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A versatile route to planar chiral diphosphines and their application in the asymmetric Heck reaction

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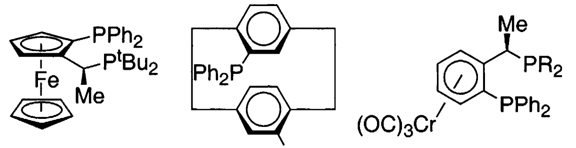
Abstract—Five chiral monophosphines and nine planar chiral diphosphines have been synthesised in good yield and enantiopurity by a modular approach; the diphosphines have been reacted with $Pd(OAc)_2$ and screened for activity in the asymmetric Heck reaction. © 2003 Elsevier Science Ltd. All rights reserved.

Planar chiral ligands such as the ferrocene 'Josiphos', **1**,[1] or the [2.2]paracyclophane 'Phanephos', **2**,[2] have proven to be very successful in asymmetric catalysis. The potential of planar chiral ligands based on (arene)tricarbonylchromium(0) complexes has also been recognised,[3] and, as a result, there has been a significant increase in activity in this area in the last two to three years leading to the successful application of planar chiral (arene)tricarbonylchromium(0) complexes as catalyst ligands in a diverse range of reactions.[4]

In view of the important role played by chelating diphosphines in transition metal catalysis, it is of interest to develop routes to diphosphine derivatives of (arene)tricarbonylchromium(0) complexes and to test their effectiveness in asymmetric reactions. To date complexes with generalised structure **3** (Fig. 1) have been synthesised and tested in palladium-catalysed allylic alkylations,[5] palladium-catalysed allylic sulfonations,[6] rhodium-catalysed hydrogenations[6] and iridium-catalysed hydroaminations.[6] Routes to complexes **3** rely on α-methylbenzyl alcohol[5] or α-methylbenzylamine[6] as their source of chirality, and the nucleophilic displacement of oxygen[5] or nitrogen[6] substituents by phosphines (either directly[5] or indirectly[6]).



1 **2** **3**

Figure 1.

We recently reported a new approach to planar chiral (arene)tricarbonylchromium(0) complexes that uses a chiral-base mediated reaction to introduce asymmetry.[7,8] We now wish to report that we have used this chemistry to generate a range of novel planar chiral diphosphine ligands, and that we have started to probe the utility of these diphosphines in asymmetric catalysis with an investigation of the asymmetric Heck reaction. To the best of our knowledge, this is the first time that (arene)tricarbonylchromium(0) based ligands have been used in the Heck reaction.

Our route to the diphosphines is depicted in Scheme 1. It starts with the reaction of readily synthesised tricarbonyl(4-*tert*-butylbenzyl alcohol)chromium(0) **4** with an alcohol R^1OH under acid catalysis to give the ether complex **5** (Step 1). Asymmetry is introduced into complex **5** by its treatment with a chiral base, the diamine precursor of which is readily available from (*R*)- or (*S*)-α-methylbenzylamine in two steps,[9] and an electrophilic quench with R^2Cl to give **6** (Step 2). Finally a diastereoselective *ortho*-lithiation of **6** followed by an electrophilic quench with R^3Cl gives the planar chiral complex **7** (Step 3).

We have previously demonstrated that the chemistry outlined in Scheme 1 can be used to synthesise a diphosphine in good yield and high enantiopurity by the synthesis of **7a** ($R^1 = Me$, $R^2 = PPh_2$, $R^3 = PPh_2$) (Table 1, entry 1).[8] During the study of the Heck

