Enantioselectivity Increases with Reactivity: Electronically Controlled Asymmetric Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by a Chiral Pyridylphenol

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Achieving enantioselective reactions through a catalytic process is recognized as one of the most important and challenging problems in organic synthesis, and therefore it has received much attention. Enormous progress has been made in this area during the past decade.[1] However, the factors governing enantioselectivity remain the subject of speculation even in reactions that have been extensively studied.[2] Enantioselectivity in catalytic asymmetric reaction is usually interpreted in steric terms.[3] Electronic effects have seldom been reported to control enantioselectivity even though the electronic properties of both the catalyst and substrate can have profound effects in fundamental organometallic processes.[4,5] In the limited number of studies[6] of electronic effects, the underlying reasons are poorly understood. Our interest in asymmetric catalysis has prompted us to design and synthesize the new biaryl chiral N,O-ligand **4**. In the catalytic enantioselective addition of diethylzinc to *p*-substituted benzaldehydes catalyzed by this chiral pyridylphenol (*R*)-(+)-**4**, we have observed for the first time that *the enantioselectivity (1) depends on the electronic nature of the aryl aldehydes in a linear free energy relationship and (2) increases with more reactive substrates.*

The chiral pyridylphenol **4** was synthesized from 2-bromo-3,5-di-*tert*-butylanisole through the Suzuki cross coupling[7] of boronic acid **1** with 2-bromo-3-methyl-pyridine (**2**) in the presence of 2.0 equiv of KO^{t}Bu and 5 mol % of Pd(Ph$_3$P)$_4$ in DME to produce **3**,[8] which was then treated with pyridine hydrochloride to afford recemic **4** (Scheme 1).

Resolution of this pyridylphenol was carried out with (*S*)-(+)-camphorsulfonyl chloride via the diastereomeric

Scheme 1. Synthesis and Resolution of Chiral Pyridylphenol 4
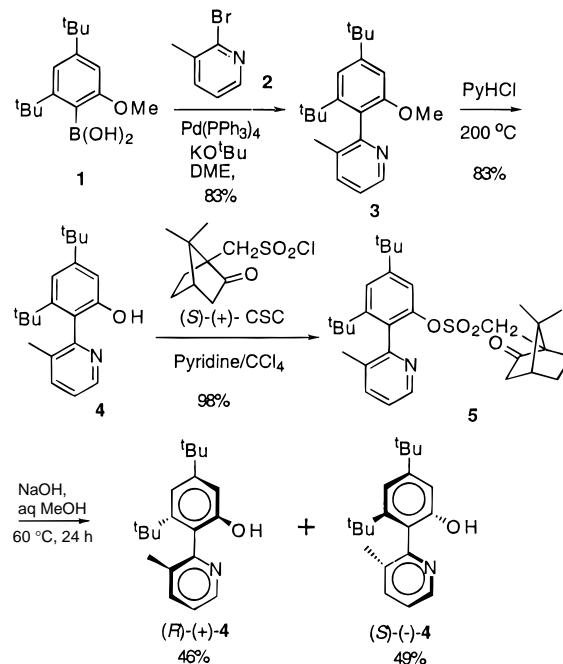
sulfonates **5**.[9] Chromatographic separation of on silica gel and subsequent alkaline hydrolysis finally yielded the enantiomerically pure ligands (*R*)-(+)-**4** and (*S*)-(−)-**4**[10] (Scheme 1).

The results of the enantioselective catalytic addition of diethylzinc to aromatic aldehydes (eq 1) by (*R*)-(+)-(**4**) are summarized in Table 1. The reactions were conducted at 0 °C in toluene in the presence of 5 mol % of (*R*)-(+)-**4** (optical purity > 99.5%) under nitrogen for 48 h with 2 equiv of Et$_2$Zn to give high yields of alcohols **7a−e** with moderate to high enantioselectivity.[10−12]
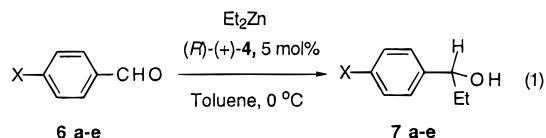
Most remarkably, the enantioselectivity of the reactions is subjected to a remote electronic effect; the

