Asymmetric Catalysis

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Palladium–($S_{,p}R$)-FerroNPS-Catalyzed Asymmetric Allylic Etherification: Electronic Effect of Nonconjugated Substituents on Benzylic Alcohols on Enantioselectivity**

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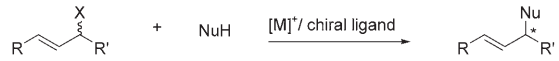
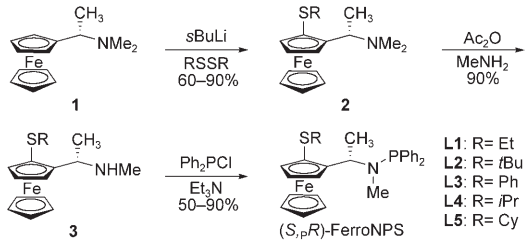
The development of efficient methods for enantioselective synthesis remains at the center of modern-day organic chemistry, as such methods have many important applications, from the total synthesis of natural products[1] to the preparation of analogues of lead compounds in the pharmaceutical industry. The ability to prepare compounds by a carbon–heteroatom bond-forming process from a common intermediate is of great significance to the drug-discovery process. In particular, the stereoselective construction of an ether linkage adjacent to a stereogenic carbon center is important for the synthesis of many biologically active targets.[2] However, this process requires further development. For example, the conventional formation of a C–O bond by a direct S_N2-type O alkylation (Williamson ether synthesis) is sometimes impractical synthetically owing to the strong basicity of the alkoxide anion, which may be incompatible with other functional groups present in the system. It would clearly be advantageous to construct C–O bonds in a catalytic manner under mild conditions rather than through traditional organic synthesis. Enantioselective transition-metal-catalyzed allylic substitution[3] has become one of the most powerful tools for the generation of carbon–carbon and carbon–heteroatom bonds with various nucleophiles. The development of the synthesis of chiral compounds containing carbon–carbon or carbon–nitrogen bonds from racemic allylic electrophiles has been documented well [Eq. (1)]. In contrast, the enantioselective allylic substitution of unactivated allylic acetates with relatively hard oxygen nucleophiles has only been studied sporadically.[4]



X = leaving group
NuH = malonate, amine

Enantioselective iridium-catalyzed[5] allylic substitution reactions with a broad range of phenols (relatively soft nucleophiles) have been reported. They generally proceed with good selectivity with monodentate phosphoramidite ligands. Asymmetric palladium-catalyzed C–O bond formation between phenols and various allylic substrates to give ethers has also been studied.[6–8] In a separate study, Kim and Lee demonstrated that the palladium-catalyzed etherification of allylic acetates with aliphatic alcohols afforded achiral ethers by using zinc alkoxides generated from diethyl zinc and an alcohol.[9] Haight et al. reported an asymmetric variant of the protocol described by Kim and Lee. However, the more reactive allylic carbonate and harsher conditions (reflux in THF) were required, and the observed enantioselectivities were rather poor.[7c] Spurred by these findings, we undertook the challenge to develop an efficient etherification process that can proceed under mild reaction conditions with good stereoselectivity. Herein, we report a general palladium-catalyzed asymmetric allylic substitution of racemic 1,3-diphenyl-2-propenyl acetate with aliphatic alcohols in the presence of newly developed fine-tunable phosphinamidite–thioether ligands with a ferrocene motif (Scheme 1) to generate chiral ethers in high yields with excellent enantioselectivities.

We recently developed a convenient synthesis of the versatile Ugi amine[10] in optically pure form with a view to using it as a building block for the development of novel and highly modular chiral ligands.[11] The chiral intermediate aminothioether **2** of FerroNPS was synthesized by diastereoselective *ortho* lithiation of the Ugi amine by treatment with *s*BuLi in Et_2O followed by quenching with the appropriate



Scheme 1. Preparation of ($S_{,p}R$)-FerroNPS ligands. Cy = cyclohexyl.

