

Asymmetric Synthesis of Acyclic Amines Through Zr- and Hf-Catalyzed Enantioselective Alkylzinc Reagents to Imines

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This paper is dedicated to Professor Richard R. Schrock on the occasion of his sixtieth birthday.

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Abstract: Readily available chiral amino acid-based ligands are used in metal-catalyzed additions of alkylzinc reagents to various aromatic and aliphatic imines; the desired amine products are formed efficiently and in high levels of optical purity. In cases where the more Lewis acidic Zr salts afford lower efficiency, Hf-based catalysts deliver significantly higher yields with similar enantioselectivities. Critical structural

features of the N-activating groups as well as the optimal chiral ligands are discussed. A mechanistic working model is presented to rationalize the existing data and to serve as a predictive tool.

Keywords: asymmetric alkylation; asymmetric catalysis; chiral amines; hafnium; imines; zirconium

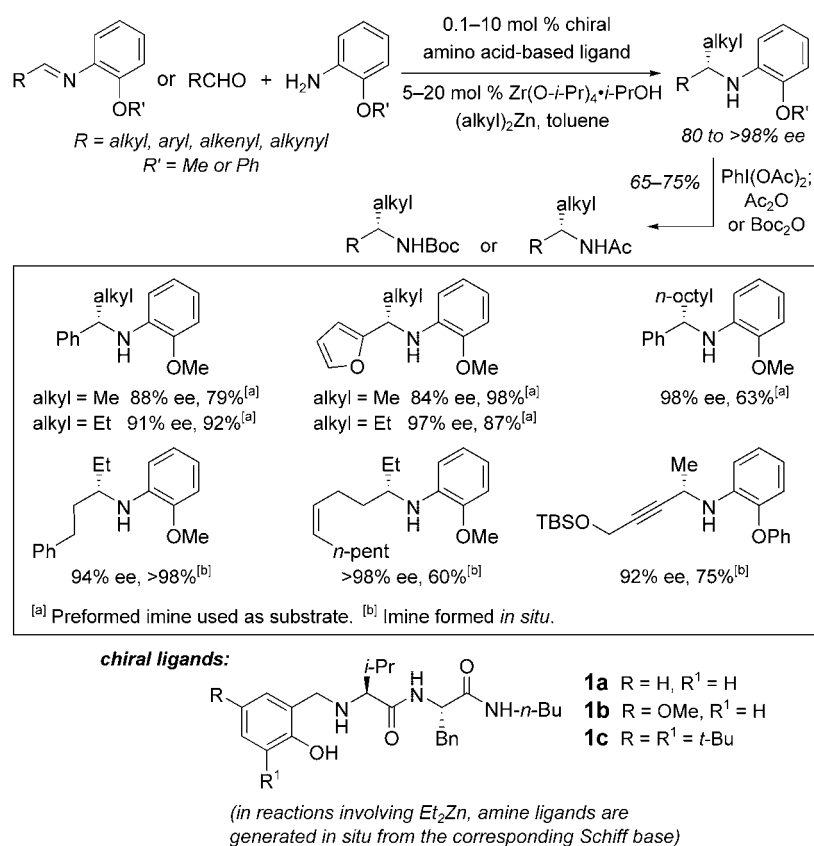
Introduction

Research in these laboratories in recent years has focused on the discovery of readily available and modular amino acid-based chiral ligands that in the presence of various metal salts promote efficient enantioselective additions of carbon nucleophiles to various electrophiles such as alkenes,^[1] carbonyls^[2] and imines.^[3] In this context, in 2001 we reported the first catalytic asymmetric method that allows for the enantioselective addition of a range of alkylzinc reagents to arylimines derived from various aldehydes and *o*-anisidine.^[5a] Later on, we extended the Zr-catalyzed^[4] protocol to include enantioselective additions to aliphatic and alkynylimines.^[5a–d] Such transformations, representative examples of which are illustrated in Scheme 1, provide efficient access to a range of acyclic saturated and unsaturated amines in high optical purity.^[6,7]

