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Design and synthesis of a tridentate ligand for asymmetric bifunctional catalysis

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Abstract—Covalent attachment of a quinine moiety to a Schiff base ligand through an ester linkage generates a novel tridentate ligand that gives a new Lewis acid–Lewis base (LA–LB*) bifunctional catalyst having a mixture of the LA configurations. The LB*-dependent asymmetric bifunctional catalysis was demonstrated using the addition of diethylzinc to 2-methoxybenzaldehyde as a test reaction and the substrate scope of the new catalyst was illustrated using aromatic aldehydes.

The allure of using small molecule catalysts to emulate enzymatic catalysis for chemical synthesis has inspired the development of metal-based multifunctional/bifunctional catalysts that have contributed tremendously to the field of asymmetric catalysis.[1] Shibasaki's laboratory has popularized the field of asymmetric bifunctional catalysis in which an achiral Lewis base (LB) is covalently attached to a chiral Lewis acid (LA*, * denotes chirality) to form Lewis acid–Lewis base bifunctional catalysts (LA*–LB) having the chirality centered at the Lewis acidic metals.[2] The rapid advance in the field of asymmetric bifunctional catalysis witnessed in recent years has been fueled by the early development of some extraordinary ligands (e.g., BINOL) invented for generating chiral Lewis acids.[1,3] For example, ligand modification of BINOL by Shibasaki through the introduction of two phosphine oxides as achiral Lewis basic components afforded LA*–LB bifunctional catalyst.[2c] By introducing two morpholines as the achiral LB into a chiral salen framework, Kozlowski generated salen-based LA*–LB bifunctional catalysts to promote the asymmetric addition of diethylzinc to aldehydes.[2f] Hoveyda and Snapper developed an elegant bifunctional catalytic system based on tridentate Schiff base ligands by the incorporation of chiral amino acids for enantioselectivity.[2e]

LA–LB bifunctional catalysts derived from a chiral LA* and an achiral LB rely on the LA* chiral space to exert enantioselectivity during catalysis. In contrast, using the LB* chiral space in a bifunctional catalyst for enantioselectivity has received relatively less attention.[4] For example, Lectka's elegant bidentate ligand displayed bifunctional catalytic activity for the syntheses of β-lactams by activating the glyoxylate derived *N*-tosyl imines in a bidentate fashion,[4a,b] while a remarkably active LA*–LB* bifunctional catalyst recently developed in our laboratory activates an enolizable aldehyde[4c] and aromatic aldehydes for the asymmetric Wynberg reaction in a monodentate fashion.[4d]

Herein, we report the design and synthesis of a novel tridentate ligand (Scheme 1, **1**) for asymmetric bifunctional catalysis aiming at exploring the LB* chiral space for asymmetric induction. Our new ligand (**1**) utilizes readily available quinine as the desired LB*,[5] which is covalently tethered to a Schiff base ligand designated for chelating Lewis acidic metals.[6] Coordination of ligand **1** to metals (e.g., **2**) would generate the desired LA–LB* bifunctional catalysts having at least two different configurations at the LA (e.g., **3** and **4**, Scheme 1).

Ligand **1** was synthesized efficiently from Boc-glycine **5** and quinine (Scheme 2). Coupling of Boc-glycine with quinine afforded the desired ester **6** in 89% yield. Deprotection of the Boc group with TFA in methylene chloride unveiled an amino group, which was condensed with 1 equiv of 3,5-di-*t*-butyl-2-hydroxybenzaldehyde to give gram quantities of ligand **1** in 94% yield.

The bifunctional catalytic activity of tridentate ligand **1** was demonstrated using the addition of diethylzinc to 2-methoxybenzaldehyde and the intramolecular

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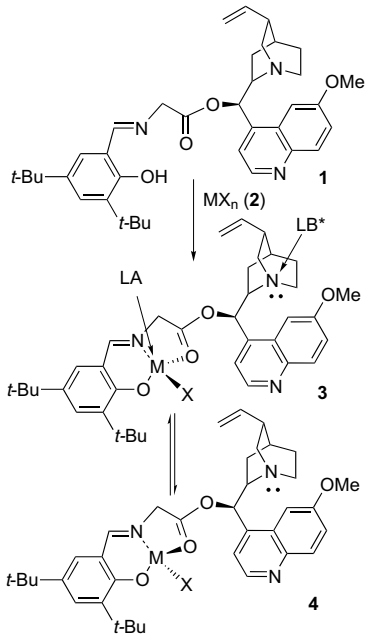
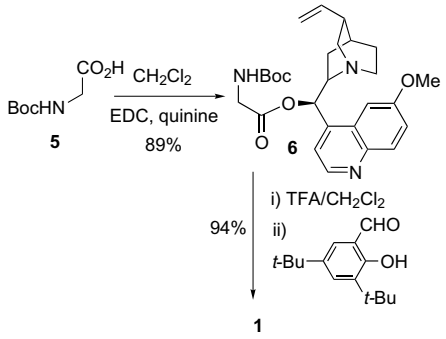


Scheme 1. Design of a new LA–LB* bifunctional catalyst from a tridentate ligand.



