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Synthesis of novel ferrocenylphosphine–amidine ligands and their application in Pd-catalyzed asymmetric allylic alkylation

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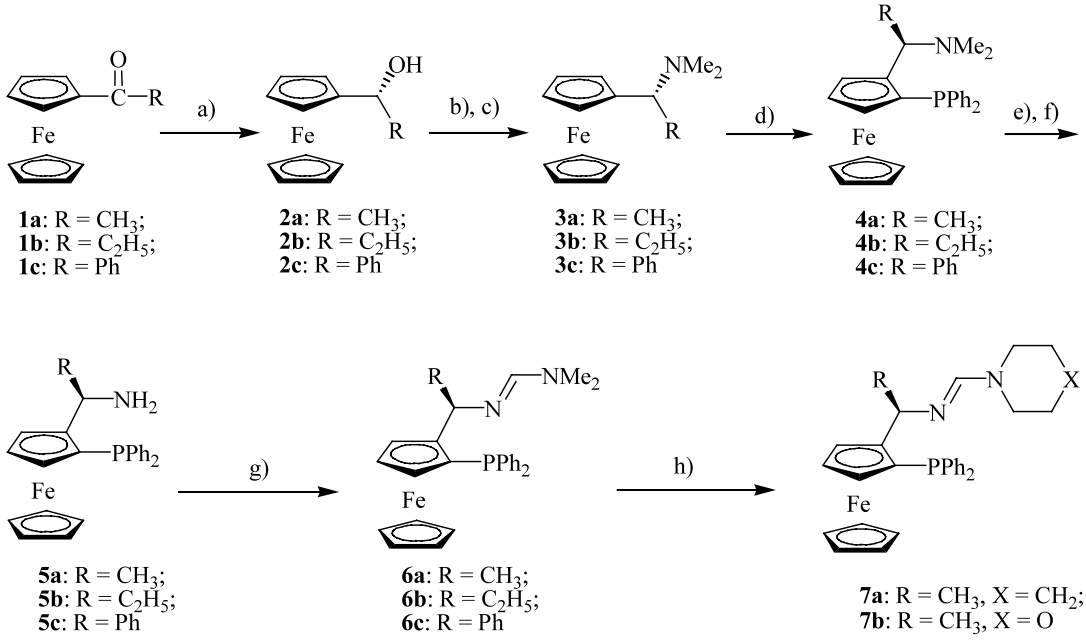
Abstract—A family of novel ferrocenylphosphine–amidine ligands derived from (*R*)-(*S*)-PPFNH$_2$-R **5** was applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl acetate **8a** or pivalate **8b** with dimethyl malonate. Up to 94% e.e. was achieved when ligand **6b** was used.

Since the pioneering work of Ugi and co-workers on the preparation and the resolution of *N*,*N*-dimethyl-1-ferrocenylethylamine three decades ago,[1] a great number of chiral ferrocene derivatives have been prepared, which mainly utilize the highly diastereoselective *ortho*-lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine and its analogues followed by introduction of an appropriate electrophile.[2] The further structural modification of these ferrocenyl compounds is straightforward due to the fact that nucleophilic substitution reactions on the ferrocenylmethyl position are easily carried out and proceed with retention of configuration on the stereo-



Scheme 1. *Reagents and conditions*: (a) (*S*)-5,5-diphenyl-2-methyl-3,4-propan-1,3,2-oxazaborolidine, BH_3SMe_2, THF, 0°C; (b) Ac_2O/pyridine, rt; (c) $HNMe_2/CH_3CN$; (d) *n*-BuLi/Et_2O, $ClPPh_2$; (e) Ac_2O, 100°C; (f) NH_3/CH_3CN, 80°C; (g) $Me_2NCH(OMe)_2$, rt, overnight; (h) piperidine or morpholine, reflux, overnight.

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genic carbon center. Through introduction of a desired functional group on the side chain according to the reaction type, modified ferrocenyl ligands can bring about high enantioselectivity in a variety of catalytic asymmetric reactions including hydrogenation, cross-coupling, cyclopropanation, allylic alkylation, aldol reactions, the addition of dialkylzinc to aldehydes and so on.[3] Herein we report the synthesis of a new type of ferrocenyl P,N ligand where an amidino group was introduced on the ferrocenylmethyl position and that high enantioselectivity can be obtained in palladium-catalyzed asymmetric allylic alkylation by using these ligands.

