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Enantioselective Synthesis

Enantioselective Addition of Dialkylzinc to Aromatic Aldimines Mediated by Camphor-Derived Chiral β-Amino Alcohols

Wei-Ming Huang and Biing-Jiun Uang*[a]

Abstract: The enantioselective addition of diethylzinc or dimethylzinc to *N*-(diphenylphosphinoyl)imines mediated by **1** or **2** could be achieved in high yields (70–97%) and enantioselectivities (85–98% *ee*). The catalytic loading of **1** or **2a** could be reduced to 10 mol% for methylation or ethylation of imines in high yields and enantioselectivities (79–96%) when the reaction was conducted in the presence of 1.8 equiv of methanol. *N*-Monosubstituted amino alcohols induced higher enantioselectivity than their *N*,*N*-disubstituted congener in our catalytic system.

Introduction

Chiral amines are widely used in the synthesis of natural products, physiologically active substances, and pharmaceuticals. They are also used as chiral auxiliaries in asymmetric synthesis.[1] Recently, many *N*,*O*-ligands have been developed to catalyze the enantioselective addition of dialkylzinc to imines with high enantioselectivity.[2–10] Representative ligands include 2-azanorbornylmethanol,[2] 9-fluorenone derivatives,[3] 1,2-diphenyl-2-aminoethanols,[4] chiral oxazoline,[5] cinchonine and cinchonidine,[6] norephedrine,[7] and prolinol derivatives.[8] Although additions to imines that are derived from aromatic aldehydes have been extensively studied, excess dialkylzinc reagent and a stoichiometric amount of chiral ligand are normally required to ensure high conversion and enantioselectivity due to the poor electrophilic character of imines. Therefore, the development of a more easily accessible and economical enantioselective catalytic system is still worthwhile.

We previously reported that (+)-(1*S*,2*R*)-1-morpholinoisonorborneol (Figure 1) is an effective catalyst to catalyze the asymmetric addition of diethylzinc to aldehydes with high enantioselectivities.[11] Herein, we report our findings on the use of **1** and *N*-monosubstituted amino alcohols (**2a–i**) (Figure 1) as efficient promoters for the enantioselective addition of dialkylzinc to *N*-(diphenylphosphinoyl)imines.

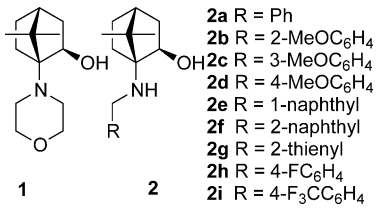

Figure 1. Chiral β-amino alcohols **1** and **2a–i**.

Results and Discussion

At the outset, imine **3a**[12] was dissolved in toluene, due to the poor solubility of **3a** in hexanes, and reacted with diethylzinc (5 equiv, 1.0 M in hexanes) in the absence of **1** at 28 °C for 48 h. It was found that a 1:1 mixture of addition product **4a** and reduction product **4a′** was present after work-up of the reaction mixture (Table 1, entry 1). To our delight, no reduction product **4a′** was detected when the reaction was conducted in the presence of 0.5 equiv of **1** for 48 h and it gave addition product **4a** in 82% yield with 91% *ee* (Table 1, entry 2). We then turned to examine the enantioselective addition of diethylzinc to imine **3a** at different loadings of **1** (0.4 and 0.6 equiv) and at different reaction temperatures in the co-solvent system (toluene/hexanes). The enantioselectivity decreased to 85% when 0.4 equiv of **1** was used (Table 1, entry 3). However, the enantioselectivity was improved to 93% if the amount of **1** was increased to 0.6 equiv (Table 1, entry 4). High enantioselectivity was maintained while the amount of organozinc was decreased from 5 equivalents to 4 or 3 equivalents (Table 1, entries 5–6). When the reaction was conducted at 0 °C or −10 °C, there was no substantial improvement concerning the enantioselectivity, and the reaction took a longer time to give a reasonable yield (Table 1, entries 7–8). A slight decrease in enantioselectivity was observed when the reaction was carried out at 50 °C (Table 1, entry 9). Therefore, the condition in entry 6 was selected for the study of substrate scope and limitations.

