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**COMMUNICATION**

# Highly effective chiral phosphorus amidite–olefin ligands for palladium-catalyzed asymmetric allylic substitutions†

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**This paper describes the development of a type of novel P–olefin hybrid ligand by the incorporation of terminal olefins onto phosphorus amidite ligands for palladium-catalyzed asymmetric allylic alkylations of indoles and substitutions with amines to give the desired products in 70–97% yield with 91–98% ee.**

Chiral olefins as steering ligands for transition-metal-catalyzed asymmetric reactions have received intensive attention, and considerable progress has been made in this lately emerging area.[1,2] Besides the rapid growth of chiral diene ligands,[3] several hybrid ligands combining olefins with heteroatoms such as phosphorus[4] or nitrogen[5] have also been well developed since Grützmacher and co-workers reported the first phosphane–olefin ligand for iridium-catalyzed asymmetric hydrogenation.[4a] Especially, in some cases, the olefin moieties were found to be essential for the high reactivity and enantioselectivity. However, compared with the phosphorus and nitrogen ligands, the quantity and the application scope of the hybrid olefin ligands are still very limited. Further efforts on the design of highly active and selective hybrid ligands are therefore of great importance.[1]

During the course of exploring novel and easily synthesized chiral diene ligands, we found that flexible ligands incorporating terminal olefins as binding elements were effective for rhodium-catalyzed asymmetric reactions.[6] A strategy for the development of P–olefin ligands by the incorporation of terminal olefin and phosphorus atom was then adopted in our group, and ligands **1** and **2** were successfully developed for palladium-catalyzed asymmetric substitutions (Fig. 1).[7] Due to their ease of synthesis, their good stability and their wide application, chiral phosphorus amidites have become one class of "privileged ligands" in asymmetric catalysis.[8] Olefin moieties have also been introduced into this type of ligands by Carreira and co-workers *via* a one-step synthesis (Scheme 1).[4e] Inspired by this beautiful work and the wonderful characters of chiral phosphorus amidite ligands, we envisioned that the combination of terminal olefins with phosphoramidite ligands would provide a good opportunity for the development of highly active and selective P–olefin hybrid ligands (Fig. 1). Herein, we wish to report our preliminary results on this subject.

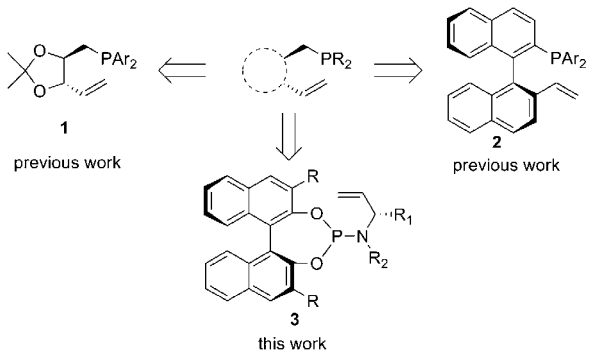
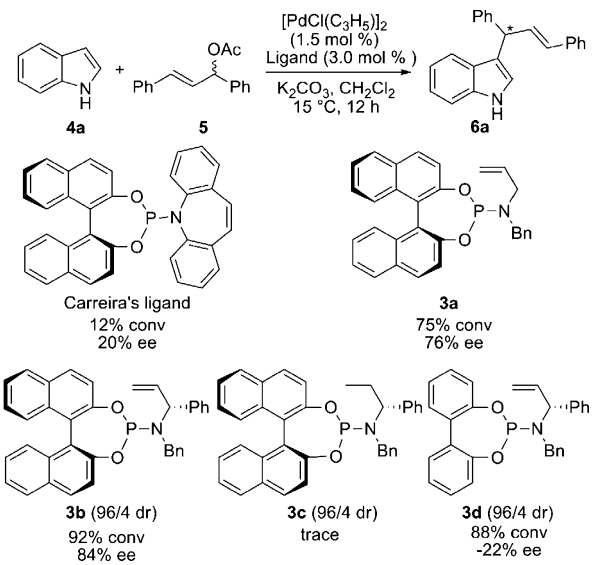



