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Subtle effects of ligand backbone on the efficiency of iron-diphos catalysed Negishi cross-coupling reactions

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Substantially more active iron catalysts for a standard Negishi cross-coupling are obtained when bis(diarylphosphino)thiophenes are employed in place of the benchmark ligand bis(diphenylphosphino)benzene. The thiophene ligands have the advantages of ease of synthesis and ready modification.

There is great interest in the application of organoiron catalysts to reactions that have traditionally employed platinum group metal catalysts because of the potential advantages of lower expense and lower toxicity.[1] Iron complexes have been found to be competent catalysts for the coupling of Grignard reagents with alkyl halides.[2] Bedford *et al.*[3] and Nakamura *et al.*[4] have reported Fe-diphos catalysed Negishi couplings and recently Fe-monophos catalysed Negishi couplings.[5] From the screening of several diphosphines, it has been established that Fe-catalysts for cross-coupling are sensitive to the ligand backbone and the P-substituents; in fact, the only diphos ligands that have produced significant activity and selectivity in Negishi couplings are derivatives of dpbz and, to a lesser degree, dppp and dppe (Chart 1).[6] The mechanisms of Fe-catalysed cross-coupling reactions have been the subject of much discussion and an explanation of the ligand effects has yet to emerge.[7]

In view of the range of catalytic processes to which dpbz and its derivatives have been applied,[8] it is surprising that diphosphinothiophenes have attracted little attention as ligands for catalysis,[9] despite their ready synthesis and facility for modification compared to their dpbz analogues. Furthermore, thiophenes have garnered great interest because they are readily polymerised to give materials that have a raft of applications in the fields of organic LEDs and photovoltaics.[10] Here the synthesis of a range of chelating diphosphinothiophenes is reported and it is shown that the Fe complexes of these ligands can match or outperform the best Fe-diphos catalysts in terms of activity and selectivity currently available for the coupling of benzyl halides with diarylzinc reagents.
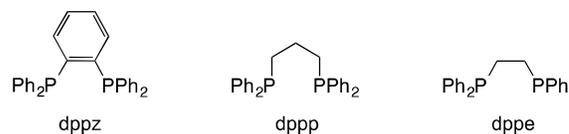
Chart 1

The routes to the nine new bis(diarylphosphino)thiophenes reported here are given in Schemes 1 and 2. The isomeric L_{1a} and L_{2a} were prepared as air-stable solids from the corresponding dibromothiophenes. The *o*-tolyl and *m*-xylyl derivatives L_{1b} and L_{1c} were made similarly from the corresponding chlorophosphines. The unsymmetrical ligand L_{1d} was prepared in high purity by the sequence of lithiation-phosphination steps shown in Scheme 1. The introduction of Me_3Si groups at the remaining unsubstituted thiophene sites in L_{1a} and L_{2a} to give $L_{1a'}$ and $L_{2a'}$ was readily achieved by the sequence of lithiation-silylation steps shown in Schemes 1 and 2. The ease of silylation of the backbone in the diphosphinothiophene contrasts with the inherent difficulty of functionalisation of diphosphinobenzenes.[11]

The ligands L_1 and L_2 have been tested in the Fe-catalysed Negishi coupling reaction shown in Scheme 3 and the results are given in Table 1. The three products are the desired cross-coupled product **A** and the two homocoupled species **B** and **C**. The yields of **A** and **B** have been calculated with respect to 3-methoxybenzyl halide since some of the zinc reagent is consumed in the formation of the catalyst; the byproduct **C** partly arises from the initial reduction of the Fe(II).

The 3-methoxybenzyl bromide is the standard substrate[3a] for screening the Fe-diphos catalyzed Negishi coupling. From the results in Table 1, the following can be concluded. (1) The activity and selectivity of the catalysts derived from L_{1a} (Entry

2) and **L₂ₐ** (Entry 7) are at least as good as those for the benchmark dpbz-Fe catalyst (Entry 1). (2) Efficient catalysts are also generated with the ligands containing one $SiMe_3$ group on the thiophene backbone, namely **L₁ₐ'** (Entry 5) and **L₂ₐ'** (Entry 8). (3) The catalysis is sensitive to the P-substituents: the *o*-tolyl groups in ligand **L₁ᵦ** (Entry 3) are deleterious to the

Scheme 1

Scheme 2

Scheme 3

catalysis whereas the xylyl groups in **L₁𝒸** (Entry 4) are not. (4) The mixed $PPh_2/P(o\text{-Tol})_2$ ligand **L₁𝒹** (Entry 5) appears to produce a catalyst whose performance lies between that of the symmetrical congeners **L₁ᵦ**/**L₁𝒸**.

