in catalyst **9** to Co(III) using $AgSbF_6$,[12] we observed an improved catalytic activity (Scheme 3). The Co(III)-based bifunctional catalyst **10** (5 mol%) promoted the [2+2] reaction to produce the desired β-lactone **8** in 45–65% yields and >99% ee (entries 3 and 4, Table 1), when ketene was generated in situ by slowly adding (*via* a syringe pump) acetyl chloride to the reaction containing



Scheme 3

Hünig's base. It is important to add the acetyl chloride methylene chloride solution over a period of six hours in order to produce the desired β-lactone in good yields. In contrast, regular drop-wise addition of acetyl chloride to the reaction gave very little conversions. The isolated ketene dimer by-product is presumably produced from the reaction between the unreactive ketene and the ammonium enolate species.

In addition to the variable isolated yields (entries 3 and 4, Table 1), employing the acetyl chloride/Hünig's base protocol for generating the ketene in situ has two apparent limitations in the LA*–LB* catalyzed enantioselective cyclization reaction. First, ketene formation from the acetyl chloride could be the rate-determining step. This possibility would diminish the catalytic efficacy of the LA*–LB* bifunctional catalyst. Second, the chloride anion formed during the reaction could coordinate to the Co(III), sequestering the cationic Co(III) catalytic species into a stable hexacoordinate complex. In order to avoid the pre-equilibrium ketene-forming step that limits the overall reaction rate, we decided to employ Wynberg's protocol[3] that utilizes pure ketene in the LA*–LB* catalyzed reaction. Employing pure ketene in the reaction would eliminate the competitive side reaction between the ammonium enolate and the acetyl chloride. Without generating the chloride anion during the reaction, its coordination to the Co(III) would be avoided. Thus, it would prevent converting the LA* from the cationic Co(III) into a less Lewis acidic species.

In addition, pure ketene can be generated conveniently from inexpensive acetone via pyrolysis, through a modified ketene lamp.[13] Remarkably, after the ketene gas was bubbled into the reaction at –78 °C, the Co(III)-derived bifunctional catalyst **10** (5 mol%) promoted the reaction rapidly. The reaction was complete within eight minutes, affording the β-lactone **8** in 82% yield and >99% ee (entry 5). The *R*-configuration of the β-lactone **8** was established experimentally. It can be noted that the correct configuration is in agreement with that assigned from our empirical model.[9] In contrast, the (*S*)-Co(II)-based bifunctional catalyst **9** proved to be inactive for the same reaction, under similar reaction conditions (entry 6). Taken together, these initial studies suggested that the enhanced Lewis acidity is the key for a very active LA*–LB* bifunctional catalyst, which is essential for the unprecedented rate acceleration. In addition, it is important to employ pure ketene, rather than the acetyl chloride/Hünig's base as the ketene source in the reaction, in order to attain the desired rate acceleration.

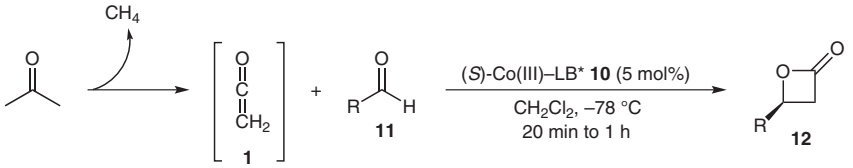
Table 2 Reaction Rate Acceleration Enabled by Tethered Lewis Acid–Lewis Base Bifunctional Catalysis

Entry[a]	R (**11**)	Time	Yield **12** (%)[b]	ee% (*R*/*S*)[c]
1	3-FC_6H_4-	20 min	87	>99 (*S*)
2	3-ClC_6H_4-	20 min	97	>99 (*S*)
3	2-ClC_6H_4-	20 min	95	>99 (*S*)
4	2-FC_6H_4-	20 min	87	>99 (*S*)
5	$PhCH_2$-	20 min	96	>99 (*R*)
6	$PhCH_2CH_2$-	1 h	96	>99 (*R*)
7	*n*-C_6H_{13}-	1 h	74	>99 (*R*)
8	*n*-$C_{11}H_{23}$-	1 h	71	>99 (*R*)