**Fig. 1** Strategy for the development of chiral P–olefin ligands.




**Scheme 1** Initial studies on Pd-catalyzed asymmetric alkylation of indole with the use of P–olefin ligands.[14]

Palladium-catalyzed asymmetric allylic alkylations[9] of indoles provide an efficient approach to the synthesis of optically active indoles, which are widely present in various biologically and medically important compounds.[10–12] However, to the best of our knowledge, only a few chiral ligands including P/S ligands developed by Chan and co-workers,[13a] binaphthyl-based P/S

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ligands developed by Hagiwara's group,[13b] and P–olefin ligands **2** developed by us[7b] were found to be effective for this asymmetric transformation. Therefore, further searching for other highly effective ligands is still desirable.

Initially, we subjected phosphorus amidite–olefin ligands to the palladium-catalyzed asymmetric alkylation of indole (**4a**) with 1,3-diphenyl-2-propenyl acetate (**5**) to examine the reactivity and enantioselectivity for this type of ligands (Scheme 1). It was found that Carreira's ligand[4e] gave 12% conversion with 20% ee and (*S*)-BINOL derived ligand **3a** bearing a terminal double bond gave 75% conversion with 76% ee. We were pleased to find that ligand **3b** incorporating chiral amine moieties was more effective for this reaction. Control experiments employing **3c** and **3d** as ligands led to extremely low reactivity or enantioselectivity, which strongly indicated that both the terminal olefin moieties and the binaphthyl backbone of ligand **3b** were essential for the observed high activity and selectivity.

With these promising results in hand, several new ligands were synthesized (Fig. 2) and the reaction conditions such as base or solvent were optimized in order to further improve the enantioselectivity. As shown in Table 1, the base and solvent were found to have an obvious effect on both reactivity and enantioselectivity (entries 1–9). Interestingly, ligand **3e** derived from (*S*)-BINOL and a racemic amine led to a reasonable conversion with 87% ee (Table 1, entry 10). While ligands **3f** and **3g** with different axial chiralities showed similar activity, ligand **3f** gave a much better ee (Table 1, entries 11 *vs.* 12), which suggested that the absolute configuration of product was controlled by the ligand's axial chirality rather than the amine chirality. Ligand **3h** incorporating internal olefin moieties was less effective than ligand **3f** (Table 1, entries 13 *vs.* 11). Overall, ligand **3f** gave the best conversion and enantioselectivity (Table 1, entry 11).

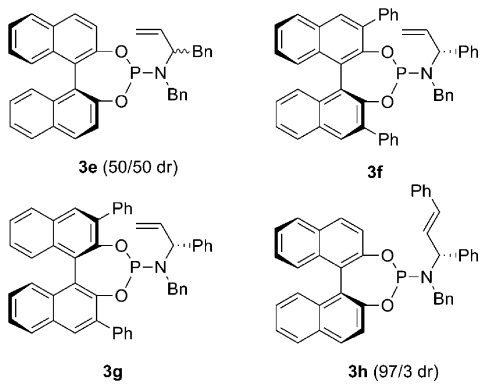



**Fig. 2** Selected phosphorus amidite–olefin ligands.[14]

Under the optimal conditions involving 3 mol% Pd, $CH_2Cl_2$/THF (2/1) as a solvent and $K_2CO_3$ as a base, we examined the substrate scope for ligand **3f** in the palladium-catalyzed allylic alkylations of indoles **4** with 1,3-diphenyl-2-propenyl acetate (**5**). It was found that different substituents on the indoles were well tolerated, and all the reactions proceeded smoothly to give the desired products **6** in 72–96% yield with 91–98% ee (Table 2, entries 1–10). Compared with the previously reported ligand **2**,[7b] ligand **3f** showed a better selectivity in most cases.