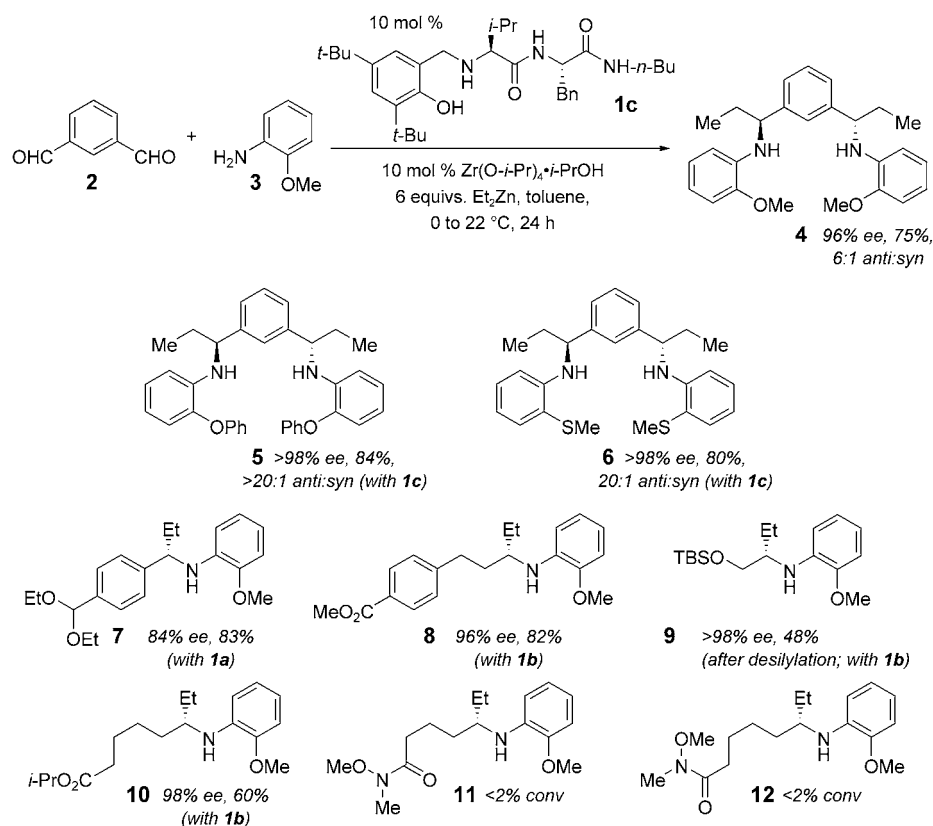
One of the attractive features of the Zr-catalyzed protocol is that the requisite chiral amino acid-based ligands can be synthesized in a few steps from inexpensive and commercially available^[8] amino acids and salicylaldehydes. Our studies have allowed us to establish that dipeptide *amines*, such as **1a–c**, give rise to efficient Zr-based chiral catalysts; the corresponding Schiff base ligands are only highly effective when Et₂Zn is used as the alkylating agent, since *in situ* reduction likely gener-

ates the more active amine.^[9] Furthermore, imine substrates can be either first prepared and then used in the catalytic asymmetric process or they can be synthesized *in situ*, with the alkylzinc reagent serving as the dehydrating agent.^[5b, d] As the examples in Scheme 1 indicate, Zr-catalyzed enantioselective C–C bond forming reactions can be readily carried out with aromatic, aliphatic and alkynyl imine substrates. Oxidative removal of the *o*-anisidyl group can be effected to access the derived amines in 65–75% isolated yields.

In this article, we disclose several critical aspects of the metal-catalyzed enantioselective imine alkylation method. Among such features are the facility and selectivity of reactions involving imines bearing Lewis basic functional groups that are capable of deactivating the Lewis acidic chiral catalysts. We provide data demonstrating that reactions carried out in the presence of Hf (vs. Zr) salts lead to notably more efficient and equally enantioselective asymmetric additions. The significance of some of the particular structural attributes of the chiral ligands, as well as imine activating groups, will also be elucidated. Finally, based on a number of related observations, a mechanistic working model will be presented for this class of metal-catalyzed transformations.



Scheme 1. Zr-catalyzed enantioselective synthesis of amines and derivatives.



Scheme 2. New examples of Zr-catalyzed enantioselective imine alkylations.

