Efficient Chiral Amidophosphine Ligand for Copper-catalyzed Asymmetric Addition of Diethylzinc to *N*-Sulfonylimines

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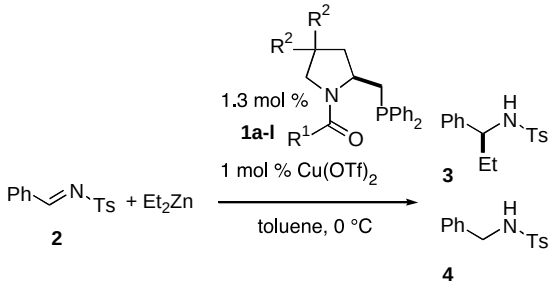
Structure study of a chiral amidophosphine ligand for copper-catalyzed asymmetric addition reaction of diethylzinc with the *N*-tosylimine reached to the new chiral phosphine bearing the bulky substituent on the pyrrolidine ring, which significantly improved catalytic performance to give the adduct in 96% yield and 93% ee after 3 h.

Considerably energetic approaches toward catalytic asymmetric addition of organometallic reagents to C=N of imines have appeared in this decade.[1] Among these, chiral amino alcohol-catalyzed addition of zinc acetylide[2] and organozinc,[3] chiral allylpalladium-catalyzed allylation with allylstannane or allylsilane,[4] and rhodium-monophosphine-catalyzed arylation with arylstannanes[5] showed impressive success.[6] Recently we have documented the highly enantioselective addition of diethylzinc to C=N of a broad range of *N*-sulfonylimines in the presence of catalytic amount (1 mol%) of copper(II) triflate and a chiral amidophosphine **1h** (1.3 mol%).[7] We describe herein the structure-efficiency relationships of **1** and, as a result of the studies, highly efficient chiral amidophosphines **1l**.

At the outset of the study on the structure and catalytic performance relationships of the amidophosphines, a series of ligands **1a-f** bearing various length and size of acyl group on a nitrogen atom of a simple pyrrolidine skeleton was prepared,[8] and their catalytic activity was examined. A hexane solution of 2 equiv of diethylzinc was added to a mixture of 1 mol% of copper(II) triflate and 1.3 mol% of a phosphine ligand **1** in toluene. The whole was stirred at room temperature for 20 min and then cooled to 0 °C. Then, a toluene solution of *N*-tosylimine **2** of benzaldehyde was added. The whole was stirred till completion at 0 °C for the requisite time. Usual workup and purification by column chromatography gave an addition product **3** and a reduction product **4** (Scheme 1).

Amidophosphines **1a-d** bearing normal acyl group varying from acetyl to nonanoyl on the pyrrolidine nitrogen atom showed the similar level of catalytic activity giving **3** in 69–82% chemical yield after 24 h (Table 1, entries 1–4). The enantioselectivity of **3** was also in the similar and unsatisfactory level, 58–65% ee. Production of a reduced sulfonamide **4** was observed in a significant yield, 10–22%. Amidophosphine **1f** bearing more bulky pivaloyl group behaved as a better ligand for copper accelerating the reaction and gave **3** in 79% yield after 4 h, while adamantylcarbonylphosphine **1e** did not show any benefit giving **3** in 64% yield (entries 5 and 6). The enantioselectivity was also in the unsatisfactory level, 51% by **1e** and 63% by **1f**. Production of **4** was not suppressed. One of the common features of these reactions was precipitate derived from amidophosphine-copper complex, which was probably responsible for lower catalytic activity compared with the soluble complex derived from **1h**.[7]



Scheme 1. Copper-catalyzed asymmetric ethylation of *N*-tosylimine **2** using amidophosphines **1a-l**.

Next, we examined influence of the substituent on the pyrrolidine ring of pivaloylphosphine **1** (R^1 = *t*-Bu). A pivaloylphosphine **1g** bearing two methyl groups on the pyrrolidine ring promoted the reaction within 5 h giving the product **3** in 79% yield. Enantioselectivity was improved to 79% ee (entry 7). Undesirable reduction was not suppressed to give **4** in 19% yield. It was so delightful to learn that pivaloylphosphine **1h** bearing two benzyl substituents gave **3** after 2 h in 94% yield and 90% ee (entry 8).[7] Production of **4** was suppressed into 5% yield. Comparison of three pivaloylphosphines **1f-h** bearing no substitution, methyl, and benzyl groups on the pyrrolidine ring apparently indicated that the bulkier substituent gave better catalytic performance; the reaction selectivity giving **3** versus **4**, yield of **3**, and enantioselectivity of **3** (entries 6–8). It is also important to note that solubility was in the order of **1h**-copper, **1g**-copper, and **1f**-copper complex.