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(9) The *R* and *S* configurations of **4** were determined by X-ray analysis of (*S*,*S*)-**5**, which after alkaline hydrolysis afforded (*S*)-(−)-**4**.[10] X-ray structure analysis of (*S*,*S*)-(+)-**5**: $P2_12_12_1$; $a = 11.284(2)$ Å, $b = 12.846(2)$ Å, $c = 19.739(2)$ Å, $V = 2861.2(10)$ Å^3, $Z = 4$, $\rho_{calc} = 1.188$ g cm$^{−3}$; Mo Kα radiation (graphite monochromator); scan range $3° \leq 2\theta \leq 50°$; total number of reflections 2850, observed reflections 1786 ($F_o > 4.0\sigma$ (F)), $R = 0.0491$, $R_w = 0.0506$; GOF = 1.17. Siemens P4 four-circle X-ray diffractometer, data calculated with SHELXTL-PC on a PC486. (*R*)-(+)-**4**: $[\theta]_{251} = −5940°$, $\Delta\epsilon_{251} = −1.80$, $[\alpha]^{27}_D = +24.6$ ($c = 0.35$, CHCl$_3$), optical purity > 99.5% (chiral Daicel OD HPLC colomn, t_R = 18.6 min, flow rate 0.3 mL/min, hexane/2-propanol = 4:1). (*S*)-(−)-**4**: $[\theta]_{251} = +5346°$, $\Delta\epsilon_{251} = +1.62$, $[\alpha]^{27}_D = −24.8$ ($c = 0.35$, CHCl$_3$), optical purity >96% (chiral Daicel OD HPLC colomn, t_R = 13.0 min, flow rate 0.3 mL/min, hexane/2-propanol = 4:1). The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Table 1. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by Chiral Pyridylphenol (*S*)-(+)-4

product	X	% yield	% ee[a]	config[b]
7a	NMe$_2$	88	40	*R*[c]
7b	OMe	96	66	*R*
7c	H	92	75	*R*[d]
7d	Cl	97	80	*R*
7e	CN	92	89	*R*[d]

[a] Determined by chiral Daicel OD HPLC column. [b] Absolute configurations determined by comparison of reported optical rotations.[11] [c] Absolute configurations determined by comparsion of the same sign as the *R* isomer of **7b**−**d**. [d] Absolute configurations determined by ^{1}H NMR of its ester of (S)-*O*-methylmandelic acid.[12]

Figure 1. Plote of the optical yields of alcohols vs Hammett constant σ_p.

substrates bearing electron-withdrawing groups in the para-positions of aryl aldehydes afforded higher enantioselectivity than those with electron-donating groups. From the Hammett plot of log (*R*/*S*)[13] versus Hammett constants σ_p,[14] a straight line was obtained with R^2 = 0.99 (Figure 1). The enantioselectivity of **7e** is 89% ee but that for **7c** is only 75% ee, for example; this corresponds to a difference of more than 0.5 kcal mol^{-1} in $\Delta\Delta G^{\ddagger}$ for the two reactions.

The enantioselectivity remarkably increases with more reactive substrates. By competiton experiments, the relative reactivities of the *p*-arylaldehydes were found to be CN (4.8), Cl (3.4), H (1.0), and Me$_2$N (0.1). This reactivity pattern parallels the enantioselectivity. To the best of our knowledge, only one other report has mentioned this phenomenon.[6e]

The origin of these remarkable electronic influences on the enantioselectivity remains unclear. The mechanism of diethylzinc addition to aldehydes catalyzed by amino alcohols has been eluciated to involve dinuclear zinc species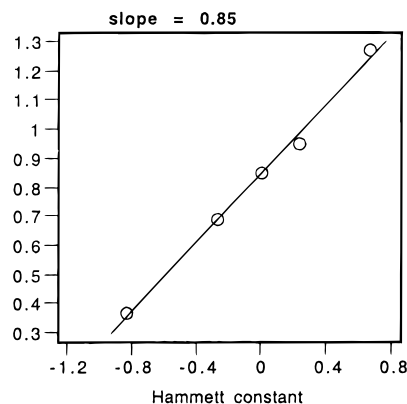.[15] The enantioselectivity was observed to be lower both at 25 and −23 °C (ee < 1 and 35%, respectively), and an inversion temperature likely fell at around 0 °C.[16] Diasteromeric binding of aldehydes to zinc leading to more reactive and less stable intermediates for electron-deficient aldehydes might be possible to account the electronic influence in a manner similiar to that proposed by Halpern for the mechanism of asymmetric hydrogenation.[17]

In summary, the novel chiral pyridylphenol (*R*)-(+)-**4** has been shown to catalyze the addition of diethylzinc to aromatic aldehydes with moderate to high enantioselectivity. Most importantly, *this enantioselectivity follows a linear free energy relationship with higher enantioselectivity obtained for more reactive aryl aldehydes.* Further modification of ligands, applications in asymmetric catalysis, and theoretical calculations are in progress.

Supporting Information Available: ^{1}H and [1]C NMR data and spectra for **4**, **5**, and **7** and experimental procedures (8 pages).

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(13) The term ln (*R*/*S*) is proportional to −$\Delta\Delta G^{\ddagger}$ according to the following equation:

$$\log (R/S) = -\Delta\Delta G^{\ddagger}/RT$$

Here, −$\Delta\Delta G^{\ddagger}$ is the free energy difference between two diastereomeric transition states leading to enantiomeric products.

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