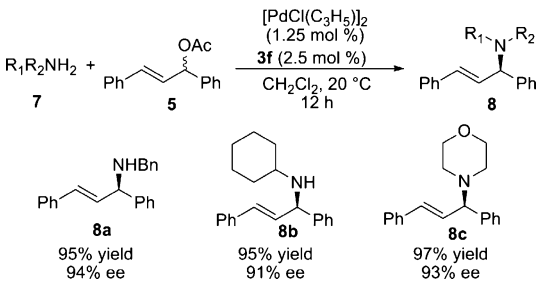
The application of ligand **3f** can be extended to palladium-catalyzed asymmetric allylic amination to give the desired products

**Table 1** Optimization of reaction conditions and evaluation of chiral ligands[a]

| Entry | Ligand | Solvent | Base | Conv (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **3b** | $CH_2Cl_2$ | $K_2CO_3$ | 92 | 84 |
| 2 | **3b** | $CH_2Cl_2$ | $Na_2CO_3$ | *NR* | *ND* |
| 3 | **3b** | $CH_2Cl_2$ | $Cs_2CO_3$ | 90 | 82 |
| 4 | **3b** | $CH_3CN$ | $K_2CO_3$ | 91 | 83 |
| 5 | **3b** | toluene | $K_2CO_3$ | 92 | 86 |
| 6 | **3b** | $Et_2O$ | $K_2CO_3$ | 74 | 86 |
| 7 | **3b** | THF | $K_2CO_3$ | 44 | 92 |
| 8 | **3b** | $CH_2Cl_2$/THF (2/1) | $K_2CO_3$ | 92 | 89 |
| 9 | **3b** | $CH_2Cl_2$/THF (1/1) | $K_2CO_3$ | 91 | 90 |
| 10 | **3e** | $CH_2Cl_2$/THF (2/1) | $K_2CO_3$ | 68 | 87 |
| **11** | **3f** | **$CH_2Cl_2$/THF (2/1)** | **$K_2CO_3$** | **95** | **95** |
| 12 | **3g** | $CH_2Cl_2$/THF (2/1) | $K_2CO_3$ | 93 | −74 |
| 13 | **3h** | $CH_2Cl_2$/THF (2/1) | $K_2CO_3$ | 52 | 63 |

[a] All reactions were carried out with indole (**4a**) (0.20 mmol), **5** (0.24 mmol), Pd/L = 1/1 (3 mol% Pd), base (0.60 mmol), and solvent (1.0 mL, entries 1–7, 1.2 mL, entries 8–13) at 15 °C for 12 h. [b] The conversion was determined by crude $^1$H NMR. [c] The ee values were determined by chiral HPLC with the *N*-Boc-protected derivative of **6a**.

**8** in 95–97% yield with 91–94% ee (Scheme 2). A control experiment employing ligand **3c** for the palladium-catalyzed asymmetric amination reaction of 1,3-diphenyl-2-propenyl acetate (**5**) with benzylamine (**7a**) only led to product **8a** in 85% yield with 7% ee, which further demonstrated the importance of the terminal olefin moieties of ligand **3f**.




**Scheme 2** Pd/**3f** catalyzed asymmetric allylic amination.

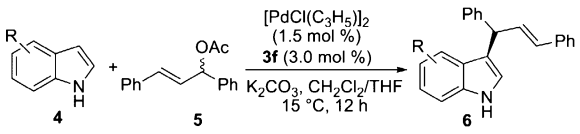
Hydroxylamine hydrochloride (**9**) is a cheap and low-molecular-weight nitrogen source. However, to the best of our knowledge, the successful utilization of hydroxylamine hydrochloride (**9**) as a nitrogen source for Pd-catalyzed asymmetric allylic amination has seldom been reported. Under our catalytic system, the reaction of 1,3-diphenyl-2-propenyl acetate (**5**) and hydroxylamine hydrochloride (**9**) catalyzed by 2.5 mol% Pd/**3f** complex went efficiently to give the desired product **10** in 70% yield with 95% ee (Scheme 3). The ee can be further improved to >99% after a recrystallization in hexanes. The hydroxyl group was easily removed by treating with Zn/HOAc according to the reported method[15] to give a free amine **11**[16] in quantitative yield without losing any ee value.

