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A Lewis Acid–Lewis Base Bifunctional Catalyst from a New Mixed Ligand

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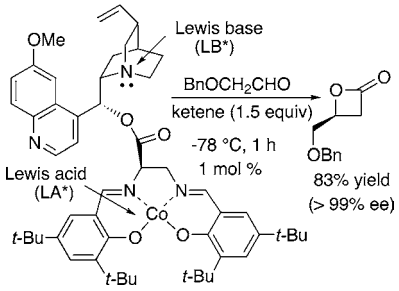
ABSTRACT



Covalent attachment of quinine to a salen framework through a racemic linker gave a new mixed ligand in a 1:1 diastereomeric mixture, from which an active Lewis acid–Lewis base (LA*–LB*) bifunctional catalyst derived from Co(II) was discovered by the screening of metal complexes. The remarkable intramolecular bifunctional catalytic activity (1 mol % catalyst loading) of the new catalyst was demonstrated using a proof-of-principle reaction.

Asymmetric catalysis has played an important role in many important chemical reactions, making it an indispensable tool for contemporary science. Its rapid progress has been propelled by the development of novel ligands as chiral auxiliaries that impart chirality transfer from the catalysts to the products. Over the last three decades, many enantiomerically pure ligands have been developed to chelate Lewis acidic metals in order to generate chiral Lewis acids (LA*, * denotes chirality).[1] During the ligand discovery process, certain small molecules have emerged as extraordinary ligands that display remarkable reaction and substrate generality.[2] Modification of the diamine backbone of the C_2-symmetric salen ligand (**1**, Figure 1) has been exploited extensively in order to chelate metals for asymmetric catalysis.[2a,3] In the absence of metals, quinine (**2**)/quinidine and their derivatives have also been utilized extensively in catalysis,[4] as exemplified by Wynberg's catalytic enantioselective synthesis of chiral β-lactones from ketene.[4a]

Interestingly, a strategy that combines a salen ligand and a cinchona alkaloid for developing novel mixed ligands has never been reported. We envisioned that a novel hemilabile, pentadentate ligand (**3**, Figure 1), could be readily made available by covalent attachment of quinine (**2**) to the salen framework using an ester linkage. Coordinations of ligand **3** to transition metals would furnish metal complex **4** (M = Cu^{2+}, Ni^{2+}, Cr^{3+}, Co^{2+}, etc.) that might have Lewis acid−Lewis base (LA*−LB*) bifunctional catalytic activity.[5] The LA*−LB* bifunctional catalyst (**4**) would feature a chiral LA* at the metal center and a chiral LB* at the bridgehead

† Undergraduate participants.

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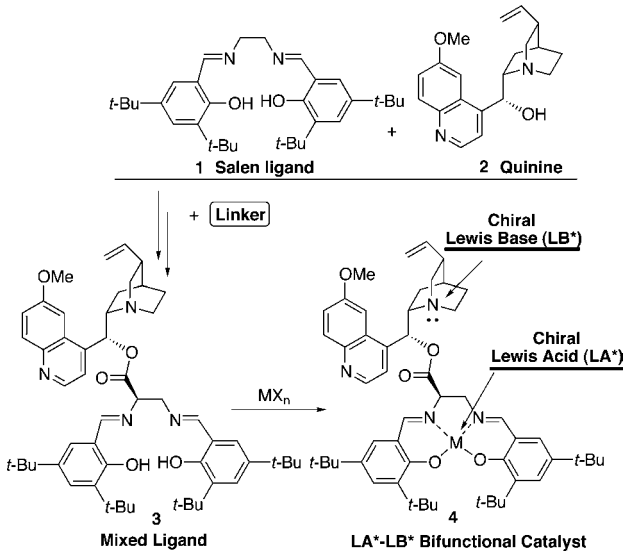


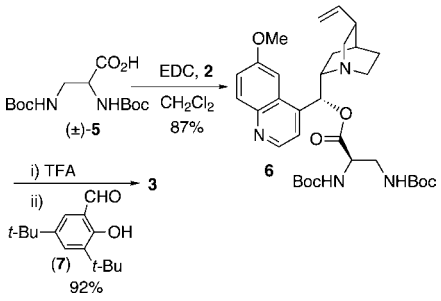
Figure 1. New mixed ligand from salen and quinine.

nitrogen of the quinine moiety that is remote from the metal. Using a modified Wynberg reaction that requires an active LA* and/or an active LB* for catalysis[4a,b,6a−d] as the proof-of-principle reaction, the desired metal suitable for generating an active LA*−LB* bifunctional catalyst could be discovered through the screening[5f,g,7] of metal complex **4**. Based on the elegant catalytic system developed by Lectka for activating *N*-tosylimines derived from glyoxylates,[5f,g] the prospect of discovering an active bifunctional catalyst from mixed ligand **3** seemed promising if an appropriate Lewis acidic metal can be identified.