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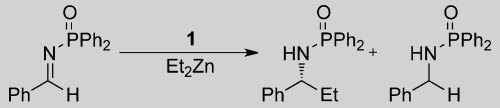
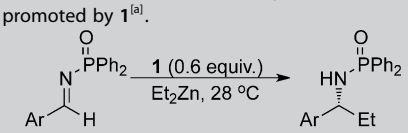
Table 1. The addition of diethylzinc to **3a** mediated by β-amino alcohol **1**.



Entry	**1** [equiv]	Et_2Zn [equiv][a]	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	–	5	28	48	44 (43)[e]	-
2	0.5	5	28	48	82	91
3	0.4	5	28	82	82	85
4	0.6	5	28	48	87	93
5	0.6	4	28	48	90	93
6	0.6	3	28	42	93	92
7	0.6	3	0	48	91	93
8	0.6	3	−10	139	88	93
9	0.6	3	50	5	94	90

[a] 1.0 M Et_2Zn in hexanes. [b] tol = toluene, hex = hexanes; [imine] = concentration of imine. [c] Isolated yield. [d] Determined by HPLC using a Chiralcel OD-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data.[2–10] [e] Yield of the corresponding reduction product is given in parenthesis.

Table 2. Enantioselective addition of diethylzinc to *N*-(diphenyphosphinoyl)imines promoted by **1**[a].

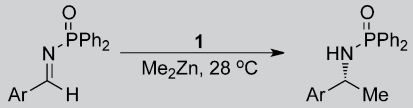


Entry	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	42	93 (**4a**)	92
2	2-Tol	51	90 (**4b**)	89
3	3-Tol	51	93 (**4c**)	93
4	4-Tol	51	95 (**4d**)	93
5	2-MeO-Ph	25	97 (**4e**)	92
6	3-MeO-Ph	25	87 (**4f**)	93
7	4-MeO-Ph	25	88 (**4g**)	98
8	2-Cl-Ph	25	92 (**4h**)	85
9	3-Cl-Ph	30	84 (**4i**)	87
10	4-Cl-Ph	25	92 (**4j**)	90
11	4-MeO_2C-Ph	25	97 (**4k**)	87

[a] The reaction was conducted by using Et_2Zn (3 equiv) with imine (0.085 M) in toluene/hexanes (3:1). [b] Isolated yield. [c] Determined by HPLC using a Chiralcel OD-H or AS-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data;[2–10] Products **4f** and **4k** were tentatively assigned to be (*R*) by the retention times of the enantiomers on HPLC analysis according the observations with products **4c** and **4d**.

With the optimal reaction conditions in hand, we explored the scope and limitations of the reaction with other imines.[12] The results are summarized in Table 2. In the presence of **1**, imines **3a–k** gave the corresponding addition products in high enantioselectivities (85–98%) and yields (84–97%), regardless the electronic nature of the substituent on the aromatic ring.

Table 3. Enantioselective addition of dimethylzinc to imines mediated by **1**[a].



Entry	Imine **3** (Ar)	**1** [equiv]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**3a** (Ph)	0	48	-	-
2[d]	**3a** (Ph)	0.6	168	70	96
3	**3a** (Ph)	1	24	86	97
4	**3d** (4-Me-Ph)	1	24	85	97
5	**3g** (4-MeO-Ph)	1	24	86	98
6	**3k** (4-MeO_2C-Ph)	1	24	86	97

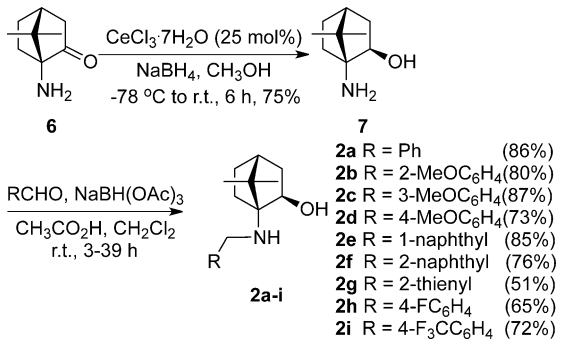
[a] The reaction was conducted by using Me_2Zn (10 Wt% Me_2Zn in hexanes, 5 equiv) with imine (0.065 M) in toluene/hexanes (1.4:1). [b] Isolated yield. [c] Determined by HPLC using a Chiralcel OD-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data;[2–10] Product **5k** was tentatively assigned to be (*R*) by the retention times of the enantiomers on HPLC analysis according the observations with products **5d** and **5g**. [d] Me_2Zn (10 wt% in hexanes, 3 equiv) were used.

