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Predicting the *R*/*S* absolute configuration in asymmetric bifunctional catalysis (ABC)

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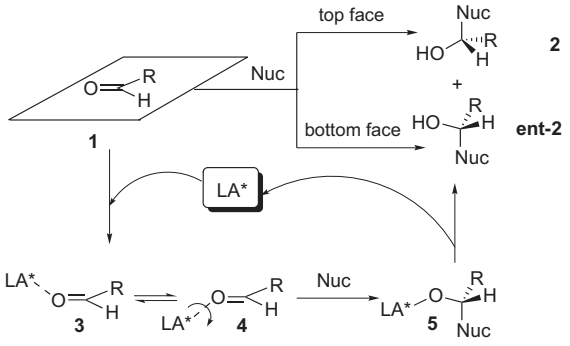
Abstract—A predictive model for assigning the *R*/*S* absolute configuration in chiral Lewis base-dependent asymmetric bifunctional catalysis (ABC) has been developed. Chiral Lewis base (LB*)-dependent ABC abolishes the chiral Lewis acid (LA*) component as the stereochemical determining factor in asymmetric catalysis. By correlating the constant LB* chirality to the facial preference for the LA*-bound carbonyl group for nucleophile delivery, the *R*/*S* absolute configuration of the products can be predicted a priori.

The addition of nucleophiles to a carbonyl group is an important C–C bond forming reaction. In the absence of a chiral environment, the nucleophile attacks the carbonyl group from either enantiomeric face with equal opportunity, thus affording a racemic product (Scheme 1). Because chirality plays an essential role in molecular recognition between small molecules and their biological targets, differentiating the two enantiomeric faces of the carbonyl groups in order to achieve asymmetric induction (ideally >99% ee) is highly desirable. One contemporary approach to impart asymmetric induction in the addition of carbon nucleophiles is to employ a chiral Lewis acid (LA*, * denotes chirality).[1] Coordination of the LA* to the carbonyl oxygen activates the carbonyl group and imparts chirality transfer from the LA* to the product (i.e., LA*-dependent asymmetric induction).



Scheme 1. The LA* catalyzed carbonyl addition reaction.

While the ee from the LA*-catalyzed reactions can be readily determined (e.g., using chiral HPLC), predicting the *R*/*S* absolute configuration of the product prior to reaction execution is very challenging.[1d] In addition to the dynamic equilibrium between the two structurally different LA*-aldehyde complexes **3** and **4**, the steric and electronic properties of the LA* fluctuate during catalysis (Scheme 1). Addition of the nucleophile (Nuc) to the LA*-activated C=O generates a more Lewis basic alkoxide ligand that can coordinate to the LA* to form a modified LA* **5**. In addition to inhibiting catalyst turnover, this coordination event could lead to the replacement of hemiliable chiral ligands that are indispensable for asymmetric induction. To date, developing a reliable model for predicting the *R*/*S* absolute configuration prior to the reactions remains a considerable challenge in asymmetric catalysis.[2]

We have designed a Lewis acid–Lewis base (LA*–LB*) bifunctional catalytic system **6** that features a planar LA*, aiming at abolishing its role as a determining factor in chiral induction (Fig. 1).[3,4] Because both apical coordination sites in bifunctional catalyst **6** are openly accessible and the bound carbonyl group can freely rotate, asymmetric induction is impossible for the background reaction, catalyzed by the LA* alone. In contrast, the LB* moiety of catalyst **6** converts the Nuc into a transient chiral species, and it is this LB*-bound chiral species that ultimately determines

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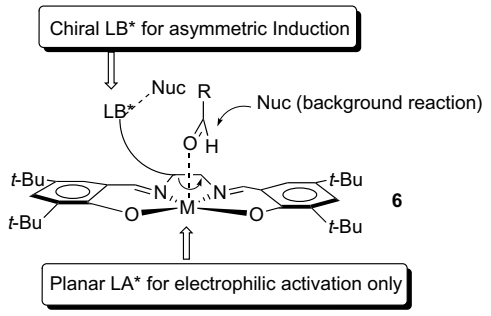


Figure 1. Design of a predictable asymmetric bifunctional catalytic system.