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[**] We thank the University Grants Committee Area of Excellence Scheme (AoE/P-10/01) and The Hong Kong Polytechnic University (Area of Strategic Development) for financial support of this study. FerroNPS refers to a series of P,S ligands with a ferrocenyl motif and an amine linkage.

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disulfide (Scheme 1). The treatment of **2** with hot acetic anhydride and an aqueous solution of methylamine gave the ferrocenyl methylamine **3**. A simple phosphanylation step with Ph_2PCl under basic conditions then afforded the enantiomerically pure ferrocenyl-scaffolded ligands **L1**–**L5**. This route has the potential to offer ready access to a large array of ligands with modular steric and electronic properties at both the thioether and the phosphanyl moieties.[12] In fact, a small modification at the thioether group of FerroNPS ligands leads to improved reactivity or enantioselectivity.[13]

The absolute configuration of **L2** was determined unambiguously to be $S_{,p}R$ by single-crystal X-ray crystallography (Figure 1). The ORTEP representation of the structure shows

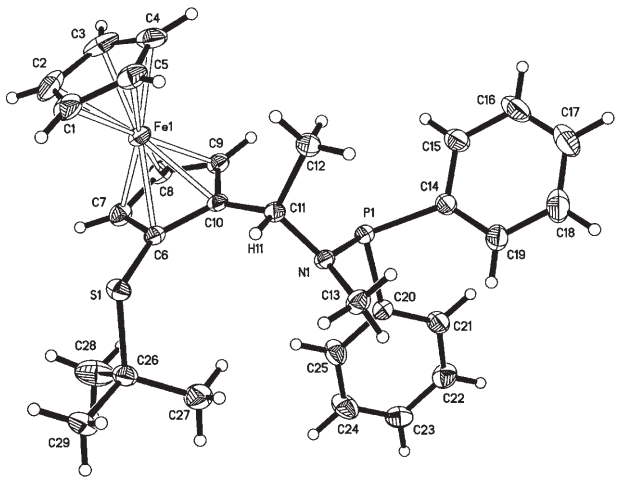
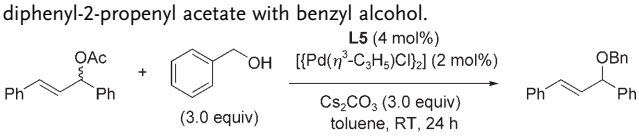


Figure 1. X-ray structure of **L2** (ORTEP view; thermal ellipsoids at 30 % probability).

that the sulfur and stereogenic carbon atoms lie in the plane of the Cp ligand C6–C10. In the free ligand, the *tert*-butyl group and the methyl group are oriented such that they point away from each other, presumably to minimize steric congestion. The even bulkier diphenylphosphanyl moiety is located further away from the thioether group.

We first tested the reactivity of chiral ($S_{,p}R$)-FerroNPS-Cy (**L5**) in conjunction with a palladium precatalyst in the asymmetric allylic etherification (AAE; Table 1). Benzyl alcohol and racemic 1,3-diphenyl-2-propenyl acetate were chosen as model substrates and treated with allylpalladium dimer and Cs_2CO_3 in CH_2Cl_2 at room temperature. The desired ether product was obtained in 91 % yield with 89 % *ee* (Table 1, entry 1). Other bases that are commonly used for allylic substitution, such as *N*,*O*-bis(trimethylsilyl)acetamide (BSA),[14] were tested, and the use of Cs_2CO_3 was found to be crucial to the success of the reaction. The polarity of the solvent was not found to have a significant effect on product formation or enantioselectivity. Although the highest enantioselectivity was observed when THF was used as the solvent, the best result in terms of the yield of the product (93 %) was observed with toluene, along with only a minor decrease in enantioselectivity (90.7 % *ee*; Table 1, entries 2 and 3). To investigate the efficiency of other ligands in the family, we studied the influence of the thioether substituent

Table 1: Initial screening of the asymmetric allylic etherification of 1,3-diphenyl-2-propenyl acetate with benzyl alcohol.



