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A new type of ferrocene-based phosphine-*tert*-butylsulfinamide ligand: synthesis and application in asymmetric catalysis†

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A new type of ferrocene-based phosphine-*tert*-butylsulfinamide ligand has been synthesized and applied to the enantioselective formation of C–C and C–N bonds. The palladium complex derived from ligand **4a** was an efficient catalyst in asymmetric allylic substitution of several substrate types. Enantioselectivites with the difficult substrate 3-acetoxycyclohexene of up to 91% ee are achieved.

Chiral ligands have been considered one of the most important topics in asymmetric catalysis over the last three decades owing to their fruitful applications in asymmetric synthesis.[1] Among the thousands of chiral ligands prepared, bidentate ligands have become the most powerful tool in metal-catalyzed asymmetric processes since chelation provides the rigidity required to firmly allocate the chiral information around the metal center. Usually, the chirality of most bidentate ligands resides in the carbon backbone. However, some have a chiral phosphorus or sulfur center, and few have both a chiral scaffold and a chiral phosphorus or sulfur center. The ligands with chirality at the metal-coordinating atom, which bring the chiral information into the closest possible proximity to the catalytic center, might increase enantioselectivities of the catalytic transformations that the catalyst is mediating. Indeed, P-stereogenic bidentate diphosphine ligands are extremely proficient in asymmetric transformations.[2] However, the synthesis of chiral-phosphorus ligands is often complex and difficult. In contrast, the preparation of chiral sulfur compounds is more convenient and several chiral sulfoxides and sulfinamides are commercially available.[3] Pioneered by Ellman,[4] both enantiomers *tert*-butylsulfinamide is now available in large amounts and is used as a sacrificial chiral auxiliary in a wide range of synthetic processes.[5] The ease of synthesis, stability, resident chirality, and potential for metal coordination of the S, N and O atoms of *N*-*tert*-butanesulfinamides also provides excellent opportunities for the development of *N*-sulfinyl-based ligands for asymmetric catalysis.[6]

However, the ligands containing a sulfinamide moiety are rare.[7] Verdaguer reported ligand **1** for the intermolecular asymmetric Pauson–Khand reaction and ligand **2** for asymmetric hydrogenation (Fig. 1).[8] These ligands coordinate readily to rhodium, palladium and other metals to give either P,O or P,S bidentate coordination.[9] Recently, ligand **3** was developed and applied in the Pd-catalyzed asymmetric allylic alkylation by Bolm.[10] Very recently, Zhang described Ming-Phos for the enantioselective gold-catalyzed cycloaddition reaction of 2-(1-alkynyl)-alk-2-en-1-ones with nitrones.[11] As a part of our continuous research on the development of ferrocene-based chiral ligands and catalysts,[12] we are interested in exploring the potential of ferrocene-based bidentate ligands containing *tert*-butylsulfinamide moiety. Herein, we describe the synthesis of ferrocene-based phosphine-*tert*-butylsulfinamide ligands **4** and the preliminary results of their palladium complexes catalyzed asymmetric allylic substitution reaction.

Phosphine-*tert*-butylsulfinamide **4** was easily synthesized from (*R*)-Ugi's amine **5** in three steps (Scheme 1). Highly diastereoselective *ortho*-lithiation of **5** followed by treatment with $ClPR_2$ gave compound **6**, which was transformed into aminophosphine **7** by reaction with Ac_2O, and then ammonolysis with a large excess of ammonia or amine.[13] Ligand **4a–g** were obtained by sulfinylation of the lithium salts of **7** (formed *in situ* by deprotonation of **7** with *n*-BuLi) using an enantiopure *tert*-butanethiosulfinate. These ligands were characterized by ^1H NMR, ^{13}C NMR, ^{31}P NMR and mass spectrometry.

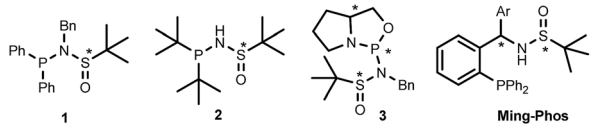

Fig. 1 Known phosphine-*tert*-butylsulfinamide ligands.

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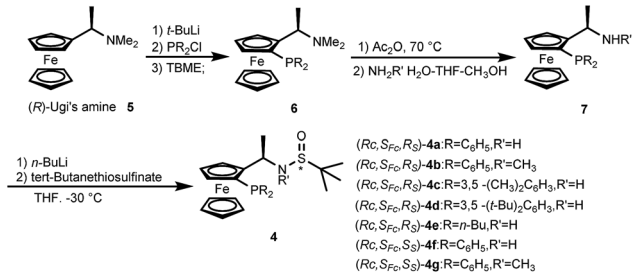


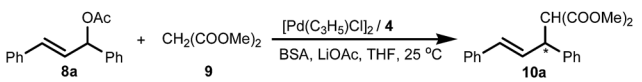
Scheme 1 Synthesis of ligand **4**.