Results and Discussion^[10]

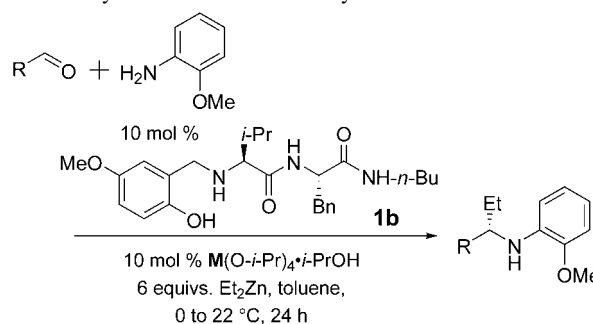
New Examples of Zr-Catalyzed Enantioselective Alkylations of Imines with Alkylzinc Reagents

Several new examples of Zr-catalyzed enantioselective additions of Et_2Zn to imines are illustrated in Scheme 2. As shown in the context of catalytic enantioselective synthesis of chiral diamines **4**, **5** and **6**, multiple C–C bond formation can be effected within a single substrate molecule through an efficient *in situ* process to obtain the desired products in >75% yield and in $\geq 96\%$ ee. It is worthy of note that, whereas imines derived from *o*-anisidine (**3**) lead to the formation of **4** as a 6:1 mixture of diastereomers (96% ee for the major diastereomer), those obtained from reactions of the *o*-phenoxy- ($\rightarrow$ **5**, Scheme 2) and *o*-thiomethylanilines ($\rightarrow$ **6**, Scheme 2) proceed with significantly higher stereoselectivity.^[11] Efficient asymmetric synthesis of acetal **7** (84% ee), aromatic ester **8** (96% ee) and aliphatic silyl ether **9** (>98% ee) indicate that the Zr-catalyzed method is effective in the presence of a range of heteroatom-containing functionalities. However, the significant difference in the efficiency of formation of amine **10**, bearing an ester group, compared to that of amides **11** and **12** indicates that subtle structural variations within substrate molecules (e.g., ester vs. amide terminus) can have a notable influence on the efficiency of catalytic asymmetric processes. A possible rationale for the adverse influence of Lewis basic functionalities on alkylation rates will be presented later.

Hf- vs. Zr-Catalyzed Asymmetric Imine Alkylations

One of the more noteworthy attributes of the Zr-catalyzed imine alkylation is that it can be readily applied to aliphatic as well as aromatic substrates (see Scheme 1 for examples).^[5b] Nonetheless, as the representative cases in Table 1 indicate (entries 1, 3, 5 and 7), reactions involving aliphatic imines often lead to isolation of the desired optically enriched amines in moderate yields. Examination of unpurified reaction mixtures suggest that adventitious imine decomposition, presumably through enamine generation, may be responsible for the reduced yields. Accordingly, we set out to establish whether reactions in the presence of the less Lewis acidic $\text{Hf}(\text{O}-i\text{-Pr})_4$ can lead to higher yields of the desired optically enriched products. The results of these studies are summarized in entries 2, 4, 6 and 8 of Table 1; these data clearly indicate that the Hf-catalyzed method affords optically enriched aliphatic amines in significantly higher yields with similar levels of asymmetric induction as observed with the original Zr-catalyzed protocol.

Table 1. Hf- vs. Zr-catalyzed imine alkylations. A comparison in efficiency and enantioselectivity.^[a]



Entry	M	Product	Yield [%] ^[b]	ee [%] ^[c]
1	Zr		62	97
2	Hf		91	95
3	Zr		58	95
4	Hf		76	91
5	Zr		60	>98
6	Hf		83	95
7	Zr		83	98
8	Hf		>98	97

[a] For details see the Supporting Information.

[b] Isolated yields after silica gel chromatography.

[c] Enantioselectivities determined through chiral HPLC analysis.

Effect of Chiral Ligand and Substrate Structure on the Efficiency and Enantioselectivity of Catalytic Asymmetric Imine Alkylation

Efficient and highly enantioselective imine alkylations require that reactions are carried out in the presence of imines bearing the appropriate N-activating group; use of chiral peptidic ligands that bear proper structural features is critical as well (e.g., amino acid moieties). Documentation of such structural factors allows for an appreciation of some of the mechanistic subtleties of this class of Zr-catalyzed asymmetric C–C bond forming reactions.