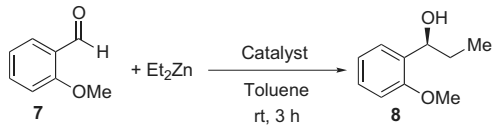
Scheme 2. Ligand synthesis.

bifunctional activation was demonstrated through a series of control experiments. The addition of diethylzinc to aldehydes requires an active LA for catalysis,[7] especially for 2-methoxybenzaldehyde, a substrate that is particularly nonreactive without catalysis. In addition, the LA identity would be unambiguous during catalysis. Not surprisingly, this reaction has been utilized extensively as a benchmark reaction for examining the catalytic activity of newly developed catalytic systems.[2f,7]

Bifunctional catalyst **3/4** ($M = Zn^{2+}$, Scheme 1) was generated in situ from ligand **1**. Treatment of 2-methoxybenzaldehyde (**7**) with diethylzinc in the presence of 10 mol % of the LA–LB* catalyst gave a complete reaction and afforded the desired benzyl alcohol **8** in 94% yield with 92% ee (Table 1, entry 1). It is noteworthy that the LA–LB* catalyzed reaction proceeds rapidly at rt and does not rely on lowering the reaction temperature and/or slow addition of substrates to achieve an excellent ee.

Because the LB* is the only source of chirality for this reaction, there is a possibility that the excellent ee we observed might be promoted by the LB* alone. In order to rule out this possibility, we sought a ligand that is incapable of forming a metal complex but preserves the same LB* during the reaction. Replacing the Schiff base component in tridentate ligand **1** with a noncoordinating ligand would afford a control ligand. *O*-Benzylquinine **9** (Fig. 1, BnQ) employed by Deng is an excellent ligand for this control experiment.[9] The benzyl group of this readily synthesized ligand is *nonchelating* and its chiral space is identical to that in tridentate ligand **1**. Under otherwise identical reaction conditions (solvent, temperature, and reaction time), using 10 mol % of BnQ **9** to replace ligand **1** as catalyst gave only 35% yield in 3 h without any enantioselectivity (Table 1, entry 2). Thus, the BnQ catalyzed reaction proceeds at a much slower reaction rate, compared to the LA–LB* catalyzed reaction. The lack of asymmetric induction and the modest catalytic activity attained by BnQ **9** suggest that the LB* alone in the LA–LB* bifunctional catalyst **3/4** is not sufficient to attain excellent enantioselectivity.

Table 1. Bifunctional catalytic activity of tridentate ligand **1**



Entry	Ligand (10 mol %)	Reaction time (h)	Yield[a] (%)	ee[b] (%)
1	**1**	3	94	92 (*S*)[c]
2	**9** (LB* alone)	3	35	<2
3	**10** (LA alone)	3	47	0
4	**9**+**10** (LA + LB*)	3	55	<2
5	***ent*-1**	3	86	93 (*R*)[c]

[a] Except for the catalysts employed, all reactions were carried out under otherwise identical conditions and the reported yields are isolated yields.

[b] ee determined by chiral GC–MS(EI) using a chiral column (Restek RT-BetaDEXsm 0.25 mm × 0.25 μm × 30 m). Initial oven temperature = 40 °C; temperature program: 40 °C (6 min) 15 °C/min to 220 °C (20 min). For the *R* enantiomer, retention time $t_R = 16.77$ min; for the *S* enantiomer, retention time $t_R = 17.02$ min.

[c] Absolute configuration determined by ^{1}H NMR analysis of its (+)-*O*-methylmandalate.[8]

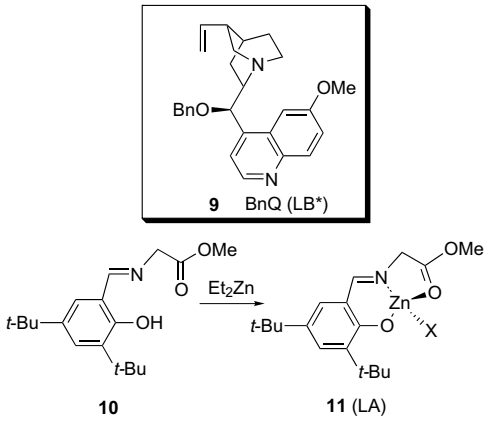


Figure 1. LB* and LA for control experiments.