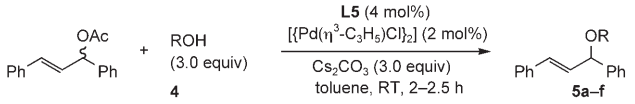
Entry	L (mol %)	Solvent	Yield [%][a]	*ee* [%][b]
1[c]	**L5** (4)	CH_2Cl_2	91	88.9 (*S*)
2[c]	**L5** (4)	THF	83	91.0 (*S*)
3[c]	**L5** (4)	toluene	93	90.7 (*S*)
4[c]	**L5** (4)	CH_3CN	83	88.5 (*S*)
5	**L1** (4)	toluene	93	81.8 (*S*)
6	**L2** (4)	toluene	92	87.8 (*S*)
7	**L3** (4)	toluene	92	86.0 (*S*)
8	**L4** (4)	toluene	93	88.6 (*S*)
9	**L5** (4)	toluene	96	91.5 (*S*)
10[d]	**L5** (4)	toluene	95	95.5 (*S*)

[a] Yield of the isolated product after chromatography. [b] The *ee* value was determined by HPLC on a chiral stationary phase. The absolute configuration was established by correlation with literature data.[7c] [c] Cs_2CO_3 was weighed in air rather than under nitrogen in a dry box. [d] The reaction was performed at 0 °C for 17 h. Bn = benzyl.

(Table 1, entries 5–9). Thioether ligands with a *tert*-butyl, phenyl, or isopropyl group showed somewhat lower enantioselectivities (Table 1, entries 6–8) than that of **L5**. Higher enantioselectivity was observed when the reaction temperature was lowered to 0 °C (Table 1, entry 10).

To test the effectiveness of the Pd–**L5** catalytic system, we examined a series of substituted benzylic alcohols (Table 2).

Table 2: Enantioselective allylic etherification of 1,3-diphenyl-2-propenyl acetate with 4-substituted benzylic alcohols under the catalysis of a Pd–**L5** complex.



Entry	R	**4**, **5**	*t* [h]	Yield [%][a]	*ee* [%][b]
1	CH_2Ph	**a**	2	98	91.6 (*S*)
2	$CH_2C_6H_4$-*p*-OMe	**b**	2.5	94	94.5
3	$CH_2C_6H_4$-*p*-Me	**c**	2.5	94	93.4
4	$CH_2C_6H_4$-*p*-F	**d**	2.5	95	89.6
5	$CH_2C_6H_4$-*p*-Cl	**e**	2.5	92	88.8
6	$CH_2C_6H_4$-*p*-CF_3	**f**	2.5	93	77.4

[a] Yield of the isolated product after chromatography. [b] The *ee* value was determined by HPLC on a chiral stationary phase.

In general, the reaction proceeded smoothly under the optimized conditions to afford the desired product in excellent yield. We observed an intriguing relationship between the enantioselectivity of the reaction and the electronic nature of the substituted benzylic alcohol. Higher enantioselectivity was observed when the benzylic alcohol contained an electron-rich *para* substituent, and the selectivity diminished gradually as the substituent became more electron deficient.

The aromatic electronic effect can be represented by a Hammett relationship.[15] The Hammett plot of log(ratio of

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enantiomers) against σ_p shows a linear free-energy relationship (Figure 2; $\rho = -0.77$, $r = 0.975$) between enantioselectivity and the electronic character of the substituent. This electronic effect appears to be significant in this nonconjugated system. To the best of our knowledge, such an electronic effect of a nonconjugated substrate on enantioselectivity has not been reported to date. This observation may provide a useful tool for predicting the enantioselectivity of asymmetric allylic substitution when substituted benzylic alcohols are used as nucleophiles. It is complementary to the well-known electronic effect on stereoselectivity of either a substrate or a ligand composed of conjugated aromatic systems.[16]