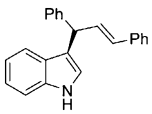
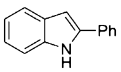
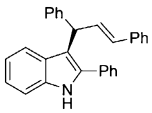
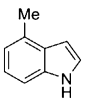
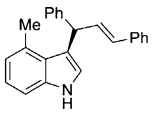
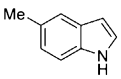
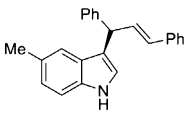
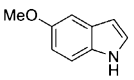
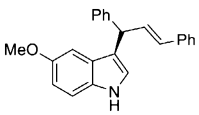
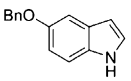
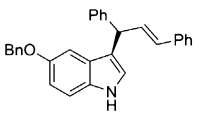
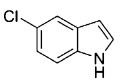
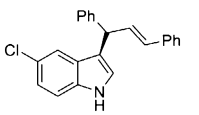
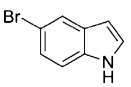
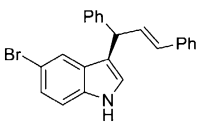
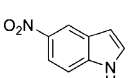
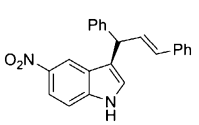
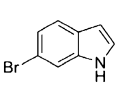
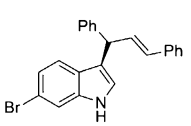
## Conclusion

In summary, we have successfully developed a novel type of P–olefin ligand by the incorporation of a terminal olefin onto chiral phosphorus amidite ligands. Ligand **3f** was highly effective for palladium-catalyzed asymmetric allylic alkylations of indoles,

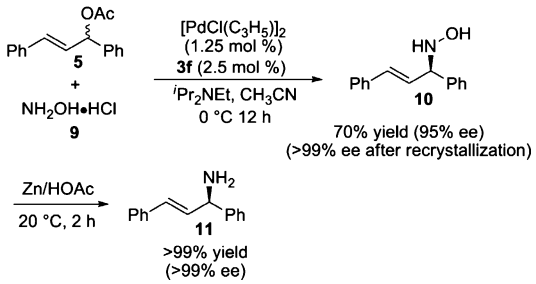
 

**Table 2** Pd/**3f** catalyzed asymmetric allylic alkylation of indoles[a]




| Entry | Indole | Product[b] | Yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 |  |  | 94 | 95 |
| 2 |  |  | 84 | 94 |
| 3 |  |  | 72 | 92 |
| 4 |  |  | 77 | 91 |
| 5 |  |  | 88 | 98 |
| 6 |  |  | 91 | 95 |
| 7 |  |  | 96 | 95 |
| 8 |  |  | 95 | 96 |
| 9 |  |  | 80 | 96 |
| 10 |  |  | 91 | 95 |

[a] All the reactions were carried out with **4** (0.20 mmol), **5** (0.24 mmol), $[PdCl(C_3H_5)]_2$ (0.003 mmol), ligand **3f** (0.006 mmol), $K_2CO_3$ (0.60 mmol) and $CH_2Cl_2$/THF (2/1) (1.2 mL) at 15 °C for 12 h. [b] The absolute configuration was tentatively assigned according to ref. 7b. [c] Isolated yield based on indoles. [d] The ee values were determined by chiral HPLC with the *N*-Boc-protected derivatives of **6**.




**Scheme 3** Pd/**3f** catalyzed asymmetric allylic amination with hydroxylamine hydrochloride (**9**).

and aminations as well, to give the corresponding products in high yields with excellent ee's. It is noteworthy that the asymmetric allylic amination with hydroxylamine hydrochloride as a nitrogen source has been achieved with 95% ee for the first time. Importantly, the terminal olefin moieties proved to be essential for the observed high activity and selectivity. Further application of this ligand class in other transition-metal-catalyzed asymmetric reactions is underway in our laboratory.

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