As illustrated in Table 2, imines derived from *o*-anisidine are uniquely effective substrates for the Zr-catalyzed alkylation. The presence of the *o*-MeO group, critical to reaction efficiency (cf. entry 2, Table 2), does not appear to be due to steric effects (cf. entry 3, Table 2). Moreover, as the data in entry 4 of Table 2 suggest, a non-coordinating polar heteroatom substituent at the *ortho* position of the aryl unit is not alone suf-

Table 2. Effect of *N*-aryl group structure on efficiency and enantioselectivity of Zr-catalyzed imine alkylation.^[a]

10 mol % **13**
10 mol % Zr(O-*i*-Pr)₄·*i*-PrOH
3 equivs. Et₂Zn, toluene,
0 to 22 °C, 24 h

Entry	G	Conv. [%] ^[b]	ee [%] ^[c] ; Config.	Entry	G	Conv. [%] ^[b]	ee [%] ^[c] ; Config.
1		>98	94; (S)	6		10	<2; –
2		<2	n. d.	7		<2	<2; –
3		<2	n. d.	8		>98	83; (S)
4		<2	n. d.	9		<2	n. d.
5		<2	n. d.	10		73	<2; –

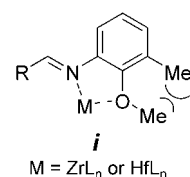
^[a–c] See Table 1.

n.d. = not determined.

ficient to promote reaction. One explanation for the lack of reactivity observed with the aliphatic N-activating group (entry 5) might relate to the rigid structure of the *o*-anisidyl unit (entropic favorability of bidentate chelation). It is also plausible that the partial positive charge developed on the oxygen of the anisidyl unit, generated upon chelation to the Lewis acidic transition metal (see **i** below) influences the electrophilicity of the C=N more effectively through the π cloud of the aromatic group.

The observation summarized in entry 6 of Table 2 illustrates that the effect of the OMe group is not purely due to electronic effects and that bidentate metal chelation involving the *o*-anisidyl group is critical to the alkylation process (e.g., complex **i**). The above contention, regarding the significance of the coordinating ability of the OMe group, is supported by the following additional data: (a) The lack of reactivity of the bulkier and less Lewis basic silyl ether activating group in entry 7 of Table 2. (b) Complete inhibition of reactivity with the functionalized *o*-anisidyl group in entry 9, where, as illustrated in **i**, the adjacent Me group may cause unfavorable steric repulsion with the OMe group upon biden-

tate metal coordination. The relatively inefficient (compared to reactions in entries 1 and 8) reaction of the unprotected N-activating (phenol) unit shown in entry 10 suggests that a dative (vs. a covalent) heteroatom-metal chelation is critical to effective enantiofacial discrimination (see below for proposed models).



Representative findings regarding the influence of the structure of the chiral ligand on the efficiency and enantioselectivity of catalytic alkylations are depicted in Table 3. Comparison of the data in entries 1 and 2 of Table 3 shows that, as is the case with the large majority of reactions promoted by this and related classes of peptide-based ligands, the presence of a second amino acid moiety is required.^[3e] The complete lack of reactivity when the reaction is attempted in the presence of dipep-

Table 3. Effect of chiral ligand structure on efficiency and enantioselectivity of Zr-catalyzed imine alkylation.^[a]

Entry	Ligand	Conv. [%] ^[b]	ee [%] ^[c] , Config.
1	 14	>98	94; (S)
2	 15	<10	n.d.
3	 16	<10	n.d.
4	 17	<10	n.d.
5	 18	70	80; (R)
6	 19	15	11; (S)

^[a-c] See Table 1.

n.d. = not determined.