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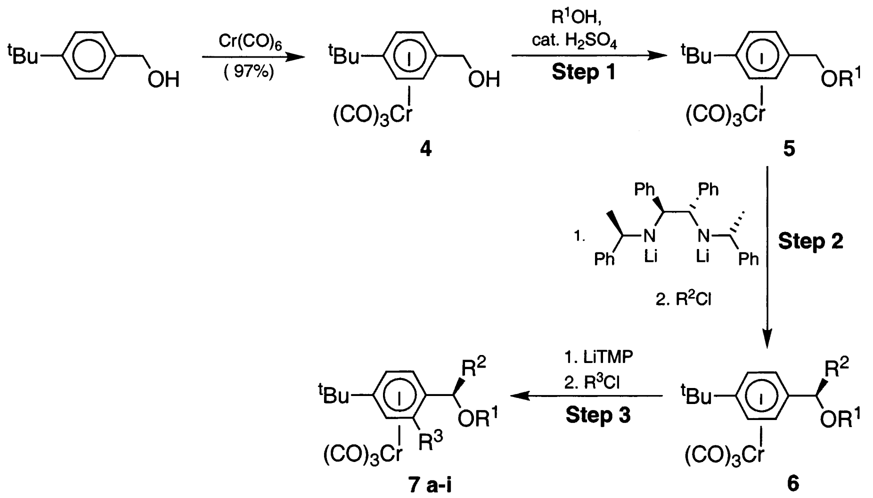
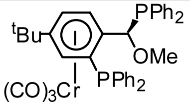
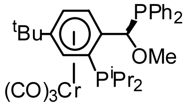
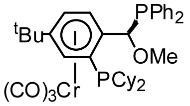
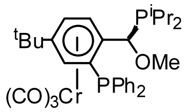
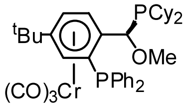
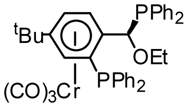
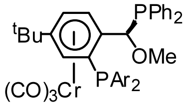
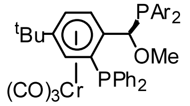
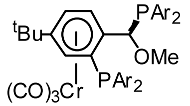


Scheme 1.

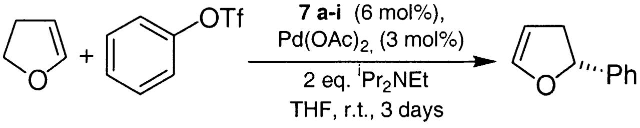
Table 1.

Entry	Complex		Step 1		Step 2			Step 3		
			R^1	Yield (%)	R^2	Yield (%)	Ee (%)	R^3	Yield (%)	Ee (%)
1.		**7a**	Me	94	PPh$_2$	90	97	PPh$_2$	98	97
2.		**7b**	Me	94	PPh$_2$	90	97	P^{i}Pr$_2$	56	97
3.		**7c**	Me	94	PPh$_2$	90	97	PCy$_2$	55	97
4.		**7d**	Me	94	P^{i}Pr$_2$	90	97	PPh$_2$	61	96
5.		**7e**	Me	94	PCy$_2$	95	96	PPh$_2$	73	97
6.		**7f**	Et	84	PPh$_2$	90	97	PPh$_2$	85	84
7.		**7g**	Me	94	PPh$_2$	90	96	PAr$_2$[a]	83	95
8.		**7h**	Me	94	PAr$_2$[a]	91	96	PPh$_2$	86	95
9.		**7i**	Me	94	PAr$_2$[a]	91	96	PAr$_2$[a]	84	96

[a] Ar = 3,5-dimethylphenyl

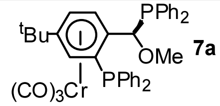
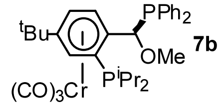
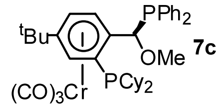
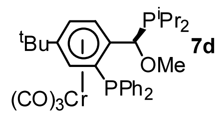
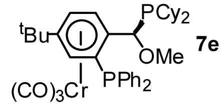
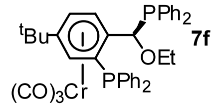
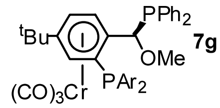
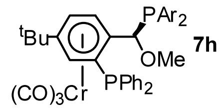
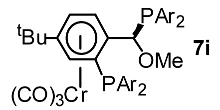
reaction described below, in addition to **7a** we required samples of the novel diphosphines **7b–i** in order to test the effect of changing the groups represented by R^1, R^2 and R^3. The syntheses of complexes **7b–i** proceeded smoothly producing the intermediate monophosphines and the required diphosphines in generally high yields and enantiopurities (Scheme 2, Table 1, entries 2–9).