The synthesis of the ferrocenylphosphine-amidine ligands is shown in Scheme 1. The initial step in the synthesis involved the catalytic asymmetric reduction of ferrocenyl ketones **1** to the corresponding alcohols **2** with the *R*-configuration using Corey's chiral *B*-methylated oxazaborolidine complex, which has been reported to be a highly effective reagent for the reduction of several ferrocenyl ketones.[4] All the alcohols **2** were obtained with high yields (>90%) and very high enantioselectivity (>98% e.e.). Following sequential treatment with Ac_2O/pyridine and $HNMe_2/CH_3CN$, chiral alcohols **2** were transformed into the optically active tertiary amines **3** with complete configurational retention and in nearly quantitative yields.[5] The highly diastereoselective *ortho*-lithiation of amines **3** followed by treatment with $ClPPh_2$ gave phosphine–amine compounds (PPFA-R) **4**,[6] which have the (*R*,*S*)-configurations. After the reaction of the ferrocenylphosphine–amines **4** with Ac_2O at 100°C followed by treatment with a large excess of ammonia in methanol or acetonitrile in an autoclave at 80°C, the Me_2N group of **4** was substituted by an NH_2 group to form the key intermediate, (*R*)-(*S*)-PPFNH_2-R **5**.[7] Nucleophilic substitution on the ferrocenylmethyl position was demonstrated to proceed with retention of configuration at the stereogenic carbon center.[1c,6b] Treatment of **5** with *N*,*N*-dimethylformamide dimethyl acetal at room temperature gave nearly quantitative yields of amidines **6**.

The replacement of the dimethylamino group of the amidines **6** by other secondary amines was also examined.[8] The exchange reaction was carried out by simply mixing compound **6a** and a large excess of piperidine or morpholine in the presence of a catalytic amount of 10-camphorsulfonic acid at the corresponding reflux temperature to give the modified amidine ligands **7a** and **7b** in 56 and 88% yields, respectively. However, attempts to prepare the pyrrolidine modified amidine ligand failed and no amidine product was detected even after 24 h at reflux.

The chiral ferrocenylphosphine-amidine ligands were then applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl acetate or pivalate (**8a**, **8b**) with dimethyl malonate.[9] This reaction was carried out in the presence of 2.0 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5.0 mol% of the chiral ligand, a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of metal acetate.

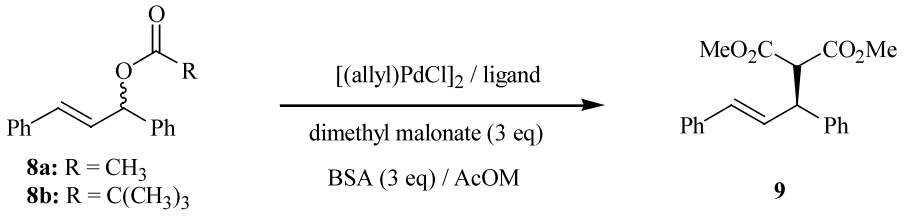
Optimization of the reaction conditions was first examined using ligand **6a**. The results are listed in Table 1. The reaction was initially carried out in toluene by using 1,3-diphenylprop-2-en-1-yl acetate **8a** as the substrate and KOAc as the base to afford the product in 87% e.e. (entry 1). Replacing **8a** with **8b** as the substrate, the enantioselectivity was significantly increased to 92% e.e. in 96% yield (entry 2). The effects of bases were also evaluated. Using sodium acetate or lithium acetate instead of potassium acetate, the product was obtained in 90 and 99% yields with 88 and 84% e.e's, respectively (entries 3 and 4). The use of cesium acetate gave comparable enantioselectivity (92% e.e.) (entry 5). The reduction of the amount of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ from 0.02 to 0.01 mol. equiv. caused a decrease in the reaction rate, and only a slight drop in enantioselectivity (entry 6). The effect of solvents on this reaction was also investigated and a remarkable variation in the catalytic activity due to the nature of the solvent was observed. CH_2Cl_2, which is usually a good solvent for Pd-catalyzed allylic alkylation, proved to be not so good for our catalytic system, and only a 65% e.e. with a 31% yield was obtained (entry 7). The reaction proceeded at a low reaction rate with only moderate enantioselectivity in THF (entry 8). When the reaction was carried out in benzene or Et_2O, somewhat lower enantioselectivities with a slightly increased yield were obtained (entries 9 and 10). Increasing the reaction temperature resulted in decreased enantioselectivity (entry 11) while lowering the reaction temperature decreased both the enantioselectivity and reactivity (entry 12). The configuration of the product **9** from these reactions was proved to be *S* by comparing the specific rotation with literature values.[10]

