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Nonlinear Effects with Diastereomeric Ligand Mixtures in Enantioselective, Catalytic Additions of Terminal Alkynes Involving Copper−PINAP Complexes

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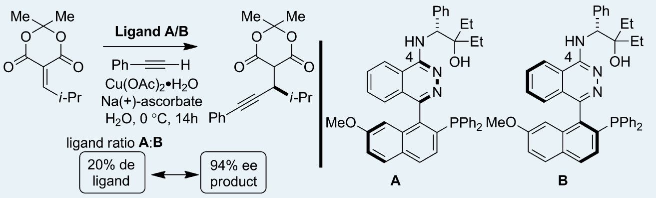
Supporting Information

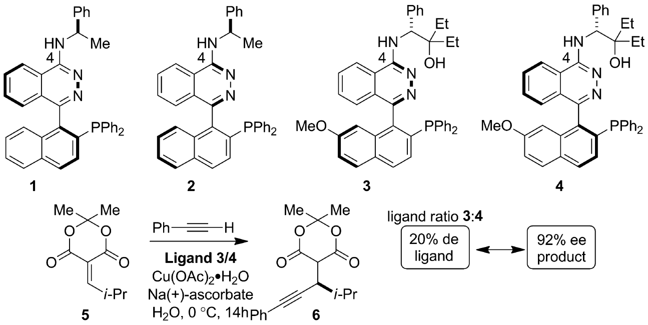
ABSTRACT: A strong positive NLE has been observed with mixtures of ligand diastereomers in the addition of terminal alkynes to Meldrums' acid-derived acceptors and imminium ions using PINAP ligands. This NLE is such that the diastereomeric ligand mixture obtained from synthesis (10−26% de) can be employed directly in the conjugate addition reaction or imminium additions, furnishing products in high ee.



KEYWORDS: *nonlinear effects, ligand design, asymmetric catalysis, alkynes, Cu*

Bidentate ligands that incorporate electronically different donors have been shown to be useful in an increasing number of important transition-metal-catalyzed asymmetric transformations. The most notable of these include N (amine) and P (phosphorus) donor groups and have come to be known as P,N-ligands. We have developed a class of readily available atropisomeric P,N-ligands **1**−**4** (Scheme 1), which were shown to serve as convenient alternatives to QUINAP,[1] and documented their application in asymmetric acetylide additions to aldimines[2,3] and asymmetric conjugate addition of copper acetylides to Meldrums' acid-derived acceptors.[4,5]

Scheme 1



In our studies of this novel class of nonsymmetrical ligands, we have come across some unusual observations, which we report herein, involving strong nonlinear effects with diastereomeric mixtures of ligands. Thus, when the addition of phenyl acetylene and **5** was conducted with a 60:40 mixture of diastereomeric ligands **3** and **4** (20% de), the product of conjugate addition **6** was obtained in 94% ee. The results have important practical consequences in the discovery and preparative reaction chemistry of this ligand class. Given the increasing number of ligands and catalysts incorporating multiple stereocenters, the results described suggest the effect may be quite useful and general.

First reported in 1986 by Kagan, nonlinear effects (NLE) are a testament to the fact that higher-order molecular associations can have dramatic effects in asymmetric catalysis.[6−9,10] For example, in the most common case involving a positive nonlinear effect, a catalyst can furnish reaction products in high enantioselectivity even when these are derived from ligands that are far from optically pure.[10] The primary use of this effect by investigators in the field has been in its ability to provide mechanistic insight.[11] There also have been reports of its use in catalytic asymmetric synthesis.[12−15] For example, Bolm reported the use of diastereomeric mixtures of ferrocenyl hydroxyoxazolines in the addition of Et_2Zn to benzaldehyde, wherein it was noted that a 43:57 mixture of diastereomeric ligands led to high product enantioselectivity (90% ee);[15] however, despite the potential benefits of the use of scalemic ligands, it has had limited impact in practice because the common ligands employed in asymmetric catalysis are typically available in enantiomerically pure form.