It had been reported previously that dimethylzinc is much less reactive than diethylzinc.[2a,8a,13] The addition reaction of dimethylzinc to imine **3a** gave neither the addition product nor the reduction product in the absence of **1** (Table 3, entry 1). The methylation of **3a** with dimethylzinc (3 equiv) in the presence of **1** (0.6 equiv) gave **5a** in 70% yield and 96% *ee* at 28 °C (Table 3, entry 2). To improve the yield of **5a**, methylation of **3a** by using 5 equivalents of dimethylzinc and a stoichiometric amount of **1** was conducted and gave **5a** in 86% yield and 97% *ee* (Table 3, entry 3). Other imines (**3d**, **3g**, **3k**) were also examined. The corresponding addition products were obtained with excellent enantioselectivities (97–98% *ee*) and high yields (85–86%) (Table 3, entries 4–6).

It had been reported that *N*-monosubstituted amino alcohols exhibited slightly higher enantioselectivities than their *N*,*N*-disubstituted congener.[4b,c] Although **1** was successfully employed for the addition of dialkylzinc to imines with high enantioselectivity, we surveyed the *N*-monosubstituted amino alcohols **2a–i** for the feasibility of promoting the enantioselective addition reaction.

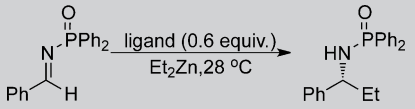
N-monosubstituted amino alcohols **2a–i** were prepared according the synthetic route of scheme 1. The reduction of chiral amino ketone **6**[11] with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ afforded the *exo*-aminoalcohol **7** exclusively. Subsequently, *exo*-amino alcohol **7** was converted into **2a–i** in moderate to good yields by reductive amination with the corresponding aldehyde in the presence of $NaBH(OAc)_3$.

The enantioselective addition of diethylzinc to imine mediated by *N*-monosubstituted amino alcohols **2** were investigated by using conditions reported in Table 2, and the results are summarized in Table 4. It was found that *N*-monosubstituted amino alcohols **2** were also good ligands for the enantioselective addition of diethylzinc to imine **3a** and gave good yields



Scheme 1. The preparation of *N*-monosubstituted amino alcohols **2a–i**.

Table 4. Diethylzinc addition to *N*-(diphenylphosphinoyl)imine **3a** in the presence of chiral amino alcohols **2**[a].

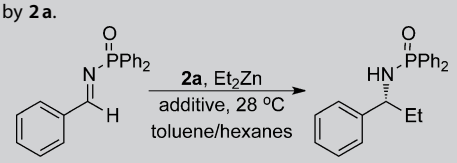


3a (*R*)-**4a**

Entry	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	24	91	93
2	**2b**	48	94	91
3	**2c**	48	99	94
4	**2d**	25	87	95
5	**2e**	48	91	95
6	**2f**	48	94	93
7	**2g**	48	93	92
8	**2h**	45.5	94	92
9	**2i**	45.5	92	91

[a] The reaction was conducted by using Et_2Zn (3 equiv) with imine (0.085 M) in toluene/hexanes (3:1). [b] Isolated yield. [c] Determined by HPLC using a Chiralcel OD-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data.[2–10]

Table 5. The effects of additives on the addition of diethylzinc to **3a** mediated by **2a**.



