'Evans Auxiliary' Based P–N Ligands for Pd-Catalyzed Asymmetric Allylic Alkylation Reactions

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Abstract: A new type of chiral P–N ligands has been prepared which incorporates the Evans auxiliary as chiral ligand. They were found to act as effective ligands in the Pd-catalyzed allylic alkylation reactions. Using these ligands with allylpalladium chloride dimer as catalyst, the coupling of 1,3-diphenyl-3-acetoxyprop-1-ene and dimethyl malonate proceeded smoothly at –10 °C providing the desired product with enantiomeric excess up to 87% and excellent yield.

Key words: asymmetric allylic alkylation, palladium catalysis, P–N ligand, Evans auxiliary

One of the most powerful approaches for the formation of carbon–carbon or carbon–heteroatom bond is the metal-catalyzed asymmetric allylic alkylation (AAA) reaction.[1] This reaction has been broadly studied and has become a model reaction to evaluate new chiral ligands.[2] Over the past several years, many useful chiral ligands such as C_2,C_1-symmetric bidentate chiral ligands[3,4] have been extensively applied in this field.

The Evans auxiliary has been employed in a number of synthetic transformations including aldol condensation,[5] Diels–Alder reaction,[6] and alkylation[7] and a high level of enantio- and diastereoselectivity has been achieved.[8] However, to the best of our knowledge, no example of a P–N ligand incorporating the Evans auxiliary has been reported. Considering their ease of synthesis and commercial availability, it would be ideal to design a chiral ligand that links the Evans auxiliary with a phosphino fragment for metal-catalyzed asymmetric transformations. Herein, we report the preparation of this new class of ligands **1** (Figure 1) and evaluate them in the palladium-catalyzed AAA reactions.

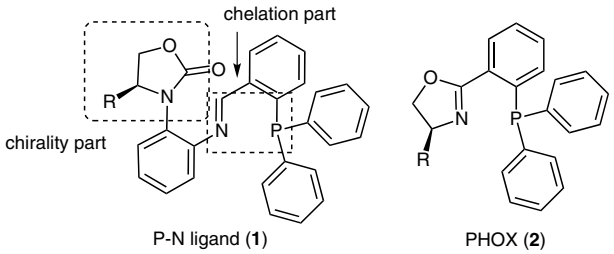
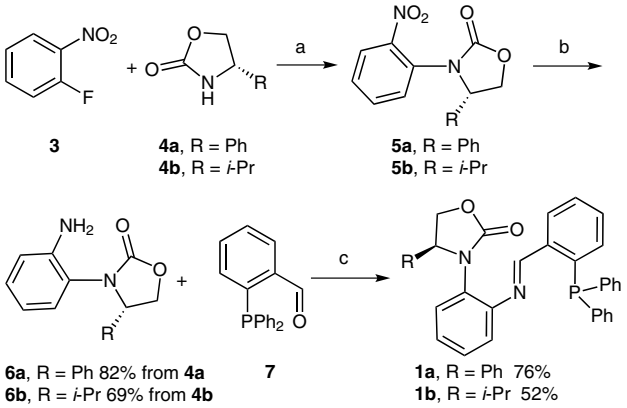


Figure 1 New type of P–N ligands and Pfaltz scaffolds

Inspired by the phosphine oxazoline ligand (PHOX) for their excellent enatioselectivity and high reaction rate shown in the allylic alkylation reactions,[3,9] we envisaged incorporating the Evans chiral auxiliary next to the imino group that could lead to novel P–N ligand **1**. This new class of ligands was designed to possess two independent parts: an Evans auxiliary moiety providing a chiral recognition environment and a phosphinoimine unit coordinating with the metal center for catalysis.

The synthesis of ligand **1a**(**b**) proved to be rather straightforward from the commercially available Evans auxiliary. Compound **4a**(**b**) was converted into *N*-aryl oxazolidin-2-one **5a**(**b**) via a S_NAr reaction[10] with 2-fluoronitrobenzene. Reduction of the nitro group with Pd/C provided the corresponding aniline **6a**(**b**). Condensation of anilines **6a**(**b**) with phosphinoaldehyde **7** in the presence of 4 Å MS and a catalytic amount of zinc chloride resulted in the efficient formation of ligands **1a**(**b**) as shown in Scheme 1.