We first tested the ligands in the Pd-catalyzed asymmetric allylic alkylation of racemic (*E*)-1,3-diphenylallyl acetate **8a** with dimethyl malonate **9** as a model reaction using standard conditions (Table 1). The results indicated that the chiralities of ferrocenyl moiety in the ligands play the decisive role in the Pd-catalyzed asymmetric allylic alkylation, giving (*R*)-**10a** (Table 1, entries 1–6). While the carbon-centred chirality and the planar chirality of ferrocene scaffold are the main governing factors, the sulfur-centred chirality of sulfinamide moiety is also important, and (R_C,S_{Fc},R_S)-**4** are the ligands with the matched chiralities (entry 1 *vs.* 6).

Notably, when replacement of NH of sulfinamide moiety with *N*-Me, both the activity and enantioselectivity decreased dramatically, suggesting that a sterically bulky substituent is disfavoured or a hydrogen-bonding donor is essential for the stereoinduction (Table 1, entries 1 *vs.* 2, 6 *vs.* 7). With regard to the effect of the P-substituents, the aryl groups were highly beneficial in terms of enantioselectivity and catalytic activities (Table 1, entries 1, 3, 4 *vs.* 5). But the bulky aryl groups had a deleterious effect on enantioselectivity (Table 1, entries 1 *vs.* 3, 4).

To further improve the chemical yield and enantioselectivity, we optimized the reaction conditions. The effect of solvent, reaction temperature, base and additives on the catalytic activity and enantioselectivity were investigated using **4a** as the ligand. As shown in Table 2, the solvent was observed to play a crucial role, and THF proved to be superior.

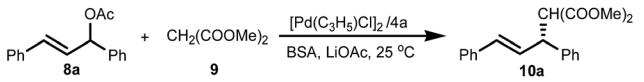
Table 1 Screening of the ligands in asymmetric allylic alkylation[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**4a**	65	77(*R*)
2	**4b**	34	5(*R*)
3	**4c**	65	67(*R*)
4	**4d**	52	71(*R*)
5	**4e**	35	52(*R*)
6	**4f**	75	27(*R*)
7	**4g**	36	9(*S*)

[a] The reaction was conducted with *rac*-(*E*)-1,3-diphenylallyl acetate **8a** (0.4 mmol), dimethyl malonate **9** (1.2 mmol) $[Pd(C_3H_5)Cl]_2$ (0.008 mmol), ligand **4** (0.024 mmol), BSA (1.2 mmol), LiOAc (0.034 mmol) in THF at 25 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis using a chiral column (Chiralcel AD-H column, hexane/i-propanol = 80 : 20). Absolute configuration was assigned by comparing the optical rotation values with those reported in the literature.

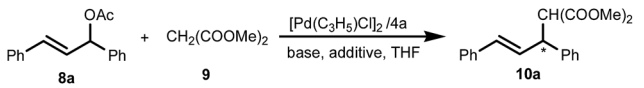
Table 2 The effect of solvents on the asymmetric allylic alkylation using ligand **4a**[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	63	49
2	THF	65	77
3	Toluene	73	55
4	$ClCH_2CH_2Cl$	66	73
5	Dioxane	63	65
6	Et_2O	29	55
7	DMF	72	72
8	CH_3CN	55	41

[a] The reaction was conducted with *rac*-(*E*)-1,3-diphenylallyl acetate **8a** (0.4 mmol), dimethyl malonate **9** (1.2 mmol) $[Pd(C_3H_5)Cl]_2$ (0.008 mmol), **4a** (0.024 mmol), BSA (1.2 mmol), LiOAc (0.034 mmol) in solvent at 25 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis using a chiral column (Chiralcel AD-H column, hexane/i-propanol = 80 : 20).