3a (*R*)-**4a**

Entry	**2a** [equiv]	Et_2Zn [equiv]	Additive [equiv]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	0.2	3	–	68.5	86	71
2	0.2	3	TIPSCl (1.0)	43	76	70
3	0.2	3	$B(OMe)_3$ (0.3)	48	97	70
4	0.2	3	$B(OMe)_3$ (0.9)	48	86	73
5[c]	0.2	3	TIPSCl (1.0)	43	29	85
6	0.2	3	MeOH (0.4)	24	87	77
7	0.2	3	MeOH (0.7)	24	91	83
8	0.2	3	MeOH (1.1)	24	81	88
9	0.2	4	MeOH (1.1)	24	90	87
10	0.2	5	MeOH (1.1)	24	89	88
11	0.2	5	MeOH (1.5)	24	90	92
12	0.2	5	MeOH (1.8)	24	90	93
13	0.2	5	MeOH (2.2)	24	88	93
14	0.1	5	MeOH (1.8)	24	86	91
15	0.1	5	MeOH (1.5)	24	84	86
16	0.05	5	MeOH (1.8)	48	82	86
17	0.2	5	EtOH (1.8)	24	86	86
18	0.2	5	*i*PrOH (1.7)	24	95	73
19	0.2	5	H_2O (0.8)	48	54	81
20[d]	0.1	5	MeOH (1.8)	24	76 (7)[e]	86

[a] Isolated yield. [b] Determined by HPLC using Chiralcel OD-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data.[2–10] [c] The reaction was performed at −20 °C. [d] Using **1** as chiral ligand. [e] In bracket, yield of the corresponding reduction product.

with similar enantioselectivites. There is no substantial effect on enantioselectivity and yield for the substituent on the benzyl group of the ligands.

The addition of achiral additives and Lewis acid had been found to have some effect on the enantioselectivity and chemical yield of enantioselective addition reactions.[14] It was reported that a bulky silylating agent could further activate the imine substrate and enhance the reaction rate in a dual catalytic system (amino alcohol and halosilane) for the asymmetric addition of diethylzinc to imine **3a**. However, a stoichiometric amount of ligand was required to ensure high conversion and enantioselectivity.[3] It had been demonstrated that the yield of adduct was primarily controlled by the silylating agent and the enantioselectivity was mainly dependent on the amount of the chiral ligand in the reaction.[7l]

To examine the possibility of using a lower catalytic amount of ligand **1** or **2** in the addition of dialkylzinc to imine **3**, the reaction was conducted in the presence of an additive. At the outset, ligand **2a** was selected for the investigation due to its higher catalytic ability and easier preparation. Diethylzinc (3 equiv) and imine **3a** in the presence of **2a** (20 mol%) at 28 °C was allowed to react for 68.5 h, and it gave the addition product in 86% with 71% *ee* (Table 5, entry 1). Then, the reaction was examined in the presence of a Lewis acid such as triisopropylsilyl chloride (TIPSCl), trimethyl borate ($B(OMe)_3$), or methanol as an additive due to some beneficial effects on the zinc system.[14] There was no substantial change on the enantioselectivity when the addition reaction was conducted at 28 °C in the presence of TIPSCl or trimethyl borate (Table 5, entries 2–4). When the reaction was conducted in the presence of TIPSCl at −20 °C, the enantioselectivity increased to 85%, but the yield dramatically decreased to 29% (Table 5, entry 5).

Contradictory results on using methanol as an achiral additive for the enantioselective addition of dialkylzinc to imines have been reported. One group reported that there was no effect on the enantioselectivity in the presence of 1 equiv of methanol.[2c] However, another group reported that the enantioselectivity improved significantly upon addition of 2 equivalents of methanol to the addition reaction.[6b] The drawback of the latter system is that a large excess of diethylzinc (12 equiv) was used to ensure a moderate yield (70%). We examined the effect of methanol in our system, and the results are summarized in Table 5 as entries 6–16. The enantioselectivity was increased to 88% when the amount of methanol was increased