Scheme 1 *Reagents and conditions*: (a) NaH, DMF, 100 °C, 10 h; (b) H_2, Pd/C, MeOH; (c) $ZnCl_2$, 4 Å MS, THF, r.t., 10 h.

In order to investigate the potential application of this new type of ligands in asymmetric catalysis, we first carried out the AAA reaction of 1,3-diphenylprop-2-enyl acetate (**8**) with dimethylmalonate as the prototypical substrate. Using **1a** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as catalyst with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) and a catalytic amount of LiOAc as additives in CH_2Cl_2, the reaction proceeded well, and the desired product was isolated in 95% yield with 63% ee (Table 1, entry 1).

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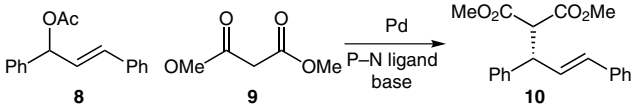
The solvent effect has also been investigated. Among the five solvents (CH_2Cl_2, THF, toluene, MeCN, and dioxane) examined, the reaction with THF gave the product in superior yield and enantiomeric excess.

Variations of the ligand-to-palladium ratio had minimal impact on the reaction outcome. Lowering the reaction temperature to –10 °C resulted in slightly improved yield and enantioselectivity (80%). Further lowering of the reaction temperature led to longer reaction time and minimum benefit of the ee value. Changing the base from BSA to other organic or inorganic bases resulted in a significant drop of yield and enantiomeric excess of the product. When switching the additive from LiOAc to KOAc, a significant drop of ee value was observed. Increasing the amount of LiOAc from catalytic to stoichiometric amount improved the ee value to 82% (Table 1, entry 17). These data suggest that the extra lithium cation is beneficial to the enantioselectivity of this reaction. Using $Pd(OAc)_2$ as Pd precursor instead of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ required longer reaction time and gave the product in lower yield (Table 1, entry 8). Combining all the findings, the reaction was performed under the optimized reaction conditions (8 mol% of **1a**, 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as catalyst, 2.0 equiv of BSA as base and 1.0 equiv of LiOAc as additive in THF). Switching to the more hindered isopropyl-substituted ligand **1b** under the same reaction conditions yielded the desired product with slightly better enantioselectivity (Table 1, entry 19).

Next, we examined the substrate scope for this new protocol, and the reaction results are summarized in Table 2.

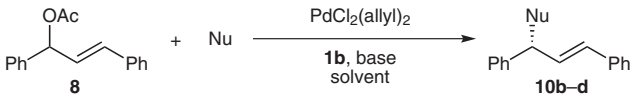
Table 1 Optimization of the Asymmetric Allylic Alkylation Using Pd/Ligand **1**[12,13]

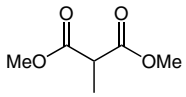
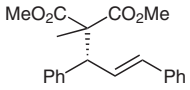
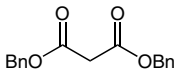
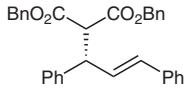
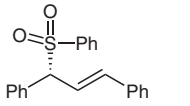


Entry[a]	Ligand (L/Pd)	Base (additives)[b]	Solvent	Temp (°C)	Time (h)	Yield (%)[c]	ee (%)[d]
1	**1a** (2:1)	BSA, LiOAc	CH_2Cl_2	20	2.0	95	63 (*S*)
2	**1a** (2:1)	BSA, LiOAc	toluene	20	2.0	96	53 (*S*)
3	**1a** (2:1)	BSA, LiOAc	THF	20	1.5	98	70 (*S*)
4	**1a** (2:1)	BSA, LiOAc	MeCN	20	2.0	94	51 (*S*)
5	**1a** (2:1)	BSA, KOAc	THF	20	1.5	97	51 (*S*)
6	**1a** (1:1)	BSA, LiOAc	dioxane	20	3.0	97	45 (*S*)
7	**1a** (3:1)	BSA, LiOAc	THF	20	2.0	98	63 (*S*)
8[e]	**1a** (2:1)	BSA, LiOAc	THF	20	8.0	62	69 (*S*)
9	**1a** (2:1)	BSA, LiOAc	THF	0	2.0	97	69 (*S*)
10	**1a** (2:1)	BSA, LiOAc	THF	–10	5.0	98	80 (*S*)
11	**1a** (2:1)	BSA, LiOAc	THF	–20	15	70	82 (*S*)
12	**1a** (2:1)	TBAF	THF	–10	5.0	87	9 (*S*)
13	**1a** (2:1)	$Ba(OH)_2$	THF	–10	5.0	0	–
14	**1a** (2:1)	Cs_2CO_3	THF	–10	8.0	95	48 (*S*)
15	**1a** (2:1)	LiOH	THF	–10	5.0	98	65 (*S*)
16	**1a** (2:1)	Li_2CO_3	THF	–10	10	90	32 (*S*)
17[f]	**1a** (2:1)	BSA, LiOAc, LiCl	THF	–10	5.0	98	55 (*S*)
18[g]	**1a** (2:1)	BSA, LiOAc	THF	–10	5.0	99	82 (*S*)
19	**1b** (2:1)	BSA, LiOAc	THF	–10	20	99	87 (*S*)