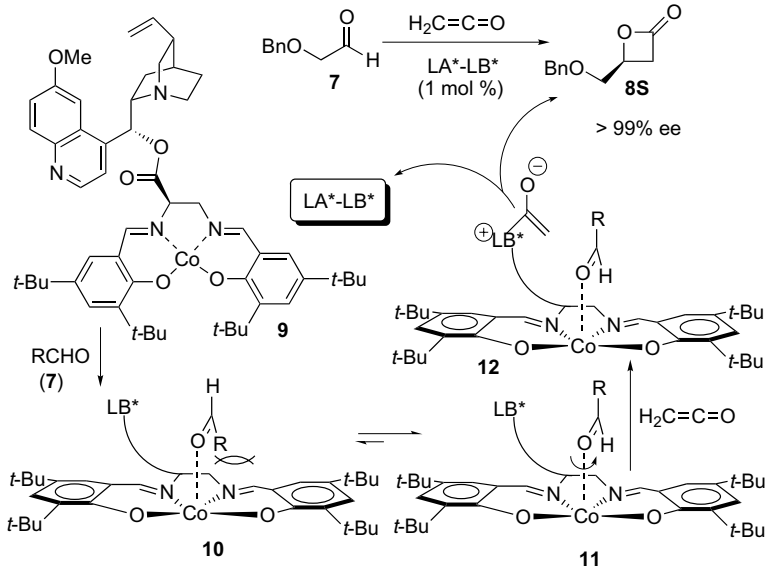
the stereochemical outcome of the reactions. Because the LB* chirality remains unchanged during the entire catalytic cycle, it is possible to predict the *R*/*S* absolute configuration of the product based on the LB* utilized. Herein, we report the development of such a predictive model and apply this model to determine the β-lactone configurations in the asymmetric Wynberg reaction.[5]

Based on the design principle outlined in Figure 1, we recently reported the discovery of an active catalyst **9** (Scheme 2).[4] Its remarkable bifunctional catalytic activity was demonstrated using the asymmetric Wynberg reaction between aldehyde **7** and ketene. We have also proposed a plausible catalytic cycle. Steric consideration favors the coordination of the planar Co(II) to the carbonyl lone pair electrons that are cis to the H (i.e., **11** > **10**, Scheme 2). This selective coordination differentiates the two enantiomeric faces of the bound carbonyl group by the ammonium enolate derived from ketene and the LB*. Thus, free rotation of the bound carbonyl group becomes irrelevant in the stereodifferentiating C–C bond forming step, in which the LB* delivers the enolate and defines the stereochemistry of the product (**12**, Scheme 2).[4]

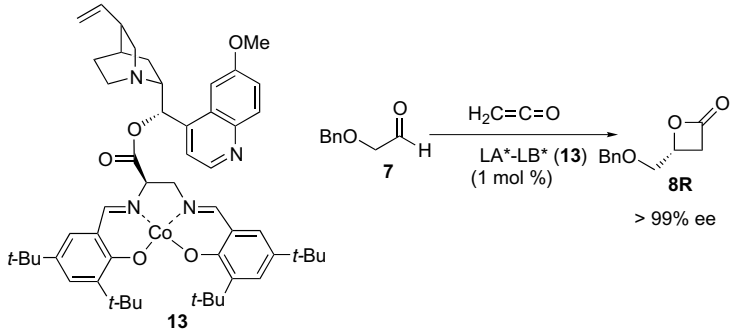
If the LB*-dependent asymmetric induction hypothesis is correct, switching the LB* chirality in bifunctional catalyst **9** from quinine to quinidine should reverse the facial selectivity of the LA*-activated carbonyl group and produce the other enantiomeric β-lactone.[6] Employing the (*R*)-2,3-diaminopropionic acid as the linker, we subsequently synthesized the quinidine-derived bifunctional catalyst **13** from its corresponding ligand and Co(II) (Scheme 3). Indeed, substituting bifunctional catalyst **13** for **9** completely reversed the facial selectivity of the bound carbonyl group. Employing 1 mol % of catalyst **13** in the Wynberg reaction between aldehyde **7** and ketene afforded the *R* enantiomeric β-lactone **8R** in 86% yield and >99% ee. This result provides additional experimental evidence to support the LB*-dependent asymmetric induction hypothesis.[4]