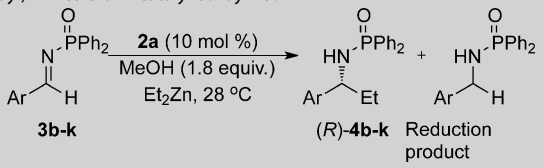
from 0.4 equiv to 1.1 equiv, but the yield slightly decreased from 87% to 81% (Table 5, entries 6–8). The yield was improved to 89% without affecting enantioselectivity when the amount of diethylzinc was increased from 3 equiv to 5 equiv in the presence of methanol (1.1 equiv) (Table 5, entries 8–10). A further increase in the amount of methanol from 1.1 equiv to 2.2 equiv resulted in a slight increase in the enantioselectivity to 93% (Table 5, entries 11–13). When the amount of **2a** was reduced to 0.1 equiv, the enantioselectivity and yield (Table 5, entry 14) of the addition reaction were similar to the result of entry 12. Interestingly, when the amount of methanol was reduced to 1.5 equiv, the enantioselectivity and yield were both slightly decreased (Table 5, entry 15). The reaction took a longer time for completion with lower enantioselectivity when the amount of **2a** was further reduced to 0.05 equiv (Table 5, entry 16). Methanol was found to be the best achiral additive so far in our catalytic system when compared with other protic additives such as ethanol, 2-propanol, and water (Table 5, entries 12, 17–19). *N*-Monosubstituted amino alcohol **2a** exhibited higher enantioselectivity than their *N,N*-disubstituted congener **1** in this system (Table 5, entry 20).

With the optimal conditions for the diethylzinc addition to imine **3a** (Table 5, entry 14) in hand, we examined the addition to imines **3b–k** to determine the scope and limitations. In the presence of **2a**, the addition of diethylzinc to imines **3b–k** gave the corresponding addition products in good enantioselectivities (84-92%) and yields (60–92%) (Table 6). It should be noted that the position of substitution on the phenyl ring of the imine had a dramatic influence on the reaction. Generally, imines bearing an *ortho*-substituted group gave a lower yield along with the reduction product (Table 6, entries 1, 5, 8) than *meta*-substituted and *para*-substituted imines. The reason is presumably the steric hindrance imposed by the *ortho*-substituted group on the phenyl ring. Interestingly, the presence of methanol could suppress the formation of reduction product and enhance the yield of the addition product (Table 6, entries 4–5).

Methylation of **3a** with dimethylzinc (5 equiv) in the presence of a stoichiometric amount of **2a** at 28 °C for 31 h gave the addition product **5a** in 92% yield with 97% *ee* (Table 7, entry 1). The yield and enantioselectivity were decreased when the amount of **2a** was decreased (Table 7, entries 2–4). Methylation of **3a** in the presence of methanol (1.8 equiv) was also found to improve both yield (71%) and enantioselectivity (96%) when compared with the reaction in the absence of methanol (Table 7, entries 4–5). No substantial change in yield and enantioselectivity was observed on prolonging the reaction time from 48 h to 72 h. When the reaction was conducted either at a higher concentration (0.24 M) or in the presence of 0.2 equiv of **2a**, it resulted in a slight increase in the yield to 78% and 77%, respectively (Table 7, entries 7–8).

The presence of a small amount of methanol not only enhanced the catalytic cycle but also improved the enantioselectivity. The exact role of methanol in our catalytic system is not fully understood at this stage.[14,15] However, based on literature reports,[2a,b,8b,13] the rationale of the stereochemical outcome of the addition reaction is shown in Figure 2. The coordination of imine and chiral aminoalcohol to both zinc atoms would lead to a favored bicyclic transition state **A**. The transfer of one of the ethyl groups on Zn_B to imine **3** would then give

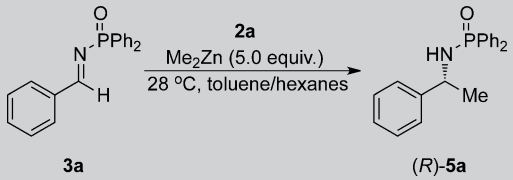
Table 6. The enantioselective addition of diethylzinc to *N*-(diphenyphosphinoyl)imines **3b–k** catalyzed by **2a**.[a]