[a] Reaction run with $(\eta^3\text{-}C_3H_5PdCl)_2$ (2 mol%) as catalyst unless otherwise noted.
[b] Using base (2 equiv) and additives (2 mol%).
[c] Isolated yields.
[d] The ee value was determined by SFC with a chiral column, Daicel chiralcel AD-H column (20% MeOH in liquid CO_2). The absolute configuration was determined by comparing the sign of optical rotation.11
[e] Using $Pd(OAc)_2$ as palladium source.
[f] Using LiOAc (2 mol%) and LiCl (1 equiv) as additive.
[g] Using LiOAc (1.0 equiv) as additive.

Table 2 Asymmetric Allylic Alkylation with Several Nucleophiles



Entry	Nucleophiles	Products	Yield (%)[a]	ee (%)[b]
1			96	82
2			86	80
3[c]	$PhSO_2Na$		67	48

[a] Isolated yields.
[b] The ee value was determined by SFC with a chiral column.
[c] This reaction was performed in THF without any additional base and using **1a** as the ligand.

When the sterically more hindered 2-methylmalonate was employed, the product was isolated in excellent yield with slightly diminished ee value (82%). Benzyl malonate gave comparable result as the corresponding methyl ester. Under the same reaction conditions, when $PhSO_2Na$ was used as the nucleophile, poor yield and lower ee was obtained (ca. 27%). Interestingly, much better yield and enantiomeric excess was obtained (Table 2, entry 3) after removing the additive LiOAc. It is possible that the lithium ion may act as a Lewis acid that coordinates with the bicarbonyl group of the malonate substrates.

In summary, a novel class of Evans auxiliary incorporating imino-type P–N ligands was synthesized from the inexpensive Evans auxiliary in three steps. This new class of ligands was successfully applied into palladium-catalyzed asymmetric allylic alkylation with several nucleophiles, under the optimal reaction conditions; the desired product could be obtained in excellent yields and good enantioselectivity. Further improvement and applications in asymmetric synthesis are in progress and will be reported in due course.

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(12) **Typical Procedure for the Preparation of 1a**
The reaction mixture of **6a** (1.75 g, 6.89 mmol) and $ZnCl_2$ (0.188 g, 1.378 mmol) and 4 Å MS (2.0 g) in THF (34.4 mL) was added **7** (2.00 g, 6.90 mmol) and stirred for 12 h at r.t. After that, the reaction mixture was filtered and diluted with CH_2Cl_2. The organic phase was washed 3 times with H_2O and brine and then separeted and dried over Na_2SO_4. Organic phase was then concentrated and chromatographed on silica

gel, eluted with hexane–EtOAc (2:1) which afford **1a** (2.358 g, 65% yield) as a yellowish solid; mp 144–145 °C; $[\alpha]_D^{25}$ +224 (*c* 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.90 (d, *J* = 5.0 Hz, 1 H), 8.27 (dd, *J* = 3.6, 7.4 Hz, 1 H), 7.62 (t, *J* = 7.5 Hz, 1 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.42 (d, *J* = 3.3 Hz, 6 H), 7.36–7.16 (m, 11 H), 7.16–7.03 (m, 2 H), 6.93 (dd, *J* = 4.8, 7.5 Hz, 1 H), 6.40 (d, *J* = 7.5 Hz, 1 H), 5.50 (t, *J* = 8.4 Hz, 1 H), 4.81 (t, *J* = 8.7 Hz, 1 H), 4.16 (t, *J* = 8.3 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2 (d, *J* = 22 Hz), 156.7, 148.6, 139.1 (d, *J* = 5 Hz), 138.8 (d, *J* = 4 Hz), 138.5, 136.4 (d, *J* = 5 Hz), 136.3 (d, *J* = 6 Hz), 134.2 (d, *J* = 3 Hz), 134.0 (d, *J* = 3 Hz), 133.6, 132.1, 130.3, 130.0, 129.8, 129.46 (d, *J* = 1 Hz), 129.4 (d, *J* = 1 Hz), 129.1, 128.9, 127.9, 126.6, 119.3, 70.5, 62.2. ^{31}P NMR (162 MHz, DMSO-d_6): δ = –14.4 (s). ESI-MS: *m/z* = 526.2 [M + H$^+$]. ESI-HRMS: *m/z* calcd for $C_{34}H_{28}N_2O_2P$ [M + H$^+$]: 527.1888; found: 527.1882.