In 1991, Hayashi reported the first example of an intermolecular asymmetric Heck reaction.[10] It involved the phenylation of 2,3-dihydrofuran with phenyl triflate-catalysed by a $Pd(OAc)_2$/(*R*)-BINAP combination.



Scheme 2.

Table 2.

Entry	Complex	Yield (%)	Ee (%)*
1.	 **7a**	60	60
2.	 **7b**	No reaction	
3.	 **7c**	No reaction	
4.	 **7d**	55	42
5.	 **7e**	58	62
6.	 **7f**	No reaction	
7.	 **7g**	52	48
8.	 **7h**	54	50
9.	 **7i**	20	62

* Ees were determined by HPLC using a Chiracel OD-H column and 99.6:0.4 hexane:isopropanol as eluent with a flow rate of 500µl/min.

Although several other substrates were examined, much of the investigation into the mechanism and reaction parameters focused around the phenylation of 2,3-dihydrofuran, and thus this has become one of the benchmark reactions for the intermolecular Heck reaction. It was thus decided to determine whether or not the planar chiral diphosphines **7a–i** would form complexes that would catalyse the asymmetric Heck reaction using this reaction. Standard conditions were employed to preform the catalyst, perform the coupling reaction, and assess the yield and enantiopurity of the product.[11,12]

The results of the Heck reactions are shown in Table 2. Using the bis-diphenylphosphine complex **7a**, (*R*)-2-phenyl-2,3-dihydrofuran **8** was generated in 60% yield and 60% e.e. (Table 2, entry 1). Encouraged by this result, we decided to determine the effect of varying (i) the phosphine substituent on the aromatic ring, (ii) the phosphine substituent on the benzylic carbon and (iii) the ether substituent R^1. Changing the diphenylphosphine aromatic substituent to a dialkylphosphine substituent resulted in no reaction taking place (Table 2, entries 2 and 3), whilst, in contrast, changing the benzylic diphenylphosphine substituent to a dialkylphosphine substituent maintained catalyst activity, but gave no significant improvement in selectivity. (Table 2, entries 4 and 5). Changing the methyl ether to an ethyl ether resulted in no reaction (Table 2, entry 6), possibly because coordination of the two phosphines to the palladium leads to an unfavourable reaction between the ethoxy group and the tricarbonylchromium(0) rotor. Finally, the diphenylphosphine substituents of **7a** were replaced with di(3,5-dimethylphenyl)phosphine groups. This led, however, to either reduced selectivity (Table 2, entries 7 and 8) or reduced activity (Table 2, entry 9).

In conclusion, we have synthesised nine planar chiral diphosphines incorporating an (arene)tricarbonylchromium(0) unit by an efficient modular approach, and we have demonstrated for the first time that this class of ligand is active in the asymmetric Heck reaction. Although the enantioselectivities observed in the Heck reaction are modest, we believe that they are sufficiently encouraging to stimulate further investigations into the use of these diphosphines in other areas of asymmetric catalysis.

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12. A mixture of the phosphine (6 mol%), $Pd(OAc)_2$ (3 mol%) and THF (5 cm^3) was stirred at room temperature under a nitrogen atmosphere for 30 min. 2,3-Dihydrofuran (3 mmol), phenyl triflate (1 mmol) and *N*,*N*-diisopropylethylamine (2 mmol) were added and the reaction was stirred at room temperature for a further 3 days. Diethyl ether (10 cm^3) was added to the product mixture and the resulting mixture filtered through a pad of Celite. The filtrate was carefully concentrated in vacuo to give the crude product which was purified by column chromatography (SiO_2; 4:1, hexane:diethyl ether) to give 2-phenyl-2,3-dihydrofuran **8** as a colourless oil. The configuration of the major enantiomer of **8** was identified as *R* by comparison of the optical rotation of the product with literature data.[11]