Because the absolute configurations of both β-lactones **8S**/**8R** have been established by Evans and Janey,[7] the relationship between the LB* chirality of catalysts **9**/**13** and their corresponding *si*-/*re*-facial preference to the LA*-bound carbonyl group can be deduced. By correlating the LB* chirality in bifunctional catalysts **9**/**13** to the corresponding *si*-/*re*-facial selectivity for delivering the nucleophile (i.e., the ammonium enolates) in the stereodetermining step,[5a] a predictive model for the *R*/*S* absolute configurations has been developed. For the sake of simplicity, we formulated the following conventions to predicting the absolute configuration of the newly created chiral center from achiral aldehydes (Scheme 4).

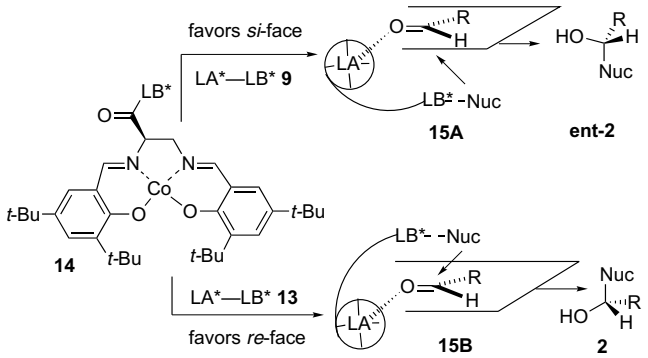
(1) Place the aldehyde on a horizontal plane by orienting the carbonyl oxygen pointing to the left and the hydrogen to the front. (2) As discussed in Scheme 2, both catalysts **9**/**13** coordinate their planar LA* to the lone pair electrons cis to the H atom (in the front) of the carbonyl group and are depicted as **15A**/**15B**. The quinine-derived bifunctional catalyst delivers the nucleophile from the bottom face (**15A**) of the bound carbonyl group, thus giving the new chiral center having the configuration



Scheme 2. LB*-dependent asymmetric bifunctional catalysis. Notes: The ester linkage and the LB* are simplified for clarity.



Scheme 3. An active bifunctional catalyst from quinidine.



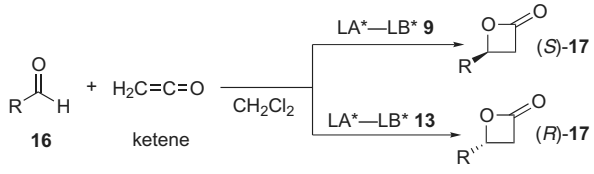
Scheme 4. A predictive model for assigning the *R*/*S* absolute configuration.

shown in **ent-2** while the quinidine-derived catalyst delivers the nucleophile from the top face (**15B**) to give the absolute configuration depicted in **2**.

The model was subsequently applied to the asymmetric Wynberg reaction for assigning the *R*/*S* absolute configurations of the resulting β-lactones. The synthetic significance of optically pure β-lactones as versatile synthons[8] (e.g., masked aldols)[9] manifests to the current research effort directed towards the development of new catalytic systems for their efficient syntheses. The catalytic, asymmetric Wynberg reaction between aldehydes and ketenes is among the most elegant approaches.[7,10] After much experimentation, we were pleased to find that LA*–LB* bifunctional catalyst **9** promoted the asymmetric Wynberg reaction between ketene and aromatic aldehydes **16** efficiently to furnish the expected β-lactones **17** in good to excellent yields and excellent ee (Table 1, entries 1–6).[11] Their *S* configurations were assigned based on the predictive model in Scheme 4.