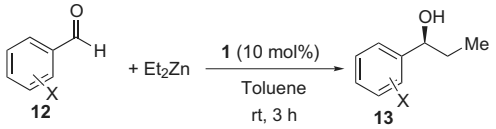
The intramolecular bifunctional activation displayed by the LA–LB* catalyst was further demonstrated through additional control experiments. Replacing the LB* in ligand **1** with a methoxy group (a nonfunctional 'dummy' group) would give a control ligand **10** (Fig. 1) that would generate an achiral LA **11** for catalyzing the diethylzinc addition reaction. The desired methyl ester **10** was synthesized by solvolysis of ligand **1** in methanol in 89% yield. In the absence of an LB* tethered intramolecularly, the LA **11** (10 mol %) derived from this tridentate ligand catalyzed the same reaction but only gave an incomplete reaction in 3 h (entry 3). Addition of 10 mol % of BnQ **9** as an external LB* to 10 mol % of LA **11** did not improve the reaction yield (entry 4), compared to the reaction catalyzed by the LA alone (entry 3).

It should be noted that the presence of the LB* in this nontethered LA + LB* catalyzed reaction did not result in any asymmetric induction. In the absence of a linker between LA and LB*, this is not surprising, presumably due to the unrestricted LA, LB* interactions. Coordination of the LB* to the LA generates a mixture of diastereomeric chiral Lewis acids (i.e., random formation of LA*), each of which would be catalytically active, but might have opposite asymmetric induction that led to an overall racemic product. These control experiments further illustrated the importance of the intramolecular bifunctional activation promoted by the LA–LB* for rate acceleration and asymmetric induction. The chirality at the LB* of the LA–LB* catalyst appeared to be the only determining factor governing the stereochemical outcome for this addition reaction because switching the LB* component in **1** from quinine to its pseudoenantiomeric quinidine completely reversed the enantioselectivity for this reaction (Table 1, ***ent*-1**, entry 5). This reversal of enantioselectivity (i.e., entries 1 and 5) offers another example of LB*-dependent asymmetric bifunctional catalysis (ABC),[4c,d] considering all the possible LA configurations present in **3/4**.

Having established that the Zn(II) complex of tridentate ligand **1** displays LA–LB* bifunctional catalytic activity at rt, we subsequently investigated the substrate scope of the LA–LB* catalyzed diethylzinc addition reaction. Employing 10 mol % of tridentate ligand **1** for aromatic aldehydes **12**, the addition reaction gave the expected benzyl alcohols **13** in good to excellent yields (entries 1–5) at rt (Table 2). Among all the substrates examined, bidentate substrate exhibits the best enantioselectivity in this reaction (entry 5). This suggests a possible bidentate coordination of 2-ethoxybenzaldehyde to the LA that restricts the free rotation of the bound carbonyl group. This result is also consistent with the excellent ee observed for 2-methoxybenzaldehyde **7** under bifunctional catalysis conditions (Table 1, entry 1), where a bidentate chelation by the LA is likely.

In summary, we have designed and synthesized a novel tridentate ligand by exploiting the readily available cinchona alkaloid quinine/quinidine as the LB* for constructing new LA–LB* bifunctional catalysts having a mixture of the LA configurations. The tethered LB* chirality is too far away from the LA to create an effective chiral pocket at the metal center for asymmetric induction. Therefore, coordination of aldehydes to the LA would not offer any intrinsic facial discrimination for the bound carbonyl group. On the other hand, chelation of diethylzinc by the bridgehead nitrogen of the LB* converts the diethylzinc reagent into a transient chiral nucleophile that ultimately differentiates the enantiomeric faces of the bound carbonyl group and determines the stereochemical outcome of the reaction. In addition, the LA–LB* bifunctional catalytic activity has been demonstrated through the diethylzinc addition reaction to 2-methoxybenzaldehyde and control experiments. The substrate scope of this new bifunctional catalyst for the diethylzinc addition reaction has been illustrated using aromatic aldehydes. The LA–LB* bifunctional catalyst derived from tridentate ligand complements other LA*–LB and LA*–LB* catalytic systems and should be very useful for asymmetric bifunctional catalysis (ABC).

Table 2. Substrate scope of the LA–LB* catalyzed diethylzinc addition reaction at room temperature



Entry	ArCHO **12** (–X)	Isolated yield (%)	ee[a] (%)
1	4-MeO–	56	42
2	H–	81	63[b]
3	4-Me–	96	63
4	4-F–	92	73[b]
5	2-EtO–	Quant.	90

[a] ee determined by chiral GC–MS.
[b] ee determined by chiral GC–MS analysis of the corresponding acetate.

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Supplementary data

Experimental procedures, spectral data, and NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.130.

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