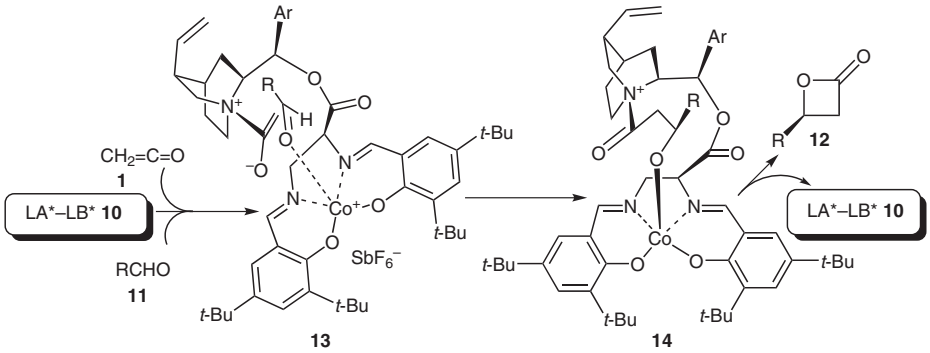
[a] All reactions were carried out in 1 mmol scale, [**11**] = 0.1 M, ketene was generated by pyrolysis of acetone.
[b] Isolated yield.
[c] The ee was determined by chiral HPLC and the *R*/*S*-configuration of the β-lactones **12** were established experimentally.

The ensuing substrate scope studies revealed that the Co(III)-based LA*–LB* bifunctional catalyst **10** was applicable to both aromatic and enolizable aliphatic aldehydes (Scheme 4, Table 2). We carried out the LA*–LB* catalyzed [2+2] reaction in 0.1 M substrate concentrations. The catalyst (5 mol%) promoted the reaction rapidly at –78 °C after ketene (~2–3 equiv) was bubbled into the methylene chloride solution. Halogenated aromatic aldehydes (entries 1–4) and phenylacetaldehyde (entry 5) gave complete reactions in 20 minutes, furnishing the corresponding β-lactones **12** in excellent yields and >99% ee. For the other enolizable aliphatic aldehydes examined, the reaction was complete within one hour and afforded the corresponding β-lactones **12** in excellent yields and >99% ee (entries 6–8). The absolute configurations of β-lactones **12** were established experimentally, and all were consistent with those predicted from our empirical model.[9]

We propose an open transition-state model intermediate **13** to account for the intramolecular bifunctional catalytic cycle (Scheme 5). The LB* moiety of catalyst **10** converts the ketene into an ammonium enolate, and delivers it to the Co(III)-activated aldehyde in an intramolecular manner. The resulting Co(III)-aldolate **14** lactonizes to furnish β-lactone **12** and regenerate catalyst **10**. The rapid catalyst turnover is indicative of a weak aldolate–Co(III) interaction, thus ensuring the catalytic cycle. Because the LA* coordination sites in catalyst **10** are openly accessible for substrates, the excellent ee of the reaction is consistent with the LB*-dependent asymmetric induction concept.[7,9]



Scheme 4



Scheme 5 An intramolecular asymmetric bifunctional catalysis working model

It is thus not surprising that the stereochemistry of the LA*–LB* catalyzed [2+2] reaction is predictable.[9]

