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Easily accessible ferrocenyl N-P/S type ligands and their applications in asymmetric allylic substitutions

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Abstract—Easily accessible novel 1,2-disubstituted phosphinamidite-thioether ligands based on a ferrocene motif have been developed, and successfully applied for asymmetric allylic substitutions with excellent yields and enantioselectivities.

1. Introduction

The transition metal-catalyzed asymmetric allylic substitution has become a powerful tool for enantioselective carbon–carbon and carbon–heteroatom bond formation.[1] Several classes of chiral ligands, such as bisphosphines,[1] monodentate phosphines,[2] and P/N mixed-donor ligands[3–5] have been extensively studied and proven to be effective ligands for Pd-catalyzed asymmetric allylic substitution reactions. In the literature, few reports concern the use of chiral P/S mixed donors for metal-catalyzed asymmetric reactions[6–9] (Fig. 1). Seminal work by Evans et al. showed that O-P/S mixed-donor ligands could mediate Rh-catalyzed hydrogenation reactions and Pd-catalyzed allylic alkylation with enantioselectivity up to 98% ee.[7] Recent works by Carretero et al. also revealed that several P/S ligands were effective for Pd-catalyzed allylic substitution reactions,[8] ring opening of oxa- and aza-bicyclic alkenes,[9,12] aza Diels–Alder reactions,[10] and 1,3-dipolar cycloaddition of azomethine ylides.[11]

Ferrocene-based chiral phosphines have found important applications for metal-catalyzed asymmetric reactions.[13] Recently, we developed chelating ferrocenyl phosphine-phosphinites **5**, phosphine-phosphoramidites **6**, and phosphine-phosphites **7**. These have been successfully applied for Rh-catalyzed hydrogenation of dehydro-α-amino acid derivatives to give hydrogenated product with excellent enantiopurity.[14] Further to these efforts, we herein report that bidendate ferrocenyl phosphinamidite-thioether ligands, such as **2**, are promising ligands for asymmetric catalysis. The results of their application in asymmetric allylic alkylation and amination will be described.

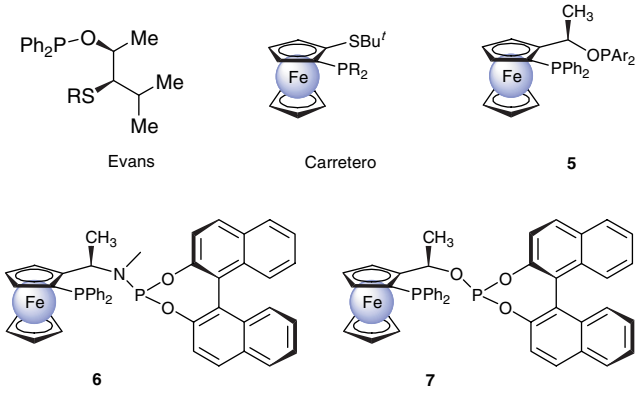

Figure 1.

2. Results and discussion

Scheme 1 depicts the synthetic route for ferrocenyl phosphinamidite-thioether ligands **2**. Starting from the

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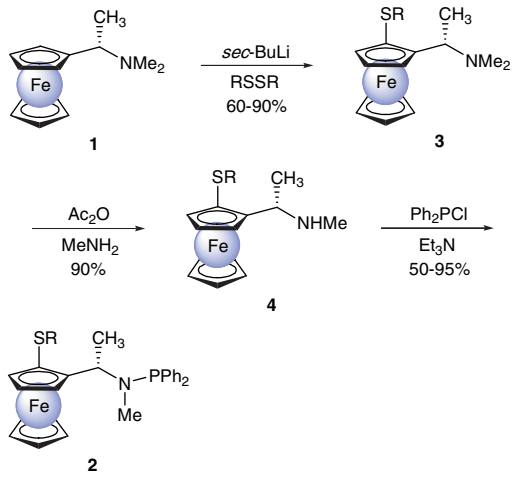
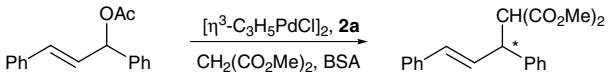


Scheme 1. Synthesis of the ferrocenyl N-P/S ligands **2**.

commercially available chiral Ugi's amine,[15] diastereoselective *ortho*-lithiation using *sec*-BuLi/Et_2O, followed by quenching with disulfides (R = Et, ^{t}Bu, Ph) afforded the 1,2-disubstituted ferrocenyl amines **3a**–**c** in 60–90% yields.[16] Treatment of **3** with Ac_2O and methylamine furnished the ferrocenyl methylamine **4** in >90% yield. The ferrocenylamine was then converted to the phosphinamidite **2** (50–95% yield) by phosphinylation using Et_3N and Ph_2PCl.[17]

When 1,3-diphenyl-2-propenyl acetate (0.5 M solution) was treated with dimethyl malonate (3 equiv) in toluene containing LiOAc as an additive (2 mol %), BSA (3 equiv), [Pd(η^3-C_3H_5)Cl]$_2$ (2 mol %) and (S,R_p)-FerroNPS-Et **2a** (4.2 mol %) at room temperature, the alkylated product was produced in >99% conversion and 87.9% ee based on chiral HPLC analysis (Table 1, entry 1). For the asymmetric substitution of 1,3-diphenyl-2-propenyl acetate, using NaOAc or KOAc as an additive did not result in better enantioselectivity (ca. 86% ee; entries 2 and 3). Herein, $Zn(OAc)_2$ was found to be the best additive; up to 90.2% ee was attained for the allylic substitution reaction (entry 4).

