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The Asymmetric Power of Chiral Ligands Determined by Competitive Asymmetric Autocatalysis

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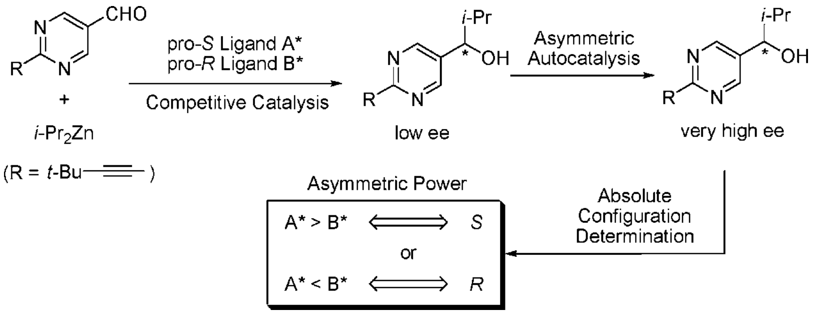
ABSTRACT



Asymmetric autocatalytic reactions were initiated by using two competing chiral ligands bearing opposite configurations. The absolute configuration of the resulting highly enantioenriched product reflects the different efficiencies of the two catalysts. Thus, our method provides a simple and efficient way to compare the asymmetric power of chiral ligands for enantioselective catalysis both qualitatively and quantitatively.

Highly enantioselective catalytic synthesis is an important field of research, because of the central role chirality plays in chemical and pharmaceutical sciences.[1] A simple and general procedure to compare chiral catalysts would greatly benefit efforts to design efficient ligands for asymmetric catalysis.

The addition of dialkylzincs to aldehydes, catalyzed by chiral amino alcohols to form chiral secondary alcohols, is one of the most useful and well-studied enantioselective catalytic reactions, as it is a highly enantioselective carbon−carbon bond-forming reaction.[2] Among the available ligands, chiral *N*,*N*-dialkylnorephedrines (DANE), which are easily obtained from cheap commercial compounds, are able to catalyze efficiently the enantioselective addition of primary or secondary dialkylzincs to aromatic or aliphatic aldehydes.[3] (1*R*,2*S*)-DANE are known to catalyze the formation of (*R*)-alcohols from aromatic aldehydes, whereas (*S*)-alcohols are obtained by using (1*S*,2*R*)-DANE.

In this paper, we report on a new method of comparing chiral ligands for enantioselective catalysis. This method will be illustrated with the comparison of DANE bearing diverse *N*-alkyl chains acting as catalysts for the enantioselective addition of dialkylzincs to aldehydes.

First, we used a conventional method to compare two chiral ligands, which consisted of carrying out a reaction catalyzed by both ligands bearing opposite absolute configurations. In this case, the major absolute configuration of the product may correspond to the catalyst having the highest efficiency. However, if both ligands have similar catalytic activities, then the enantiomeric excess of the product may be so low that its absolute configuration would be difficult to determine practically.[4]

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[2] Reviews: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

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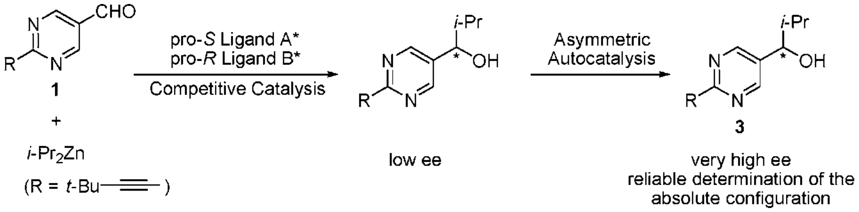
Scheme 1. Asymmetric Autocatalysis Initiated by Two Competing Chiral Ligands



During our further studies on asymmetric autocatalysis,[5] in which the chiral products act as chiral catalysts for their own production, we found that 1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methylpropan-1-ol (**3**) is able to catalyze efficiently the enantioselective addition of diisopropylzinc to 2-*tert*-butylethynylpyrimidine-5-carbaldehyde (**1**).[5c] Moreover, this autocatalytic system occurs with an amplification of ee, in that the final product has the same configuration as the catalyst, but has a higher ee.[5d] This unique amplification phenomenon may be applied in a comparison of chiral ligands for the enantioselective addition of dialkylzincs to aldehydes, regardless of their structural similarity.