Entry	Ar	*t* [h][]	Yield [%][b,c]	ee [%][d]
1	2-Tol	41	60(**b**)(24)	89
2	3-Tol	44	76(**c**)(8)	89
3	4-Tol	30	83(**d**)(4)	92
4[e]	2-MeO-Ph	24	52(**e**)(47)	79
5	2-MeO-Ph	44	71(**e**)(28)	87
6	3-MeO-Ph	30	87(**f**)(6)	88
7	4-MeO-Ph	30	86(**g**)	91
8	2-Cl-Ph	41	68(**h**)(24)	84
9	3-Cl-Ph	43	84(**i**)(6)	85
10	4-Cl-Ph	30	86(**j**)(3)	89
11	4-MeO_2C-Ph	40	92(**k**)	84

[a] The reaction was conducted by using Et_2Zn (5 equiv) and MeOH (1.8 equiv) with imine (0.072 M) in toluene/hexanes (1.76:1). [b] Isolated yield. [c] In brackets, yields of the corresponding reduction products. [d] Determined by HPLC using Chiralcel OD-H or AS-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data;[2–10] Products **4f** and **4k** were tentatively assigned to be (*R*) by the retention times of the enantiomers on HPLC analysis according the observations with products **4c** and **4d**. [e] Without MeOH.

Table 7. Enantioselective addition of dimethylzinc to imine mediated by **2a**.[a]



Entry	**2a** [equiv]	*t* [h]	Yield [%][b]	ee [%][c]
1	1.0	31	92	97
2	0.6	48	75	99
3	0.4	48	64	94
4	0.1	48	33	87
5[d]	0.1	48	71	96
6[d]	0.1	72	70	95
7[d,e]	0.1	72	78	93
8[d]	0.2	72	77	95

[a] The reaction was conducted by using 5 equiv of Me_2Zn (10 wt% in hexanes) with imine (0.065 M) in toluene/hexanes (1.6:1). [b] Isolated yield. [c] Determined by HPLC using a Chiralcel OD-H column, and the absolute configuration of the major isomer was assigned to be (*R*) by the comparison of the optical rotation and the retention time with literature data.[2–10] [d] MeOH (1.8 equiv) was added. [e] The reaction was conducted by using 5 equiv of Me_2Zn (1.2 M in toluene) with imine (0.24 M).

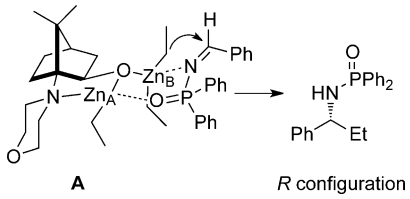


Figure 2. A plausible transition state for the addition of diethylzinc to imine **3**.

the addition product with the observed stereochemistry (*R*-form).

Conclusions

We have demonstrated that the addition of diethylzinc or dimethylzinc to *N*-(diphenylphosphinoyl) imines mediated by **1** or **2** could be achieved with high yields and enantioselectivities. The catalytic loading of **1** or **2a** could be reduced to 10 mol% for methylation or ethylation of imines when the reaction was conducted in the presence of 1.8 equivalents of methanol. The reaction is able to tolerate a wide range of functionalities. *N*-Monosubstituted amino alcohols induced higher enantioselectivity than their *N*,*N*-disubstituted congener in this catalytic system. This catalytic system provides an additional efficient entry for the preparation of chiral secondary benzylic amines.

Experimental Section

Standard procedure for the preparation of (1S,2R,4R)-N-aryl-1-amino-2-exo-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptane (2a–2i):

A solution of (1*S*,2*R*,4*R*)-1-amino-2-*exo*-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptane **7** and aryl aldehyde (1.1 equiv) in anhydrous dichloromethane was added to sodium triacetoxyborohydride (1.4 equiv) and acetic acid (1.1 equiv). The reaction mixture was stirred at 28 °C for 3–39 h and was then quenched with aqueous NaOH (1.0 M). The aqueous phase was extracted with CH_2Cl_2 (3× 30 mL), and the combined organic layer was washed with brine for three times. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude product by silica gel column chromatography with EtOAc/hexanes (1:5) as eluent gave **2a–2i**.