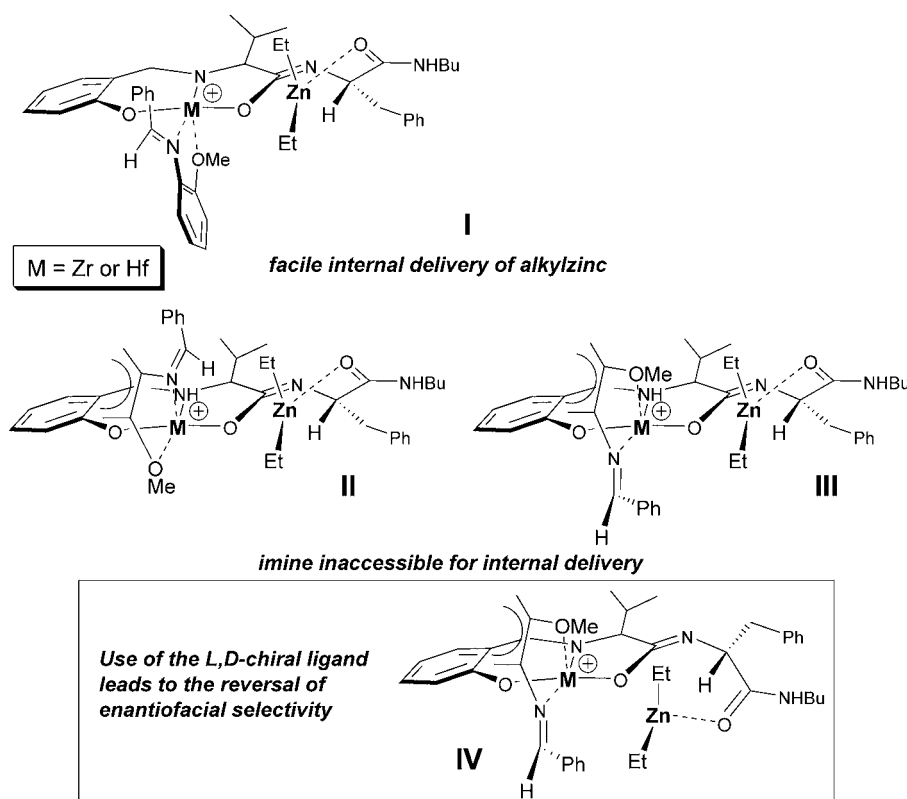
tide **16** (entry 3) underlines the significance of the presence of chirality at the AA2 position (amino acid moiety at the C-terminus). Remarkably, when L-Ala is used as the AA2 moiety in place of L-Phe, little or no catalytic alkylation is detected. The latter finding suggests that the size of the AA2 substituent plays an important role in ensuring appropriate catalyst activity; it may also be possible that the availability of an aromatic π cloud is required for effective alkylation (for reasons that are unclear at the present time). As illustrated in entry 5 of Table 3, chiral ligand **18**, which bears a D-Phe as its AA2 moiety, is less effective than the corresponding L, L-**14** but affords the opposite product enantiomer in 83% ee; this finding clearly points to AA2 as a critical determinant of the identity of the major product enantiomer. The ineffectiveness of methyl ether **19** underlines the significance of the formation of a covalent O–metal bond (see below for proposed models).

Mechanistic Models for Catalytic Asymmetric Imine Alkylations

Many of the observations discussed above are useful as they allow us to propose plausible mechanistic working models that are consistent with the available data and can be used to predict the efficiency of catalytic alkylations and the identity of the major amine enantiomer formed (but not the degree of optical purity). Accordingly, based on detailed mechanistic studies carried out in relation to other early transition metal-catalyzed reactions promoted in the presence of amino acid-based chiral ligands,^[3e] together with the observation described above, mode of addition **I** may be proposed as the favored complex that leads to the formation of preferred amine enantiomers. Delivery of the alkylzinc reagent would not be geometrically favorable through the alternative modes of substrate·catalyst association such as **II** and **III** (Scheme 3).

In the proposed mode of addition **I** bidentate association of the substrate with the Lewis acidic Zr center is expected to lead to activation of the C=N bond which is then alkylated by the alkylzinc through chelation with the Lewis basic amide carbonyl of the peptide ligand's AA2 moiety. The proposed active role for the AA2 is supported by the data presented in Table 3 regarding the influence of the chiral ligand structure on reactivity and enantioselectivity. It should be noted that previous experimental and theoretical studies suggest that coordination of a Lewis basic group to an alkylzinc reduces the bond order of the Zn–C bonds, thus enhancing the nucleophilicity of the alkylmetal reagent.^[12] The reversal of enantioselectivity observed with chiral ligand **18** (entry 5, Table 3) can be rationalized by mode of addition **IV**, where the inversion of the stereogenic center at the AA2 site results in delivery of the alkylmetal to the opposite enantioface of the C=N bond.

Based on the proposed models **I** and **IV** in Scheme 3, formation of the highly active cationic Zr complex would be favored, since loss of an *i*-PrO ligand would lead to a complex, where unfavorable steric interactions between the imine substituent (Ph) and the alkoxide ligand are avoided. An amine chiral ligand is therefore required in order to accommodate the formation of a covalent Zr–N bond (vs. a dative association formed with the derived Schiff base ligand). The lack of reactivity of substrates bearing a properly positioned Lewis basic group, such as those that would lead to amides **11** and **12** (Scheme 2) may be rationalized by suggesting that the Lewis basic substituent (vs. substrates bearing the weaker donors such as ester **10**) can minimize the activating effect of the Lewis acidic Zr center through ligation with the transition metal center. When *o*-hydroxyaniline is used as the activating group (entry 10, Table 2), formation of an O–Zn bond may lead to imine activation through internal chelation (similar to **i** but involving



Scheme 3. Proposed models for Zr-catalyzed asymmetric alkylation of imines.

an O–Zn bond), thus promoting direct, uncatalyzed and non-enantioselective alkylation.