With this aim, the addition of diisopropylzinc to 2-*tert*-butylethynylpyrimidine-5-carbaldehyde (**1**) was carried out in the presence of equimolar quantities of two chiral ligands bearing opposite absolute configurations. Through asymmetric amplification, the final enantiomeric excess of the obtained product may be high enough to easily determine its absolute configuration (Scheme 1). Indeed, this reaction catalyzed by 10 mol % of (1*S*,2*R*)-*N*,*N*-dipropylnorephedrine (DPNE) **2a** and 10 mol % of (1*R*,2*S*)-*N*,*N*-dibutylnorephedrine (DBNE) **2b** afforded the alkanol (*R*)-**3** with 95% ee (Scheme 2). The absolute configuration of the product allowed us to conclude that the pro-*R* ligand (DBNE) was more powerful than the pro-*S* ligand (DPNE) for catalyzing this reaction (Table 1, run 1). To confirm the reproducibility of this result, the same reaction was carried out in the presence of equimolar quantities of (1*R*,2*S*)-DPNE **2a** and (1*S*,2*R*)-DBNE **2b**. The (*S*)-alkanol **3** was obtained with 93% ee, with the absolute configuration of the obtained product indeed being controlled by the DBNE catalyst (run 2).

As the absolute configuration of the product depended not just on the relative initial enantioselectivity of both catalysts but also on their relative initial reactivity, we were able to define a new concept that we called "asymmetric power", which characterizes the overall ability of a chiral catalyst to control at the initial stage the absolute configuration of the product of an enantioselective reaction.

Using this method, other pseudoenantiomeric pairs of *N*,*N*-dialkylnorephedrines **2a**−**h** have been systematically compared. As expected, due to asymmetric autocatalysis, the final enantiomeric excess of the product **3** was high (>80% ee) regardless of the structural similarities between the ligands (Table 1). As asymmetric amplification by autocatalysis occurs with retention of configuration, the reliably determined absolute configuration of the final product corresponded to the slight difference in the initial efficiency between the ligands. To establish the reproducibility, the reactions were carried out by altering the absolute configurations of the pseudoenantiomeric pair of chiral ligands. By using this procedure, *N*,*N*-dipropylnorephedrine (DPNE) **2a** was found to be more efficient than *N*,*N*-diethylnorephedrine (DENE) **2c** (runs 3 and 4). DENE was found to be more powerful than piperidinenorephedrine (PiNE) **2d** (runs 5 and 6), which in turn was found to be more efficient than pyrrolidinenorephedrine (PyNE) **2e** (runs 7 and 8) and *N*,*N*-dimethylnorephedrine (DMNE) **2f** (runs 9 and 10). Thus, the asymmetric power of di-*n*-alkylnorephedrines seems to increase with increasing steric hindrance of the alkyl substituents on the nitrogen atom of the ligand. However, as *N*,*N*-dibutylnorephedrine **2b** is also more effective than *N*,*N*-dipentylnorephedrine **2g** (runs 11 and 12) and *N*,*N*-dioctylnorephedrine **2h** (runs 13 and 14), the structure of DBNE seems to be the optimum required for achieving the highly enantioselective catalysis of diisopropylzinc addition to aldehydes.

Scheme 2

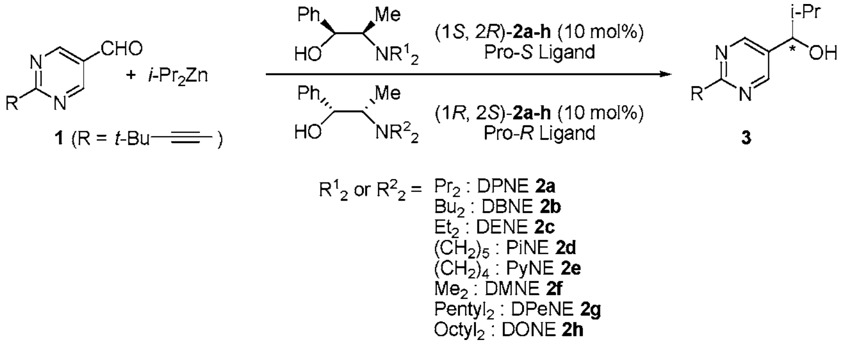


Table 1. Qualitative Comparison of the Asymmetric Power of Diverse *N*,*N*-Dialkylnorephedrines **2a**−**h** by Competitive Asymmetric Autocatalysis