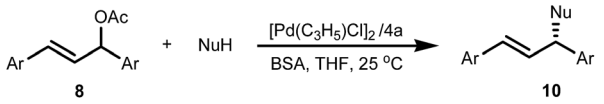
Table 3 Further optimization of reaction conditions[a]



Entry	Base	Additive (mol%)	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	None	None	25	15	43(*R*)
2	*n*-BuLi	None	25	77	11(*R*)
3	NaH	None	25	65	12(*S*)
4	KOH	None	25	70	33(*S*)
5	Cs_2CO_3	None	25	59	29(*S*)
6	K_2CO_3	None	25	40	*rac*
7	BSA	LiOAc (9)	25	70	77(*R*)
8	BSA	LiOAc (6)	25	69	81(*R*)
9	BSA	LiOAc (3)	25	66	82(*R*)
10	BSA	NaOAc (9)	25	60	71(*R*)
11	BSA	KOAc (9)	25	62	51(*R*)
12	BSA	CsOAc (9)	25	45	67(*R*)
13	BSA	AgOAc (9)	25	55	74(*R*)
14	BSA	None	25	60	89(*R*)
15	BSA	None	40	64	84(*R*)
16	BSA	None	0	30	75(*R*)

[a] The reaction was conducted with *rac*-(*E*)-1,3-diphenylallyl acetate **8a** (0.4 mmol), dimethyl malonate **9** (1.2 mmol), $[Pd(C_3H_5)Cl]_2$ (0.008 mmol), **4a** (0.024 mmol), base (1.2 mmol), additive in THF 25 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis using a chiral column (Chiralcel AD-H column, hexane/i-propanol = 80 : 20). The absolute configuration was determined by comparing the specific rotation with a literature value.

Table 4 Scope of asymmetric allylic alkylation using ligand **4a**[a]



Entry	Ar	NuH	Yield[b] (%)	ee[c] (%)
1	C_6H_5 (**8a**)	$CH_2(COOMe)_2$	62	89
2	C_6H_5 (**8a**)	$CH_2(COOEt)_2$	65	88
3	C_6H_5 (**8a**)	$CH(CH_3)(COOMe)_2$	55	76
4	C_6H_5 (**8a**)	Acetylacetone	41	29
5	4-MeC_6H_4 (**8b**)	$CH_2(COOMe)_2$	55	62
6	4-ClC_6H_4 (**8c**)	$CH_2(COOMe)_2$	59	78

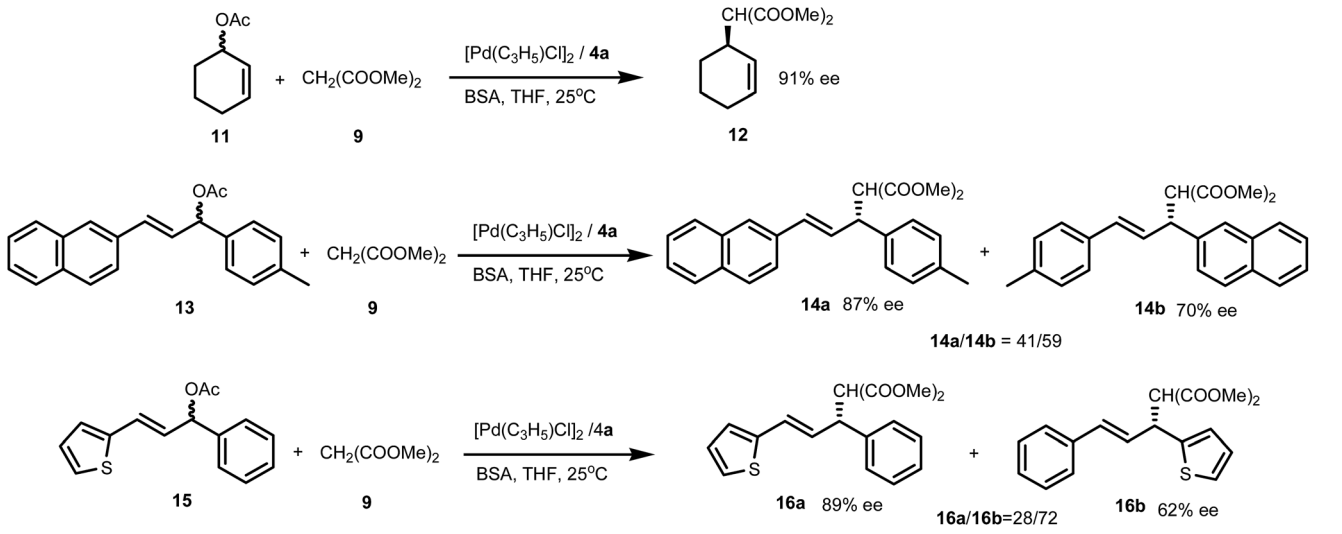
[a] The reaction was conducted with *rac*-(*E*)-1,3-diarylallyl acetate **8** (0.4 mmol), NuH (1.2 mmol), $[Pd(C_3H_5)Cl]_2$ (0.008 mmol), **4a** (0.024 mmol), BSA (1.2 mmol) in solvent at 25 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis using a chiral column. (Entry 1: Chiralcel AD-H column, hexane/i-propanol = 80 : 20; entry 2: Chiralcel AD-H column, hexane/i-propanol = 93 : 7; entry 3: Chiralcel AD-H + AD-H column, hexane/i-propanol = 99 : 1; entry 4: Chiralcel AD-H column, hexane/i-propanol = 99 : 1; entry 5: Chiralcel AD-H column, hexane/i-propanol = 94 : 6; entry 6: Chiralcel AD-H column, hexane/i-propanol = 85 : 15).