It should be emphasized that the above proposals are intended merely as working models and do not address a variety of important issues. For example, the hypotheses suggested require a pathway for facile exchange between Zr and Zn metals after the alkylation event; the geometric requirements for such a transfer may be critical to the overall mechanism of the catalytic cycle. It may be suggested that dimeric or even oligomeric complexes influence the outcome of the catalytic C–C bond formation; such a possibility is underlined by the preliminary studies illustrated in Figure 1, where a positive non-linear effect is detected in one representative Zr-catalyzed asymmetric imine alkylation.^[13] However, Zr-catalyzed imine alkylations carried out in the presence of ligands on polystyrene solid support proceed with similar efficiency and selectivity.^[5a] These observations collectively suggest that although heterodimeric complexes may be less reactive (cf. data in Figure 1), catalytic alkylations can proceed with monomeric systems such as those shown in Scheme 3. Regardless, there is little doubt that a more detailed mechanistic picture will likely be more complex in nature and must await the outcome of extensive studies.

Conclusion

Enantioselective alkylations of aryl-, alkyl- and alkynyl-imines are promoted efficiently in the presence of readily accessible amino acid-based chiral ligands. Although such transformations can be promoted in the presence of $\text{Zr}(\text{O}-i\text{-Pr})_4 \cdot i\text{-PrOH}$, the desired chiral amines are isolated with high optical purities and in significantly improved yields when $\text{Hf}(\text{O}-i\text{-Pr})_4 \cdot i\text{-PrOH}$ is used instead. The structural requirements that lead to the selection of the most effective imine-activating group include the presence of the sterically accessible and Lewis basic *o*-MeO group which allows for effective bidentate chelation with a Lewis acidic metal center (Zr or Hf). The structural features of the dipeptide Schiff base ligands that are required for high reactivity and enantioselectivity include the presence of a chiral AA2 moiety that bears a sufficiently bulky substituent. The absolute stereochemical identity of the AA2 moiety is critical in determining the identity of the major product enantiomer: a chiral ligand bearing two L-amino acids can afford the opposite enantiomer compared to that formed in the presence of one that contains an L- and a D-amino acid. Finally, mechanistic working models that account for the above structural requirements as well as observed enantioselectivities have been provided.