From the reaction condition screening experiments, we selected **8b** as substrate, toluene as solvent, and potassium acetate as base for the completion of the palladium-catalyzed asymmetric allylic alkylation with a family of ligands. The results are summarized in Table 2.

Of the ligands **6a**–**c** possessing a different substituent, R, on the stereogenic carbon center, the ligand **6b** (R = Et) exhibited the best enantioselectivity (94% e.e.) (entry 2), while the ligand **6c** (R = Ph) gave the product with an unexpectedly low yield and enantioselectivity (entry 3). For ligands **7a**–**b** with piperidine or morpholine in place of the dimethylamino group, both yield and enantioselectivity were decreased significantly (entries 4 and 5). It was noted that using PPFA–Et (**4b**) as the ligand for the asymmetric allylic alkylation resulted in a product with much lower enantioselectivity (entry 6).

In conclusion, we have prepared a family of novel ferrocenylphosphine–amidine ligands and applied them to palladium-catalyzed asymmetric allylic alkylation. When ligand **6b** was used, up to 94% e.e. was achieved. Further applications and modification of these ligands are in progress.

Table 1. Asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl acetate or pivalate (**8a**, **8b**) using phosphine–amidine ligand **6a**[a]



8a: R = CH_3
8b: R = $C(CH_3)_3$

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Entry	Substrate	Additive salt	Solvent	Temp. (°C)	Yield (%)[b]	e.e. (%)[c] (config.)[d]
1	**8a**	KOAc	Toluene	25	93	87 (*S*)
2	**8b**	KOAc	Toluene	25	96	92 (*S*)
3	**8b**	NaOAc	Toluene	25	90	88 (*S*)
4	**8b**	LiOAc	Toluene	25	99	84 (*S*)
5	**8b**	CsOAc	Toluene	25	94	92 (*S*)
6	**8b**	KOAc	Toluene	25	84	91 (*S*)[e]
7	**8b**	KOAc	CH_2Cl_2	25	31	65 (*S*)
8	**8b**	KOAc	THF	25	79	83 (*S*)
9	**8b**	KOAc	Benzene	25	98	90 (*S*)
10	**8b**	KOAc	Et_2O	25	99	88 (*S*)
11	**8b**	KOAc	Toluene	40	99	87 (*S*)
12	**8b**	KOAc	Toluene	10	83	79 (*S*)[f]

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 equiv.), **6a** (0.05 equiv.), dimethyl malonate (3.0 equiv.), BSA (3.0 equiv.) and a catalytic amount of additive salts.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralpak AD column (eluent: hexanes/2-propanol = 9/1, 1.0 mL/min).
[d] Determined by comparison of the specific rotations with the reported data, see: Ref. 10.
[e] The reaction was carried out using 1.0 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 2.5 mol% ligand.
[f] The reaction was carried out for 48 h.

Table 2. Asymmetric allylic alkylation of allylic pivalate **8b** using ligands **6**, **7** and **3**[a]

Entry	Ligand	Yield (%)[b]	e.e. (%)[c] (config.)[d]
1	**6a**	96	92 (*S*)
2	**6b**	98	94 (*S*)
3	**6c**	61	37 (*S*)
4	**7a**	91	81 (*S*)
5	**7b**	90	65 (*S*)
6	**3b**	84	20 (*S*)

[a] The reactions were carried out in toluene in the presence of 2.0 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5 mol% of chiral ligand, 3 equiv. of dimethyl malonate, 3 equiv. of BSA and a catalytic amount of KOAc at rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralpak AD column.
[d] Determined by comparison of the specific rotations with the reported data, see: Ref. 10.

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