Table 1. Pd-catalyzed asymmetric allylic alkylation using (S,R_p)-FerroNPS-Et **2a** as a chiral ligand with an addition of metal acetate as an additive in various solvents[a]



Entry	Additive	Solvent	Time (h)	Conv. (%)[b]	ee (%)[c]
1	LiOAc	THF	12	>99	87.9 (*R*)
2	NaOAc			>99	86.6 (*R*)
3	KOAc			>99	86 (*R*)
4	$Zn(OAc)_2$			>99	90.2 (*R*)
5		CH_2Cl_2		>99	88.6 (*R*)
6		CH_3CN		>99	86.1 (*R*)
7		Toluene		>99	91.8 (*R*)

[a] Reaction conditions: [Pd(η^3-C_3H_5)Cl]$_2$ (2 mol %), ligand **2** (4.2 mol %), dimethyl malonate (3.0 equiv), BSA (3.0 equiv), additive (2.0 mol %), and 0.5 M of concentration, room temperature.
[b] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] The % ee value was determined by HPLC on a Chiralpak AD column (1.0 mL/min, *n*-Hex/^{i}PrOH = 95:5).

The effect of solvent for the Pd-**2a** catalyzed allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate was also investigated. As shown in Table 1, CH_2Cl_2 and CH_3CN are effective solvents for the allylic substitution reaction, and enantioselectivities of 88.6% and 86.1% ee were observed, respectively (entries 5 and 6). The best result (91.8% ee) was achieved when toluene was employed as solvent (entry 7).

Under the optimized reaction conditions: [Pd(η^3-C_3H_5)Cl]$_2$ (2 mol %); **2** (4.2 mol %), dimethyl malonate (3.0 equiv), BSA (3.0 equiv), and $Zn(OAc)_2$ (2.0 mol %) in toluene at room temperature, the effectiveness of other ferrocenyl phosphinamidites was tested using 1,3-diphenyl-2-propenyl acetate as substrate. Our results in Table 2 show that **2b** and **2c** bearing bulky R groups (^{t}Bu and Ph) are effective ligands for the Pd-catalyzed allylic substitution using diethyl malonate with ca. 93% ee being attained. Apparently, the bulkier thioether groups would necessitate longer reaction time (up to 120 min) albeit with improved enantioselectivities.

Table 2. A study of influence of the thioether group of (S,R_p)-FerroNPS ligands **2** on Pd-catalyzed AAA reaction[a]

Entry	Ligand	Concn (M)	Time (min)	Yield (%)[b]	ee (%)[c]
1	**2a** (R = Et)	0.5	45	97	91.8 (*R*)
2	**2b** (R = ^{t}Bu)		90	94	92.7 (*R*)
3	**2c** (R = Ph)		120	94	93.5 (*R*)

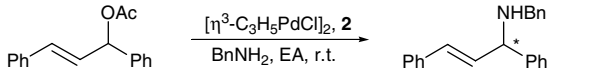
[a] Reaction conditions: [Pd(η^3-C_3H_5)Cl]$_2$ (2 mol %), ligand **2** (4.2 mol %), dimethyl malonate (3.0 equiv), BSA (3.0 equiv), $Zn(OAc)_2$ (2.0 mol %), and toluene as solvent at room temperature.
[b] Isolated yield.
[c] The % ee value was determined by HPLC on a Chiralpak AD (1.0 mL/min, *n*-Hex/^{i}PrOH = 95:5).

Having achieved enantioselective C–C bond formation using the Pd-**2a** catalyzed allylic substitution reaction, we also evaluated the ferrocenyl phosphinamidite ligands for analogous C–N bond formation. Treatment of 1,3-diphenyl-2-propenyl acetate (0.25 M) with benzylamine (3 equiv) in ethyl acetate containing [Pd(η^3-C_3H_5)Cl]$_2$ (2 mol %) and (S,R_p)-FerroNPS-Et **2a** (4.2 mol %) at room temperature, afforded the product allyl amine in 98% yield and 89.1% ee. Similarly, other ferrocenyl ligand derivatives **2b** and **2c** were also found to effect the allylic amine substitutions with enantioselectivities of 91.5% and 81.7% ee, respectively (Table 3).

3. Conclusion

In conclusion, we have successfully developed a new class of easily accessible ferrocene-based 1,2-disubstituted phosphinamidite-thioether ligands derived from Ugi's amine. These ferrocenyl P/S ligands have been employed for Pd-catalyzed asymmetric allylic alkylation

Table 3. The results of Pd-catalyzed asymmetric allylic amination using (S,R_p)-FerroNPS **2** as chiral ligand[a]



Entry	Ligand	Concn (M)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	0.25	3.5	98	89.1 (*S*)
2	**2b**	0.1 (THF)	48	86	91.5 (*S*)
3	**2c**	0.1	75	92	81.7 (*S*)

[a] Reaction conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %), ligand 2 (4.2 mol %), benzylamine (3.0 equiv), and EA as solvent at room temperature.

[b] Isolated yield.

[c] The % ee value was determined by HPLC on an OJ-H column (0.4 mL/min, *n*-Hex/^{i}PrOH = 85:15).

and amination, and excellent enantioselectivities and chemical yields were observed. Further investigation of other catalytic asymmetric reactions with these ferrocenyl N-P/S ligands is currently underway.

Acknowledgments

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