	catalytic mixture		product **3**			
run[a]	pro-*S* ligand[b,c]	pro-*R* ligand[b,c]	yield (%)	ee[d] (%)	abs config[d]	asym power
1	(1*S*,2*R*)-DPNE **2a**	(1*R*,2*S*)-DBNE **2b**	98	95	*R*	DBNE > DPNE
2	(1*S*,2*R*)-DBNE **2b**	(1*R*,2*S*)-DPNE **2a**	91	93	*S*	
3	(1*S*,2*R*)-DPNE **2a**	(1*R*,2*S*)-DENE **2c**	94	92	*S*	DPNE > DENE
4	(1*S*,2*R*)-DENE **2c**	(1*R*,2*S*)-DPNE **2a**	92	93	*R*	
5	(1*S*,2*R*)-DENE **2c**	(1*R*,2*S*)-PiNE **2d**	91	81	*S*	DENE > PiNE
6	(1*S*,2*R*)-PiNE **2d**	(1*R*,2*S*)-DENE **2c**	94	84	*R*	
7	(1*S*,2*R*)-PyNE **2e**	(1*R*,2*S*)-PiNE **2d**	92	92	*R*	PiNE > PyNE
8	(1*S*,2*R*)-PiNE **2d**	(1*R*,2*S*)-PyNE **2e**	94	90	*S*	
9	(1*S*,2*R*)-DMNE **2f**	(1*R*,2*S*)-PyNE **2e**	89	95	*R*	PyNE > DMNE
10	(1*S*,2*R*)-PyNE **2e**	(1*R*,2*S*)-DMNE **2f**	92	94	*S*	
11	(1*S*,2*R*)-DPeNE **2g**	(1*R*,2*S*)-DBNE **2b**	97	97	*R*	DBNE > DPeNE
12	(1*S*,2*R*)-DBNE **2b**	(1*R*,2*S*)-DPeNE **2g**	95	95	*S*	
13	(1*S*,2*R*)-DBNE **2b**	(1*R*,2*S*)-DONE **2h**	94	93	*S*	DBNE > DONE
14	(1*S*,2*R*)-DONE **2h**	(1*R*,2*S*)-DBNE **2b**	94	92	*R*	

[a] Molar ratio is as follows: pro-*S* ligand:pro-*R* ligand:**1**:*i*-Pr_2Zn = 0.10:0.10:1:2. [b] A chiral ligand promoting the formation of the *S* enantiomer (respectively *R*) is qualified as pro-*S* (pro-*R*). [c] DPNE = *N*,*N*-dipropylnorephedrine; DBNE = *N*,*N*-dibutylnorephedrine; DENE = *N*,*N*-diethylnorephedrine; PiNE = piperidinenorephedrine; PyNE = pyrrolidinenorephedrine; DMNE = *N*,*N*-dimethylnorephedrine; DPeNE = *N*,*N*-dipentylnorephedrine; DONE = *N*,*N*-dioctylnorephedrine. [d] Determined by HPLC analyses, using a chiral stationary phase (Chiralcel OD-H).

Following this, we became interested in quantifying the differences in asymmetric power between two chiral ligands. With this aim, the addition of diisopropylzinc to aldehyde **1** was carried out in the presence of (1*S*,2*R*)-DBNE) **2b** and (1*R*,2*S*)-DMNE **2f** *in various proportions.* The *total* concentration of ligands, however, was kept constant with regard to the concentration of aldehyde (20 mol %). In addition, all these experiments were done twice to check the reproducibility of the observations. The variations in the enantiomeric excess and the absolute configuration of the product **3** with the composition of the catalytic mixture are shown in Figure 1.