In summary, we have discovered a Co(III)-derived LA*–LB* bifunctional catalyst that is highly active for the catalytic, enantioselective [2+2] cycloaddition reaction between aldehydes and unsubstituted ketene, with unprecedented reaction rate accelerations and enantioselectivity. The current LA*–LB* bifunctional catalyst rapidly converts both aromatic and aliphatic aldehydes into the corresponding β-lactones in excellent yields. Because chiral β-lactones can be readily converted into the corresponding β-hydroxy esters (i.e. acetate aldols) with retention of configurations via alcoholysis, the LA*–LB* catalyzed [2+2] reaction offers an invaluable alternative to the catalytic, asymmetric acetate aldol reaction, without generating the required silyl ketene acetals.[14] In addition, the remarkable rate acceleration attained by the current LA*–LB* bifunctional catalyst suggests a general strategy that can be extended to organocatalysis[15] for speeding up the reactions. Applications of the Co(III)-derived LA*–LB* bifunctional catalyst to other reactions, particularly those amenable for Lewis base catalysis[16] for rate acceleration, are currently underway in our laboratory and we will report our results in due course.

LA*–LB* Catalyzed Asymmetric [2+2] Cycloaddition Reaction; Typical Procedure

(*R*)-4-(2-Benzyloxyethyl)oxetan-2-one (**8**): To a solution of catalyst **9**·2HCl (49 mg, 0.05 mmol) in methylene chloride (2.0 mL) at r.t., was added $AgSbF_6$ (52 mg, 0.15 mmol). The resulting dark-brown mixture was stirred at r.t. for 1.5 h, followed by the addition of methylene chloride (8.0 mL), diisopropylethylamine (0.10 mL, 0.61 mmol), and aldehyde **7** (164 mg, 1.0 mmol). The solution was cooled to –78 °C and ketene gas (~2–3 equiv) generated via pyrolysis of acetone was bubbled into the reaction mixture for 8 min to give a complete reaction, as indicated by TLC. The reaction was quenched with sat. $NaHCO_3$ at –78 °C, warmed up to r.t., and extracted with methylene chloride. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, concentrated and separated by flash column chromatography on silica gel (hexanes–EtOAc, 16:1→8:1→4:1) to give β-lactone **8**.

Yield: 168 mg (82%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 4.68 (m, 1 H), 4.50 (s, 2 H), 3.62 (m, 2 H), 3.53 (dd, *J* = 16.4, 5.6 Hz, 1 H), 3.17 (dd, *J* = 16.4, 4.4 Hz, 1 H), 2.11 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 137.8, 128.4, 127.8, 127.6, 73.0, 69.1, 65.7, 43.1, 34.7.

IR (neat): 1825.4, 1191.1 cm^{-1}.

Chiral HPLC analysis of β-lactone **8** gave a single peak at 15.0 min (> 99% ee). Under the same HPLC conditions, a racemic sample gave two well-resolved peaks. HPLC conditions: HPLC column = CHIRALCEL OD-H (0.46 × 25 cm); *i*-PrOH–hexanes, 15:85 (v/v); flow rate = 1.0 mL/min; UV detection: 210 nm.

Table 3 contains the HPLC conditions used to analyze the samples listed in Table 2.

Table 3 Summary of HPLC Conditions Corresponding to the Entries in Table 2

Entry	*i*-PrOH–hexanes mobile phase (v/v) and flow rate (mL/min)	T_R (min)	UV detection λ (nm)
1[a]	10:90 (1.0)	6.6	260
2[a]	10:90 (1.0)	7.7	210
3[a]	20:80 (0.5)	9.7	220
4[a]	20:80 (0.5)	8.9	260
5[b]	10:90 (1.0)	13.3	210
6[b]	10:90 (1.0)	16.3	210
7[c]	4:96 (1.0)	8.0	210
8[d]	3:97 (1.0)	12.4	210

[a] HPLC analysis was carried out on their corresponding β-hydroxy methyl esters.
[b] HPLC analysis was carried out on the β-lactones.
[c] HPLC analysis was carried out on the (*S*)-*O*-methylmandelate of its β-hydroxy methyl ester.
[d] HPLC analysis was carried out on the (*R*)-*O*-methylmandelate of its β-hydroxy methyl ester.

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