It is noteworthy that the base has a pronounced influence on the catalytic performance (Table 3). The reaction proceeded quickly in the presence of strong bases, such as *n*-BuLi, NaH, or KOH, but the enantioselectivities were poor (Table 4, entries 2–4). When N,O-bis(trimethylsilyl)acetamide (BSA) was used as a base and a catalytic amount of salt as an additive,[14] enantioselectivities were improved significantly, while chemical yield decreased slightly (Table 3, entries 7–13). Interestingly, the highest enantioselectivity were achieved in 89% ee when BSA was used as a base in the absence of salt additives (Table 3, entry 14). Examination of the temperature effects revealed that 25 °C was optimal for the reaction (Table 3, entries 14 *vs.* 15, 16).

Encouraged by these results, our attention focused on investigating the scope of this catalytic system, various nucleophiles and substrates were screened. When $CH_2(CO_2Et)_2$ was used as the nucleophile instead of $CH_2(CO_2Me)_2$, the yield and enantioselectivity were maintained (Table 4, entry 2). But bulky nucleophile decreased the ee value of product **10** (Table 4, entry 3). Employing acetylacetone as nucleophile led to a significant drop in the enantioselectivity and chemical yield (Table 4, entry 4). On the other hand, diarylallyl acetate **8** bearing either the electron-donating or electron-withdrawing substituents on the aromatic ring underwent the reaction smoothly to give the desired products in good levels of enantioselectivities (Table 4, entries 5, 6).

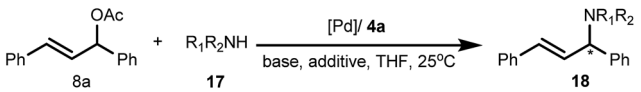
To further study the potential of ligand **4a**, we also tested it in the asymmetric allylic alkylation of more challenging unhindered cyclic substrate **11** and unsymmetrical disubstituted linear substrates **13**, **15** (Scheme 2). To the best of our knowledge, few catalysts were efficient for asymmetric allylic alkylation of these substrates.[10,15] Importantly, high enantioselectivity (91% ee) was obtained in the allylic alkylation of difficult substrate **11**. For substrates **13** and **15**, the catalytic system showed dissatisfactory regioselectivity, but ee value of each isomer were moderate to high.

Having achieved enantioselective C–C bond formation, we also evaluated the chiral phosphine-*tert*-butylsulfinamide ligands in a C–N bond formation reaction. In the presence of ligand **4**, *rac*-(*E*)-1,3-diphenylallyl acetate **8a** was reacted with benzylamine under conditions similar to those of alkylation described above. Ligand **4a** and THF were also the best ligand and solvent, respectively. Similarly, BSA was the best base, but 15 mol% NaOAc was necessary for the best enantioselectivity (Table 5, entry 10). Screening of various palladium precursors indicated that $[Pd_2(dba)_3]CHCl_3$ was superior to $[Pd(C_3H_5)Cl]_2$ and $Pd_2(dba)_3$ (Table 5, entries 6 *vs.* 2, 4). With the reaction conditions optimized, other amines were also examined in this reaction. Moderate enantioselectivities were also obtained (Table 5, entries 11, 12).



Scheme 2 Asymmetric allylic alkylation of challenging substrates using ligand **4a**.