(1*S*,2*R*)-DBNE) **2b** alone afforded (*S*)-**3** with 97% ee, while (*R*)-**3** with 91% ee was obtained by catalyzing the reaction with pure (1*R*,2*S*)-DMNE **2f**. When the reaction was carried out in the presence of (1*S*,2*R*)-DBNE **2b** and (1*R*,2*S*)-DMNE **2f** in equimolar amounts (10 mol % of each, ratio of DMNE:DBNE = 50:50), (*S*)-**3** was obtained with 96% ee. The presence of DMNE had practically no influence on either the enantiomeric excess or the absolute configuration of the product. Even by increasing the proportion of DMNE to a DMNE:DBNE ratio of 73:27 in the catalytic mixture, (*S*)-**3** with 77% ee was obtained. In sharp contrast, the reaction catalyzed by a DMNE:DBNE mixture in a ratio of 74:26 afforded a product with a 76% ee, but with the *R* configuration. Actually, nonlinear effects (NLE) have already been observed during nonautocatalytic reactions catalyzed by mixture of pseudoenantiomers or diastereomers. In these systems, however, the NLE were caused by self-inhibition of the two catalysts[6] or reflected the difference in reaction rates and turnover frequencies of the two catalysts.[7] On the contrary, in our system, the asymmetric amplification probably essentially occurs because the reaction becomes rapidly autocatalytic with amplification of ee after its catalytic initiation. This significant NLE allowed for a very precise and reliable measurement of the critical ratio between the ligands (DMNE:DBNE = 73.5:26.5) where the absolute configuration of the product changes. We therefore concluded

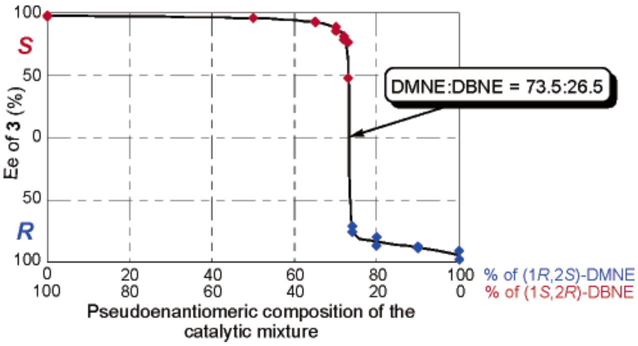


Figure 1. Quantitative comparison of the asymmetric power of *N*,*N*-dimethylnorephedrine **2f** and *N*,*N*-dibutylnorephedrine **2b**.

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(4) Enantiopure *N*,*N*-dipropylnorephedrine (DPNE) **2a** and *N*,*N*-dibutylnorephedrine (DBNE) **2b** catalyze the enantioselective addition of diisopropylzinc to benzaldehyde to afford products with 92% and 93% ee, with yields of 73% and 72%, respectively. When this reaction was carried out in the presence of 10 mol % of (1*S*,2*R*)-DPNE **2a** and 10 mol % of (1*R*,2*S*)-DBNE **2b**, an almost racemic product (<5% ee) was obtained.

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that DBNE **2b** was 2.8 (73.5/26.5 = 2.8) times more powerful than DMNE **2f** for the above reaction.[8]

In summary, an asymmetric autocatalytic reaction has been initiated by two competing chiral ligands. This simple and reliable procedure allows us to quantify the difference in initial efficiency between two chiral ligands acting as catalysts for the enantioselective addition of dialkylzincs to aldehydes, regardless of the structural similarities between the ligands. We were able to define and measure the relative "asymmetric power" of chiral ligands, characterizing the overall ability of a chiral catalyst to control the stereochemical outcome of an enantioselective reaction and depending on the initial enantioselectivity as well as the initial rate of the catalysis. The extension of this method to other chiral sources or other asymmetric reactions is currently under investigation.

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Supporting Information Available: Typical experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) To estimate the error in this critical ratio measurement, asymmetric autocatalysis has been initiated by two competing *enantiomers*, (1*S*,2*R*)- and (1*R*,2*S*)-DMNE **2f**. As the reaction catalyzed by (1*S*,2*R*)-**2f** and (1*R*,2*S*)-**2f** in a 49:51 ratio and a 51:49 ratio afforded (*R*)-**3** with 74.1% ee and (*S*)-**3** with 73.5% ee, respectively, we estimated that the experimental error relative to the loadings of each ligand is below 2%, and the error in their calculated ratio is below 4%.