From the outset of our design, we reasoned that both apical coordination sites in the LA* are openly accessible, especially when its internal ligand dissociates upon competitive substrate binding. Thus, facial discrimination of the substrates by the LA* alone would not be expected. This would render the chirality at the LA* less important than that at the LB* as the determining factor for chiral induction. Thus, we employed the racemic 2,3-diaminopropionic acid as the ester linkage for synthesizing ligand **3**.

Gram quantities of ligand **3** were synthesized efficiently from the Boc-protected (±)-2,3-diaminopropionic acid **5** and quinine (**2**), which were coupled to give a 1:1 diastereomeric mixture of ester **6** in 87% yield (Scheme 1). Deprotection

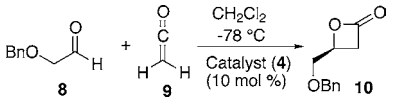
Scheme 1. Efficient Ligand Synthesis Using a Racemic Linker



of the Boc groups with TFA, followed by condensing the resulting diamines with aldehyde **7**, furnished the desired mixed ligand **3** in 92% yield as a 1:1 mixture of diastereomers.

With a large quantity of ligands in hand, intensive research effort was devoted to the search for a suitable metal as the desired Lewis acid for evolving an active LA*−LB* bifunctional catalyst from ligand **3**. We used the Wynberg reaction between 2-benzyloxyacetaldehyde **8** and ketene **9** to give chiral β-lactone **10** (Table 1) for this purpose. The

Table 1. Screening for Bifunctional Catalytic Activity



entry	catalyst (**4**) (metal)	**9**[b] (equiv)	time (h)	yield[c] (%)	ee[d] (%)
1[a]	Cu, Ni, Ti, Fe, Cr	8	2−24	0	N/A
2	Co(II)	8	3	41	>99
3	Co(II)	8	1.5	60	>99
4	Co(II)	5	2	86	>99
5	Co(II)	5	2	91	>99
6[e]	Co(II)	1.5	1	83	>99

[a] Selected metals. [b] All reactions were carried out in 0.05 M aldehyde **8**, except in entry 6. Ketene was generated in situ from acetyl chloride and diisopropylethylamine. [c] Isolated yields. [d] ee and absolute configuration of β-lactone **10** were determined by chiral HPLC analysis, according to the Evans protocol.[9] [e] 1 mol % catalyst loading and 0.025 M of substrate concentration.

importance of optically active β-lactones as versatile chiral synthons[8] underscores current research efforts for developing

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new catalytic, enantioselective methods, among which the asymmetric [2 + 2] cycloaddition between aldehydes and ketene appears the most elegant.[4a,b,6,9] For reactive, enolizable aliphatic aldehydes (e.g., 2-benzyloxyacetaldehyde), catalysts having an excellent level of asymmetric induction are still needed.

In order to screen metals for the desired bifunctional catalytic activity, metal complex **4** was synthesized from ligand **3** and the corresponding metal precursor.[3b] The catalytic activity of metal complex **4** for promoting the formal [2 + 2] cycloaddition reaction between 2-benzyloxyacetaldehyde (**8**) and ketene **9** was subsequently investigated. Using a large excess of ketene for initial metal screening, complex **4** derived from transition metals Ti(IV), Fe(III), Ni(II), Cu(II), and Cr(III) did not afford the desired β-lactone (entry 1, Table 1). Interestingly, 10 mol % of the Co(II)-derived complex (**4**, M = Co) furnished the desired β-lactone in modest yield (41%) as only one enantiomer (>99% ee, entry 2).[9] Encouraged by this initial result, we next focused our attention on optimizing the reaction conditions using Co(II) as the Lewis acid of choice.

The complete consumption of aldehyde **8** and the excellent ee obtained for β-lactone **10** suggested that the low yield of this reaction was probably due to the prolonged exposure of the β-lactone adduct to an excess of reactive ketene/acetyl chloride. In addition to the possible self-aldol condensation of aldehyde **8**, enolization of β-lactone **10** and subsequent enolate acetylation could have led to the decomposition of β-lactone **10** and contributed to the overall low yield. Indeed, stopping the reaction after only 1.5 h increased the isolated yield to 60%, with the same excellent level of ee (entry 3). A further decrease in the amount of ketene utilized from 8 to 5 equiv consistently gave excellent yield and excellent ee (entries 4 and 5). Remarkably, using as little as 1 mol % of the LA*−LB* catalyst and 1.5 equiv of ketene afforded β-lactone **10** in 83% yield and >99% ee within 1 h, even running the reaction at a lower concentration (entry 6). In the absence of Co(II), using either ligand **3** (1 mol %) or quinine **2** (1 mol %) alone (i.e., LB* alone) did not catalyze the formation of β-lactone **10** under the optimized reaction conditions used in entry 6.

The unprecedented catalytic activity displayed by catalyst **4** (M = Co) for aldehyde **8** and the necessity of the metal for its activity suggest an *intra*molecular dual activation mechanism. In order to substantiate the intramolecular bifunctional activation hypothesis, we designed a ligand (**11**, Figure 2) that is suitable for conducting additional control experiments by replacing the LB* with a methyl ester. Methyl ester **11** was synthesized from ligand **3** in 59% yield through a solvolysis reaction. The Co(II) complex (1 mol %) derived from ester **11** did not catalyze the Wynberg reaction, neither in the presence (i.e., LA* + LB*) nor in the absence (i.e., LA* alone) of 1 mol % of TMSQ (**12**). Chiral Lewis bases similar to LB* **12** have been shown independently by Nelson[6b] and Calter[6c] to promote similar reactions in the presence of other achiral Lewis acids.