Table 5 Pd-catalyzed asymmetric allylic aminations using ligand **4a**[a]



Entry	Pd	R_1R_2NH	Base	Additive (mol%)	Yield[b] (%)	ee[c] (%)
1	$Pd_2(dba)_3$	Benzylamine	None	None	47	9(*R*)
2	$Pd_2(dba)_3$	Benzylamine	BSA	NaOAc (9)	31	*rac*
3	$[Pd(C_3H_5)Cl]_2$	Benzylamine	None	None	53	37(*R*)
4	$[Pd(C_3H_5)Cl]_2$	Benzylamine	BSA	NaOAc (9)	40	13(*S*)
5	$[Pd_2(dba)_3]CHCl_3$	Benzylamine	None	None	32	17(*R*)
6	$[Pd_2(dba)_3]CHCl_3$	Benzylamine	BSA	NaOAc (9)	43	82(*R*)
7	$[Pd_2(dba)_3]CHCl_3$	Benzylamine	BSA	LiOAc (9)	40	43(*R*)
8	$[Pd_2(dba)_3]CHCl_3$	Benzylamine	BSA	KOAc (9)	55	49(*R*)
9	$[Pd_2(dba)_3]CHCl_3$	Benzylamine	BSA	NaOAc (6)	40	65(*R*)
10	$[Pd_2(dba)_3]CHCl_3$	Benzylamine	BSA	NaOAc (15)	45	87(*R*)
11	$[Pd_2(dba)_3]CHCl_3$	Morpholine	BSA	NaOAc (15)	72	55(*R*)
12	$[Pd_2(dba)_3]CHCl_3$	*p*-Methoxy aniline	BSA	NaOAc (15)	16	74(*R*)

[a] The reaction was conducted with *rac*-(*E*)-1,3-diphenylallyl acetate **8a** (0.4 mmol), R_1R_2NH **17** (1.2 mmol), palladium precursor (0.008 mmol), **4a** (0.024 mmol), BSA (1.2 mmol) and additive in solvent at 25 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis using a chiral column. (Entries 1–10: Chiralcel AD-H column, hexane/i-propanol = 90 : 10; entry11: Chiralcel OD-H column, hexane/i-propanol = 90 : 10; entry12: Chiralcel OD-H column, hexane/i-propanol = 90 : 10). Absolute configuration was assigned by comparing the optical rotation values with those reported in the literature.

A plausible mechanism for the asymmetric induction with chiral phosphine-*tert*-butylsulfinamide ligand **4a** was proposed on the basis of the stereochemical results obtained. A seven-membered chelated π-allylpalladium complex would be formed by coordination of the phosphine and the sulfinamide to palladium. The W-type π-allyl complex **19** would be more stable than the M-type complex **20**, which has repulsive interaction between the two phenyl groups in substrate **8** with the *t*-butyl group on the S atom and two phenyl groups on the P atom. The nucleophile would preferentially attack the allylic terminal carbon *trans* to phosphorus affording (*R*)-isomer (Fig. 2). Similarly, the transition state **21** would be more stable than **22** to provide (*R*)-isomer for the cyclic substrate **11**.

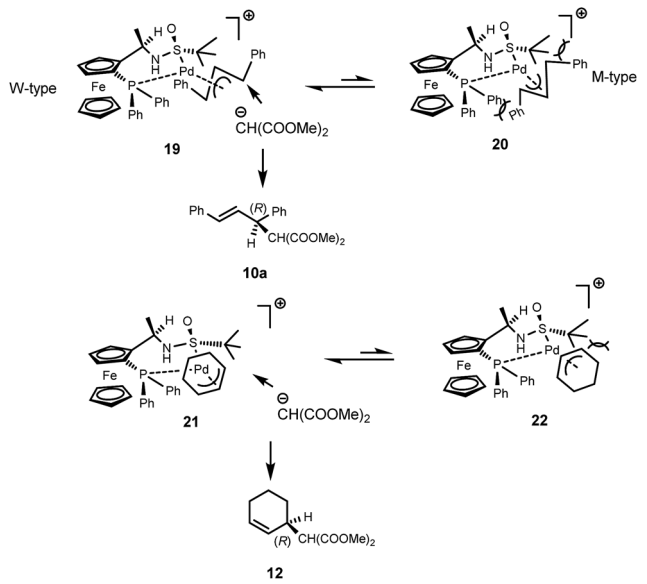


Fig. 2 Plausible transition state for the allylic alkylation using ligand **4a**.

Conclusions

A new type of ferrocene-based phosphine-*tert*-butylsulfinamide ligands have been synthesized and applied to the enantioselective formation of C–C and C–N bond. The palladium complex derived from ligand **4a** was an efficient catalyst in asymmetric allylic alkylation of symmetrical disubstituted linear substrates (up to 89% ee), unsymmetrical disubstituted linear substrates (up to 89% ee) and unhindered cyclic substrate (up to 91% ee). For the asymmetric allylic amination, good stereoselectivities were also obtained (up to 87% ee). Further studies focusing on the modification of the ligands and applications in other catalytic reactions are currently underway in our laboratory.

Acknowledgements

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