For comparisons, the asymmetric Wynberg reaction catalyzed by the LA*–LB* bifunctional catalyst **13** was examined (entries 7–10). In contrast to the uniformly excellent ee achieved by catalyst **9**, the ee of the reactions catalyzed by **13** varied from excellent (entry 7) to moderate (entries 8–10). The *R* configurations of the major enantiomers (entries 8–10) were predictable based on model **15B**, regardless of the level of asymmetric induction. Taken together, these results not only demonstrate the substrate scope of our LA*–LB* bifunctional catalysts **9**/**13**, but also illustrate their predictable asymmetric induction in which an excellent level of ee is not a

Table 1. A predictable asymmetric Wynberg reaction[a]



Entry	Aldehydes **16** (R-)	LA*–LB* (mol %)	**17** (% yield)[b]	**17** (% ee)[c]	**17** (*R*/*S*)
1	2-NO_2–Ph–	**9** (10)	90	>99	*S*
2	3-NO_2–Ph–	**9** (10)	62	>99	*S*
3	4-NO_2–Ph–	**9** (10)	87	>99	*S*
4	4-CN–Ph–	**9** (10)	96	>99	*S*
5	2-F–Ph–	**9** (20)	44	>99	*S*
6	2-Cl–Ph–	**9** (5)	60	>99	*S*
7	$BnOCH_2$–	**13** (1)	86	>99	*R*[d]
8	3-NO_2–Ph–	**13** (10)	18	78	*R*
9	4-NO_2–Ph–	**13** (10)	42	67	*R*
10	4-CN–Ph–	**13** (10)	21	74	*R*

[a] All reactions were carried out at −78 °C except for entry 5, which was carried out at −20 °C.
[b] Isolated yields.
[c] ee Determined by chiral HPLC using a CHIRACEL OD-H column.
[d] Absolute configuration known.[7]

prerequisite.[12] They also attest to the practical advantage of the LB*-dependent asymmetric catalytic processes over other catalytic systems. For aromatic aldehydes, the drastic difference between catalysts **9** and **13** in asymmetric induction is presumably due to the internal 'matched–mismatched' scenario between the LA* and the LB*.[13]

In summary, using the LA*–LB* catalyzed asymmetric Wynberg reaction in a case study, we have developed a predictive model that *foretells* the *R*/*S* absolute configuration in LB*-dependent asymmetric bifunctional catalysis. By placing the stereodetermining factor solely on the LB*, the LB*-dependent asymmetric induction abolishes the planar LA* as the stereodetermining factor. Thus, restricted rotation of substrates is not a requirement for excellent ee in our catalytic system. Our LA*–LB* bifunctional catalysts complement other bifunctional catalytic systems.[14] Furthermore, the constant LB* chirality is transcribed into that of the product in a predictable manner. The predictive model thus serves as a valuable guide in reaction planning and a practical tool for absolute configuration determination. Although this predictive model was born out of the LA*–LB* catalyzed asymmetric Wynberg reaction, it would be interesting to see if it is generally applicable to other reactions amenable for LA*–LB* bifunctional catalysis. Investigation of its generality is currently underway in our laboratory.

Acknowledgments

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11. *Experimental procedure*: To a solution of 4-nitrobenzaldehyde (45 mg, 0.3 mmol), LA*–LB* bifunctional catalyst **9** (32 mg, 0.03 mmol) in methylene chloride (9 mL) at −78 °C, was added diisopropylethylamine (0.2 mL, 1.2 mmol) under argon. A solution of acetyl chloride (0.07 mL, 1.0 mmol) in methylene chloride (1 mL) was added slowly (ca. 0.5 h) to the above solution and the reaction was stirred at −78 °C for 1 h. The reaction was quenched with saturated sodium bicarbonate solution and extracted with methylene chloride. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, concentrated, and separated by flash column chromatography on silica gel (8:1 to 4:1 hexanes/ethyl acetate) to give 50 mg (87%) of (4*S*)-4-(4-nitrophenyl)-oxetan-2-one as a single enantiomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 5.61 (dd, $J = 6.0$, 4.8 Hz, 1H), 4.02 (dd, $J = 16.2$, 6.0 Hz, 1H), 3.42 (dd, $J = 16.2$, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 148.5, 144.5, 126.6, 124.4, 69.6, 47.0; IR (neat): 1829.0, 1606.2, 1521.9, 1349.1; MS calcd. for $C_9H_8NO_4$ (MH^+): 194.2, found: 194.3.
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