In the course of developing convenient syntheses of PINAP ligands, optically active amines at C4 of the scaffold are employed as chiral controlling groups to enable separation of the atropisomeric diastereomers (Figure 1). Thus, the preparation of N−PINAP ligands **1**−**4** affords pairs of diastereomers that are subsequently separated by chromatography on silica gel or by crystallization. The synthetic approach to these ligands is greatly simplified when compared with that

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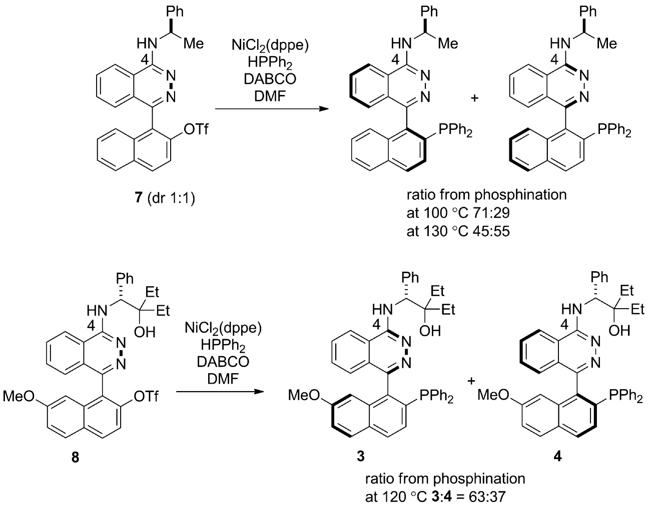


Figure 1. Last step in the synthesis of ligands **1**–**4**.

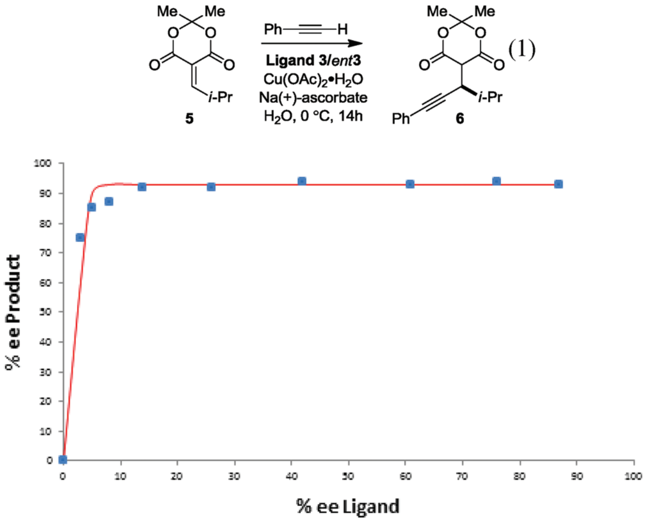


Figure 2. NLE observed with PINAP **3** in the conjugate addition reaction (eq 1).

of QUINAP, which involves separation of diastereomeric complexes of racemic QUINAP with Pd and a chiral amine.

The fact that P,N-donor ligands **1**–**4** we have studied are obtained as diastereomeric mixtures in the course of their synthesis provided for us the opportunity to examine nonlinear effects with diastereomers. This type of nonlinear effect has received scant attention, and then, only in the context of mechanistic studies.[8,9] Yet, the implication of nonlinear effects involving diastereomeric ligands may become of greater importance as an increasing number of ligands and complexes are reported that contain multiple stereogenic centers.

Diastereomer pair **1** and **2** can be regarded as pseudoenantiomers, differing only in the remote carbinamine C4 stereocenter; analogously, **3** and **4** have the same relationship. In the course of optimizing the final step in the sequence reaction (Figure 1, **7** → **1** + **2**), we took note of a modest enrichment in one of the diastereomers in the phosphination reaction.[16,17] Thus, when we commence with a 1:1 mixture of triflate diastereomers **7**, varying ratios of **1** and **2** are obtained as a function of the temperature: at 100 °C, **1**:**2** = 71:29; at 130 °C, **1**:**2** = 45:55. Similarly, the coupling reactions involving **8** furnish a 63:37 mixture of **3** and **4** at 120 °C.

In the initial investigations, we first examined the copper-catalyzed conjugate addition reaction of phenylacetylene to Meldrums' acceptor **5** using PINAP **3** of variable enantiopurity, a ligand that had been identified as optimal for high selectivity in the conjugate addition reaction (eq 1, in Figure 2).[4,5] The enantiomeric excess (percent ee) of the adduct formed in the course of conjugate addition was assayed by chiral HPLC after its conversion to the corresponding anilide. In the experiment, we observed positive nonlinear effects; thus, employing PINAP **1** with only 14% ee furnished **6** in 92% ee.