General procedure for the enantioselective addition of diethylzinc to N-diphenylphosphinoylimines (Table 2):

N-(Diphenylphosphinoyl)imine **3** (0.34 mmol) and **1** (46.0 mg, 0.20 mmol) were dissolved in dry toluene (3 mL) under argon, and the mixture was stirred for 10 min at 28 °C. The solution was cooled to 0 °C, and then Et_2Zn in hexanes (1.0 M, 1.0 mL, 1.0 mmol) was added dropwise. The cooling bath was removed, and the mixture was allowed to warm to 28 °C. The reaction mixture was stirred for an additional 25–51 h and was then quenched with saturated aqueous ammonium chloride (4.0 mL) followed by the addition of hydrochloric acid (1.0 N, 3.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Subsequent purification by silica gel column chromatography with $MeOH/CH_2Cl_2$ (1:40–1:20) as eluent afforded the corresponding addition product as a white solid.

General procedure for the enantioselective addition of dimethylzinc to imines (Table 3):

N-(Diphenylphosphinoyl)imine **3** (0.34 mmol) and **1** (76.6 mg, 0.34 mmol) were dissolved in dry toluene (3 mL) under argon, and the mixture was stirred for 10 min at 28 °C. The solution was cooled to 0 °C, and then Me_2Zn in hexanes (10 Wt%, 2.2 mL, 1.7 mmol) was added dropwise. The cooling bath was removed and the mixture was allowed to warm to 28 °C. The reaction mixture was stirred for an additional 24 h. The reaction was then quenched with saturated aqueous ammonium chloride (4.0 mL) followed by the addition of hydrochloric acid (1.0 N, 3.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Subsequent purification by silica gel column chromatography with $MeOH/CH_2Cl_2$ (1:40–1:20) as eluent afforded the corresponding addition product as a white solid.

General procedure for the enantioselective addition of diethylzinc or dimethylzinc to N-diphenylphosphinoylimines with additive (Tables 6 and 7):

A solution of *N*-(diphenylphosphinoyl)imine **3** (0.34 mmol) and **2a** (8.3 mg, 0.034 mmol) in dry toluene (3 mL) was added to MeOH (25 μL, 0.61 mmol) under argon. The mixture was stirred for 10 min at 28 °C. The solution was then cooled to 0 °C and Et_2Zn in hexanes (1.0 M, 1.7 mL, 1.7 mmol) or Me_2Zn in hexanes (10 Wt%, 2.2 mL, 1.7 mmol) was added dropwise. The cooling bath was removed, and the mixture was allowed to warm to 28 °C. The reaction mixture was stirred for an additional 24–44 h. The reaction was then quenched with saturated aqueous ammonium chloride (4.0 mL) followed by the addition of hydrochloric acid (1.0 N, 3.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Subsequent purification by silica gel column chromatography with EtOAc/hexanes (1:5–1:1) as eluent afforded the corresponding addition product as a white solid.

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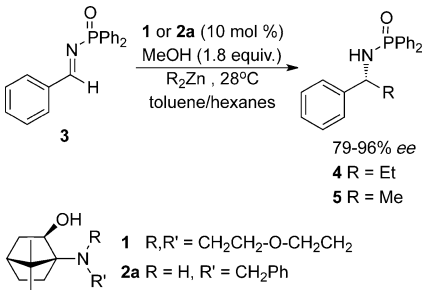
Add it up: The enantioselective addition of diethylzinc or dimethylzinc to *N*-(diphenylphosphinoyl)imines mediated by **1** or **2** could be achieved in high yields and enantioselectivities. The catalytic loading of **1** or **2a** could be reduced to 10 mol% for methylation or ethylation of imines in high yields and enantioselectivities (79–96%) when the reaction was conducted in the presence of 1.8 equiv of methanol.



Enantioselective Synthesis

*Wei-Ming Huang, Biing-Jiun Uang**

■■ – ■■

Enantioselective Addition of Dialkylzinc to Aromatic Aldimines Mediated by Camphor-Derived Chiral β-Amino Alcohols