Compound **1b**: 54%; mp 125–126 °C. $[\alpha]_D^{25}$ +174 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.92 (d, *J* = 5.0 Hz, 1 H), 8.12 (dd, *J* = 3.6, 6.9 Hz, 1 H), 7.68–7.53 (m, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.42 (d, *J* = 2.0 Hz, 6 H), 7.37 (dd, *J* = 3.5, 5.8 Hz, 1 H), 7.33–7.19 (m, 6 H), 6.89 (dd, *J* = 5.0, 6.8 Hz, 1 H), 6.46 (dd, *J* = 3.5, 5.8 Hz, 1 H), 4.53–4.30 (m, 2 H), 4.18 (dd, *J* = 4.6, 7.2 Hz, 1 H), 1.78–1.53 (m, 1 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.74 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.4 (d, *J* = 22 Hz), 156.3, 148.1, 138.5, 138.3, 138.2, 135.7 (d, *J* = 9 Hz), 135.6 (d, *J* = 9 Hz), 133.6 (d, *J* = 8 Hz), 133.4 (d, *J* = 8 Hz), 132.9, 131.5, 130.0, 129.3, 129.2, 128.8 (d, *J* = 7 Hz), 128.1 (d, *J* = 4 Hz), 126.2, 119.0, 63.5, 61.2, 54.8, 28.6, 17.1, 14.8. ^{31}P NMR (162 MHz, DMSO-d_6): δ = –14.3 (s). ESI-MS: *m/z* = 493.2 [M + H$^+$]. ESI-HRMS: *m/z* calcd for $C_{31}H_{30}N_2O_2P$ [M + H$^+$]: 493.2044; found: 493.2048.

(13) **General Procedure for the Asymmetric Allylic Alkylation**

To a Schlenk tube containing allyl palladium(II) chloride dimer (2.90 mg, 0.008 mmol), **1b** (15.3 mg, 0.032 mmol), and LiOAc (2.62 mg, 0.040 mmol) were evacuated and backfilled with nitrogen for 3 times, after that, THF (2 mL) was added and stirred for 0.5 h at r.t. Then (*E*)-1,3-diphenylallyl acetate (100 mg, 0.396 mmol) was added, and the mixture was stirred for another 10 min, dimethyl malonate (157 mg, 1.189 mmol) was added to the reaction mixture followed by BSA (242 mg, 1.189 mmol). The resultant mixture was stirred at –10 °C for 10 h. The reaction was diluted with CH_2Cl_2 and quenched by sat. aq NH_4Cl. The organic layer was washed by H_2O and brine 3 times, concentrated and purified with silica gel (EtOAc–hexane, 1:10) afforded **10a** (121 mg, 99% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 10 H), 6.51–6.46 (d, *J* = 15.6 Hz, 1 H), 6.37–6.29 (dd, *J* = 8.4, 15.9 Hz, 1 H), 4.30–4.24 (dd, *J* = 8.7, 10.8 Hz, 1 H), 3.98–3.94 (d, *J* = 10.8 Hz, 1 H), 3.71–3.70 (d, *J* = 3.0 Hz, 3 H), 3.52–3.51 (d, 3 H, *J* = 3.3 Hz, 3 H). The ee value was determined by SFC (Daicel CHIRALCEL AD-H, column size: 0.46 cm I.D. × 25 cm L, liquid CO_2/MeOH = 85:15, flow rate: 2.0 mL/min, λ = 254 nm): t_R (major) = 8.0 min; t_R (minor) = 16.77 min; 87% ee .