Our current working model for intramolecular bifunctional catalysis features a chiral LA* (one diastereomer shown),

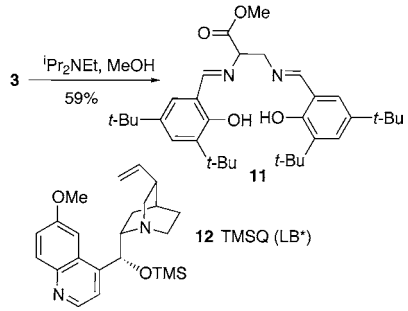
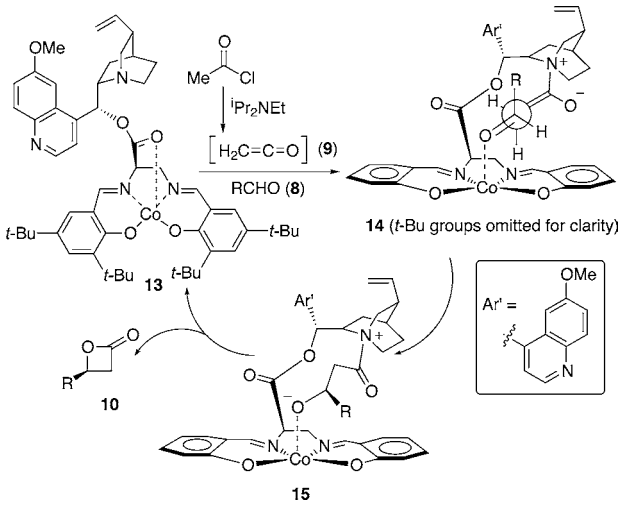


Figure 2. Control ligands.

most likely coordinated to the ester carbonyl group (i.e., internal ligand in **13**, Scheme 2). In the presence of

Scheme 2. Proposed Working Model for Intramolecular Asymmetric Bifunctional Catalysis



substrates, the internal ligand dissociates in order to activate aldehyde **8**. Coordination of the lone pair electrons of aldehyde **8** *cis* to its hydrogen atom positions its *si* face in close proximity to the nucleophilic bridgehead nitrogen (i.e., the LB*). The LB* converts ketene **9** into a transient chiral nucleophilic ammonium enolate **14**. Intramolecular nucleophilic addition of enolate **14** to the *si* face of the bound carbonyl group furnishes ammonium aldolate **15**, which collapses to afford the desired β-lactone **10** and regenerates catalyst **13**.

The rapid catalyst turnover suggests a relatively weak interaction between Co(II) and the aldolate anion in aldolate **15**, an important factor that contributes to the facile intramolecular cyclization of zwitterionic aldolate **15** to furnish β-lactone **10**. The absolute facial control (>99% ee) observed for this reaction can be rationalized through an open transition-state model (i.e., Newman projection in **14**). The

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depicted trajectory of the approaching ammonium enolate to the carbonyl *si* face minimizes the strain and nonbonded interactions, compared to all other possible nucleophilic addition scenarios to its *re* face. Close examination of a molecular model further reveals that the ammonium enolate species fits into a transient "pocket" formed between the LB* and the *si* face of the bound carbonyl group in **14**.

Combining both the rational design and metal screening approaches, we have designed and synthesized novel mixed ligands, from which an active catalyst displaying remarkable bifunctional catalytic activity has been discovered. The active catalyst is easy to prepare and can be handled in standard atmospheric environment (i.e., not air/moisture sensitive). The excellent ee derived from a 1:1 mixture of two diastereomeric LA*−LB* bifunctional catalysts (i.e., **13**) is intriguing. This suggests that the LB* chirality overrides the LA* chirality in controlling the stereochemistry of this reaction. Even though there are two opposite configurations at the LA* (from the racemic linker), the LB* chirality of both isomers in catalyst **13** is identical, suggesting LB*-dependent asymmetric bifunctional catalysis. In contrast to chiral Lewis acids and Lewis acid−Lewis base bifunctional catalysts having the chirality at the LA*, the LB*-dependent asymmetric bifunctional catalysis decouples substrate activation (i.e., by the LA*) from chiral induction (i.e., by the LB*) intramolecularly. It can be noted that electrophilic activation by our catalyst is distinctly different from that of Lectka's bifunctional catalyst that requires bidentate substrates. In our catalyst, both available coordination sites are apical,[10] which make it geometrically impossible to chelate substrates in a bidentate fashion. Given the open accessibility of both apical coordination sites in our bifunctional catalyst, it is very likely that the LA*−LB* catalyst will have broad reaction/substrate scopes. The potential generality of this catalyst is currently being explored in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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