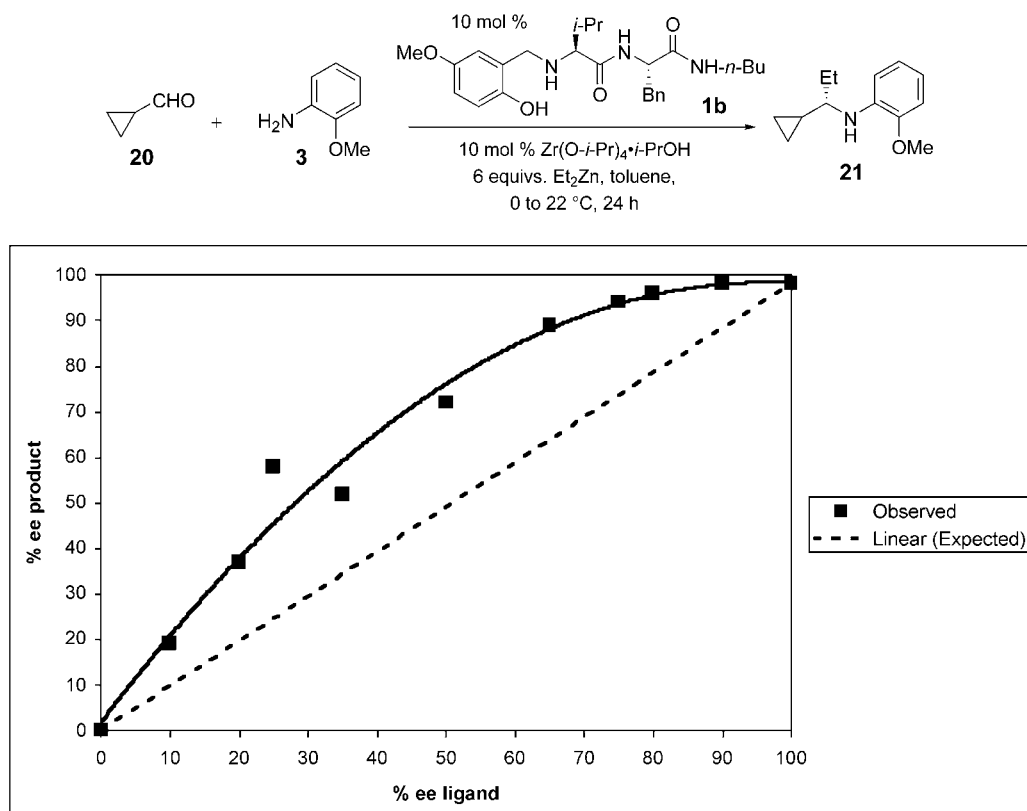


Figure 1. Plot of % ee product vs. % ee ligand for enantioselective synthesis of **21**.

Experimental Section

General Remarks

All reactions were conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry argon or nitrogen. Diethylzinc, dimethylzinc (2.0 M in toluene), $\text{Zr}(\text{O}-i\text{-Pr})_4 \cdot i\text{-PrOH}$ (99.9%), *o*-anisidine, and all commercially available aldehydes were purchased from Aldrich and used without further purification except the following: hydrocinnamaldehyde and heptaldehyde were distilled from CaCl_2 and valeraldehyde was distilled under inert atmosphere. 4-(3-Oxo-propyl)benzoic acid methyl ester,^[14] 6-oxohexanoic acid isopropyl ester,^[15] 5-oxopentanoic acid methoxymethylamide, 6-oxohexanoic acid methoxymethylamide,^[16] 2-*tert*-butyldiphenylsiloxylacetaldehyde,^[17] and 4-*tert*-butyldimethylsiloxylbutyraldehyde^[18] were prepared according to literature procedures. Bis(4-methylpentyl)zinc and dioctylzinc were prepared via a B-Zn exchange according to literature precedence.^[19] Boc-valine, Boc-phenylalanine, EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] and HOBt (*N*-hydroxybenzotriazole) were purchased from Advanced Chemtech and used without further purification. Toluene was distilled from Na/benzophenone ketyl. Dichloromethane, triethylamine, and butylamine were distilled from CaH_2 .

General Procedure for Multi-Component Zr-Catalyzed Addition of Dialkylzinc Reagents to Imines

The ligand and $\text{Zr}(\text{O}-i\text{-Pr})_4 \cdot i\text{-PrOH}$ were weighed into a flame-dried, round-bottomed flask inside a N_2 atmosphere glove-box. The contents were dissolved in toluene and the colorless solution was allowed to stir for 5 min at 22 °C. *o*-Anisidine was added to the vessel immediately followed by the addition of aldehyde. The flask was capped with a septum, sealed with PTFE tape, removed from the glove-box and the mixture allowed to stir for an additional 40 min at 22 °C. The reaction vessel was placed in an ice bath and allowed to cool to 0 °C. Dialkylzinc was added through syringe under a positive pressure of N_2 and the reaction mixture was allowed to stir. The solution was quenched with saturated NH_4Cl and poured into a separatory funnel containing Et_2O . In some instances a precipitate of ligand and Zr salts formed and was removed by filtration. The mixture was washed three times with Et_2O and the combined organics were washed with brine, dried over MgSO_4 , and concentrated. The products could be further purified by silica gel chromatography. Optical purity was determined by chiral HPLC.

Supporting Information

Characterization data for all products.

Acknowledgements

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- [9] Other alkylzinc reagents [e.g., (*n*-Oct)₂Zn] bearing a β -hydride undergo asymmetric alkylation but less efficiently than when Et₂Zn is used. This might be, at least partially, because methylenes are less efficient sources of hydride than methyl groups; see ref.^[5b]
- [10] See the Supporting Information for experimental details and spectroscopic data.
- [11] As detailed in ref.^[5d] depending on the class of imine substrates, a different type of *o*-aniline activating group may well prove to be the optimal choice (e.g., *o*-phenoxyanilines for additions to alkynylimines). The present discussion pertains largely to aryl- and alkylimine substrates.
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