Table 1. Catalytic asymmetric ethylation of *N*-tosylimine **2** giving **3** and reduction product **4** using amidophosphines **1**.[a]

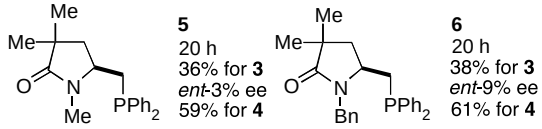
Entry	**1**	R^1	R^2	Time /h	Yield **3**/%	ee[b] **3**/%	Yield **4**/%
1	**a**	Me	H	24	77	58	18
2	**b**	Et	H	24	82	61	14
3	**c**	*n*-Bu	H	24	81	65	10
4	**d**	*n*-Oct	H	24	69	58	22
5	**e**	1-Ad[c]	H	24	64	51	30
6	**f**	*t*-Bu	H	4	79	63	20
7	**g**	*t*-Bu	Me	5	79	79	19
8	**h**	*t*-Bu	$PhCH_2$	5	94	90	5
9	**i**	Me_2N	$PhCH_2$	7	83	69	16
10	**j**	*i*-Pr_2N	$PhCH_2$	24	62	52	32
11	**k**	C_6F_5	$PhCH_2$	24	53	41	40
12	**l**	*t*-Bu	2,4,6-$Me_3C_6H_2CH_2$	3	96	93	4

[a]Two equiv of diethylzinc were used. For entries 6 and 7, three equiv of diethylzinc were used. [b]The ee was determined by HPLC analysis of **3** with a chiral stationary phase column (Daicel Chiralcel OD-H, hexane/*i*-PrOH (10/1), 254 nm, 0.6 mL/min). [c]1-Adamantyl.

Dimethylcarbamoyl and diisopropylcarbamoylphosphines **1i**,**j** were designed as better ligands for copper, because their carbonyl oxygen atoms were anticipated to coordinate more efficiently to copper. However, the reactions using **1i**,**j** as ligands gave **3** in unsatisfactory yields and reduced enantioselectivities, 69% ee and 52% ee (entries 9 and 10). Production of **4** was 16% and 32% yields. On the other hand, pentafluorobenzoylphosphine **1k** bearing an electron-withdrawing group was much more unsatisfactory giving **3** in 53% yield and 41% ee along with production of **4** in 40% yield (entry 11). These systematic examinations of *N*-acyl group and catalytic behavior relationships indicated that a pivaloyl group on the nitrogen atom and bulky substituent on the pyrrolidine ring are beneficial for high catalytic performance.

Based on the above structure-performance relationships, a pivaloylphosphine **1l** bearing two mesitylmethyl substituents on the pyrrolidine ring was designed and synthesized, and its catalytic activity was examined. To our delightful, **1l**-copper complex was soluble in toluene and performed the highest catalysis giving **3** after 3 h in 96% yield and 93% ee (entry 12). Production of **4** was suppressed to 4% yield.

These structure-catalytic performance relationships are understandable. The poor catalytic performance by **1a-d** is ascribable to the presence of rotamers. Because of less bulkiness of the normal acyl group on the nitrogen atom, rotation of the N–CO sigma bond is possible to allow the rotamer.[9] The rotamer fixes the carbonyl group to the direction opposite to phosphorus moiety like amidophosphines **5** and **6** (Scheme 2).



Scheme 2. Influence of the carbonyl group position on catalytic activity producing **3**.

Another series of chiral amidophosphines **5** and **6**[10] is characterized by the position and direction of a carbonyl functionality. The reactions were not smoothly catalyzed by these phosphine ligands-copper(II) giving **3** after 20 h in 36% and 38% yields. The enantioselectivity was marginal by **5** and 9% by **6**. It is also noteworthy that major product in these reactions was the reduction product **4** in 59% and 61% yields. The poor efficiency by **5** and **6** would be ascribed to lack of ability in forming a soluble chelate with copper or zinc, because phosphorus and carbonyl oxygen atoms point towards different directions from each other.

Steric repulsion between the methyl or *i*-propyl group on carbamoyl nitrogen and methylene group of the pyrrolidine ring of **1i**,**j** destabilizes the planarity around the carbamoyl moiety. This probably changes the direction of the carbonyl groups and might be responsible for poor performance by **1i**,**j**. Quite poor efficiency by **1k** also indicated the important role of coordinating ability of the carbonyl oxygen atom. The electron-withdrawing pentafluorophenyl group weakens the coordinating ability of the carbonyl oxygen atom and diminishes the possibility of chelate formation, although the copper complex was soluble during the reaction.

The favorite effects of the bulky substituent on the pyrrolidine ring of **1h** and **1l** were quite significant and apparent. It is possible to speculate that phosphorus and carbonyl oxygen atoms coordinate to copper or zinc and form a chelate, which is available only when the carbonyl group and phosphorus atom point to the same direction as shown in the structure **1**, but not in **5** and **6**. The bulky substituent effectively shields the one face of the chelate, which may prohibit the approach of tosylimine **2** from this face and is responsible for the high enantioselectivity.

It is also important to note that higher catalytic performance in yield and enantioselectivity was observed only when the reagent complex was soluble in toluene. The complexes generated from **1h**,**l**, copper, and diethylzinc were soluble in toluene at the initial stage of the reaction. A reaction mixture gradually became turbid as the reaction proceeded, probably because of formation of zinc salt of **3**. In contrast, the reagent mixture generated from other phosphines **1**, **5**, and **6** was a suspension or a turbid solution with brown gum, giving poor catalytic performance. However, solubility was not sufficient condition for the performance. The reagent generated from pentafluorobenzoylphosphine **1k** formed a clear solution, while the performance was quite poor.

In summary, systematic steric tuning of the amidophosphine ligand successfully and significantly improved the catalytic activity of the copper-catalyzed asymmetric addition. Rational will be the study of the next stage toward practical and reasonably efficient catalytic asymmetric reactions.

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We dedicate this work to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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9 A significant amount of rotamers (2:8–3:7) was observed by ^{31}P-NMR as well as ^{13}C-NMR for **1a**-**d**, **i**-**k**. Pivaloyl and adamantylcarbonylphosphines are likely to the structure shown by **1**, because peaks assignable to rotamers were not observed.
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