Although the nonlinear effect involving enantiomeric ligands is notable, it is of little practical consequence because the readily available, phenylglycine-derived enantiopure amines (3-((*R*)-aminophenylmethyl)pentan-3-ol or its *S* enantiomer) are used to prepare **3** and its enantiomer. This became clear to us when considering that the experiments involving mixtures of enantiomeric ligands described above necessarily required the preparation of the corresponding *R* or *S* ligands separately before mixing them. However, because the route to ligands **1**–**4** naturally leads to diastereomeric mixtures, we decided to investigate the nonlinear effect employing mixtures of diastereomers **3** and **4**. As shown in Scheme 1 and Table 1, the observed nonlinear effect is dramatic: a ligand mixture of only 20% de (60 mol % **3**/40 mol % **4**) furnishes the conjugate addition product **6** in 94% ee. An important consequence of the observation with mixtures of diastereomeric ligands is that the separation of the two stereomers in the course of the ligand synthesis becomes unnecessary. It has been previously noted that the observation of nonlinear effects may be coupled to decreased reaction rates when a substantial proportion of the complex is rendered catalytically inactive.[18] In the alkyne conjugate addition reaction (eq 1, in Figure 2), for the same reaction time, we observed little (<10%) change in product formation with a diastereomeric ratio of ligands corresponding to 60:40.

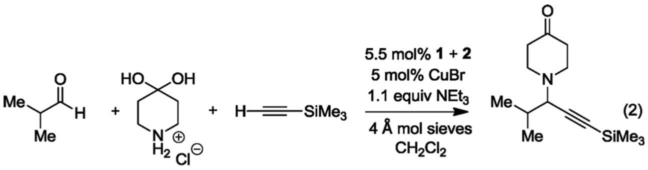
Table 1. Substrate Scope of the Conjugate Addition Reaction (eq 1, in Figure 2)

acceptor *R*	3:4 = >99:1 product yield/ee (%)	3:4 = 60:40 product yield/ee (%)	3:4 = >1:99 product yield/ee (%)
i-Pr	94/95 *R*	80/94 *R*	65/15 *R*
cy-C_6H_{11}	81/94 *R*	80/84 *R*	44/24 *R*
o-Me-*m*-OMs-C_6H_3	60/89 *S*	15/59 *S*	18/−33 *R*

[a] The enantioselectivity was determined by chiral HPLC analysis after conversion of the products into the corresponding anilides by heating in aniline/DMF.

To get more insight into the substrate dependency of the NLE, we investigated different acceptors in the conjugate addition reaction (Table 1). All cases showed nonlinear behavior; the most pronounced NLE was observed for the *i*-Pr acceptor (**5**). In general, as the ee or de of the ligands used approached 0%, the conversion, which was determined by ^1H NMR, was diminished. Thus, for example, at 14% de for **3**/**4** 25% conversion was observed in the conversion of **5** to **6**; by contrast, for the same reaction, the use of **3**/**4** corresponding to 80% de resulted in 90% conversion. This observation is consistent with the formation of thermodynamically stable hetero aggregates $[(Cu_2 \cdot \mathbf{3} \cdot \mathbf{4})_n]$ incorporating diastereomers of the ligand, which are catalytically inactive, thus reducing the amount of active catalyst.[7,8,11,18] These aggregates could serve as a reservoir, which at the same time means that the residual active complex is of increased diastereomeric purity, thus leading to the observed nonlinear behavior.

We have made analogous observations in the CuBr-catalyzed coupling of *i*-butyraldehyde, trimethylsilylacetylene, and 4-piperidone hydrochloride monohydrate (eq 2 and Figure 3) in the presence of catalytic amounts of a diastereomeric mixture of PINAP ligands **1** and **2**.[19,3] In this reaction, a pronounced NLE was observed, shown in Figure 3. Thus, when a 1.4:1 mixture of ligand diastereomers **2** and **1** (16% de), which can be obtained directly from phosphination step, was employed in the addition reaction, the enantiomeric purity of the product corresponded to 57% ee.



(2)

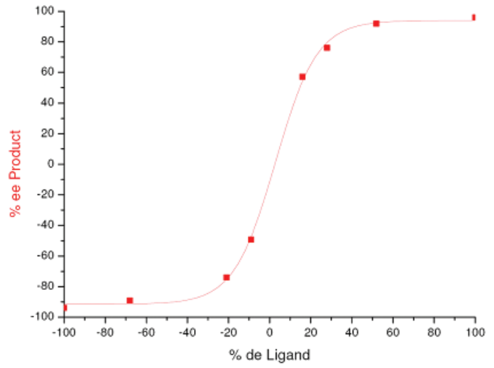


Figure 3. NLE employing the diastereomers **1**/**2** of PINAP (100% de corresponds to pure **2**; −100% de corresponds to pure **1**).

In conclusion, we have found a strong positive NLE in the addition of alkynes to Meldrums' acid-derived acceptors and imminium ions using PINAP ligands. This NLE is such that the diastereomeric ligand mixture obtained from synthesis can be employed directly in the conjugate addition reaction, furnishing product in high ee. Further studies to elucidate the mechanism of this reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) For an exception, see the work in ref 15 involving the addition of Et_2Zn to benzaldehyde.

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