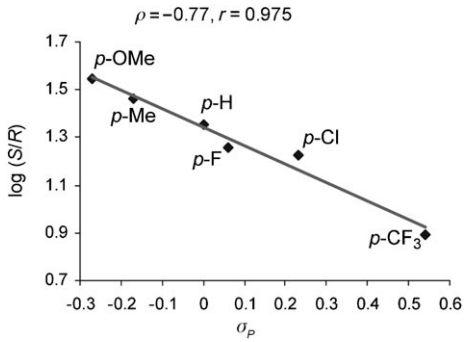
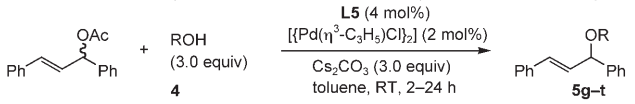


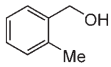
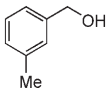
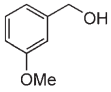
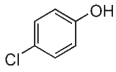
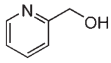
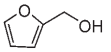
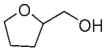
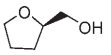
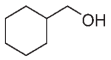
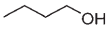
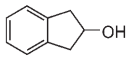
Figure 2. Hammett plot for the Pd-catalyzed asymmetric allylic etherification with **L5** (product: 77–94% *ee*).

To further extend the scope of the reaction with respect to the alcohol substrate, *ortho*- and *meta*-substituted benzylic alcohols (Table 3, entries 1–3) were applied successfully in the AAE to give the ether products in high yield with high enantioselectivity. The Pd–**L5** catalytic system was also found to be compatible with heterocycles (Table 3, entries 5–8). The reaction of the potentially problematic substrate 2-pyridinemethanol, the nitrogen atom of which might coordinate competitively to the metal center of the catalyst, proceeded smoothly to give the corresponding ether, although the reaction time had to be extended to 21 h (Table 3, entry 5). Primary aliphatic alcohols, such as allyl alcohol and *n*-butanol, underwent the desired reaction to provide the product in excellent yield with high enantioselectivity (Table 3, entries 10 and 11). The use of the secondary alcohol **4r** led to the desired product in good yield with 93.4% *ee*, whereas only moderate conversion was observed with the less strained secondary alcohol **4s** under the same reaction conditions (Table 3, entries 12 and 13). *tert*-Butanol was found to be a poor substrate for this transformation.

In summary, we have reported the synthesis of the new ferrocenyl ligand **L5** and derivatives thereof. This scaffold has several beneficial features, including ease of accessibility and the possibility of fine-tuning the steric and electronic properties of the donor atoms. The corresponding palladium complexes of the FerroNPS ligands **L1**–**L5** were employed effectively in the palladium-catalyzed asymmetric allylic etherification of racemic 1,3-diphenyl-2-propenyl acetate with a wide array of aliphatic alcohols with good to excellent enantioselectivities. To the best of our knowledge, we have described the broadest substrate scope reported to date for AAE. We also observed the first example of an electronic effect of a nonconjugated substituent on a benzylic alcohol on the enantioselectivity of a reaction. This finding may aid in predicting the enantioselectivity of certain reactions. Further mechanistic investigations into AAE and the application of N–P,S ligands with a ferrocene-motif to other enantioselective reactions are under way.

Table 3: Enantioselective allylic etherification of 1,3-diphenyl-2-propenyl acetate with a variety of alcohols under the catalysis of a Pd–**L5** complex.



Entry	ROH	4, 5	*t* [h]	Yield [%][a]	*ee* [%][b]
1		**g**	2.5	87	94.7
2		**h**	2.5	88	93.8
3		**i**	2.5	94	92.6
4		**j**	24	33[c]	n.d.
5		**k**	21	71	82.9
6		**l**	2.5	96	89.4
7		**m**	21	82	93[d]
8		**n**	21	78	93.2[d]
9		**o**	20	96	93.5
10		**p**	3	98	92.7
11		**q**	6	98	94.1
12		**r**	3	94	93.4
13		**s**	29	58 (73)[e]	96.2
14		**t**	24	trace	n.d.

[a] Yield of the isolated product after chromatography. [b] The *ee* value was determined by HPLC on a chiral stationary phase. [c] The ether product decomposed significantly on a TLC plate. [d] The *de* value is given instead of an *ee* value. [e] The conversion (given in brackets) was determined by ^{1}H NMR spectroscopy. n.d. = not determined.

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