The best performing ligands from the above reaction screen (**L₁ₐ**, **L₁𝒸** and **L₂ₐ**) have been compared against dpbz for the Negishi coupling with the more challenging 3-methoxybenzyl chloride (Scheme 3) and the results obtained are given in Table 1, Entries 9-14. It is clear that all four new ligands significantly outperformed the dpbz in this catalysis with **L₁𝒸** (Entry 12) giving a catalyst that gives quantitative conversion and >99.9% selectivity for the cross-coupled product. Remarkably, **L₁𝒸** gave quantitative conversion after 4 h when the catalysis was carried at ambient temperature (Entry 14).

The validity of these results was tested with control experiments in which the reactions were carried out under the

same conditions apart from: (i) no ligand was added (Entry 15); (ii) no $FeCl_2$ was added (Entries 16 and 17); (iii) $[PdCl_2(\mathbf{L_a})]$ was added in place of $FeCl_2$ / **Lₐ** (Entry 18). Only in the case of the $FeCl_2$ with no diphos (Entry 15) was some cross-coupling observed although selectivity was poor. The catalysis was also carried out with preformed $[FeCl_2(\mathbf{L_{1a}})_2]$ and the results

Table 1. Negishi cross-coupling catalysis[a]

Entry	Ligand	X	% Conv.	**A**	**B**	**C**
1	dpbz	Br	100	98	2	10
2	**L₁ₐ**	Br	100	98	2	6
3	**L₁ᵦ**	Br	69	56	13	20
4	**L₁𝒸**	Br	100	98	2	9
5	**L₁𝒹**	Br	98	83	15	19
6	**L₁ₐ'**	Br	100	98	2	12
7	**L₂ₐ**	Br	100	99	1	10
8	**L₂ₐ'**	Br	100	99	1	10
9	dpbz	Cl	76	76	0	8
10	**L₁ₐ**	Cl	98	98	0	6
11	**L₁ₐ'**	Cl	92	92	0	19
12	**L₁𝒸**	Cl	100	100	0	6
13	**L₂ₐ**	Cl	92	92	0	5
14[b]	**L₁𝒸**	Cl	100	100	0	10
15[c]	none	Cl	37	35	2	70
16[d]	**L₁ₐ**	Cl	0	0	0	2
17[d]	**L₁𝒸**	Cl	0	0	0	2
18[e]	**L₁ₐ**	Cl	6	0	6	15

a Yields determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. Catalyst pre-reduced[3d] and formed *in situ*. Reactions were run on a 0.5 mmol of substrate. L:Fe ratio, 2:1. X = Br: 45 °C, 4 h. X = Cl: 45 °C, 4 h. See ESI for details. *b* Conditions as described in footnote *a* except the reaction was carried out at ambient temperatures. *c* Conditions as described in footnote *a* but without addition of diphos ligand. *d* Conditions as described in footnote *a* but without addition of $FeCl_2$. *e* Conditions as described in footnote *a* but with addition of $[PdCl_2(\mathbf{L_a})]$ in place of $FeCl_2$ / **Lₐ**.
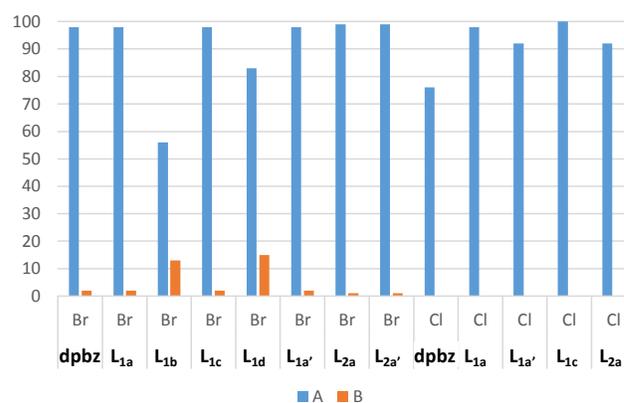
Figure 1 Plot of the conversions to products **A** and **B** from the Negishi cross-coupling shown in Scheme 3 as a function of ligand.

obtained were the same as when the catalyst was formed *in situ* (Entry 10).

In order to compare the relative rates of the dpbz-Fe catalyst with the highly efficient Fe/**L₁𝒸** catalyst, the coupling of 3-methoxybenzyl chloride was monitored by ^{1}H NMR spectroscopy as a function of time and the results are plotted in Fig. 2. It is evident from Fig. 2 that the reaction was 50%

complete at *ca.* 75 min for the dpbz system, at *ca.* 13 min for **L$_{1a}$**, and at < 2 min for the **L$_{1c}$** system. Estimates of the initial relative rates of conversion are thus 1:5:20 for dpbz : **L$_{1a}$** : **L$_{1c}$**.
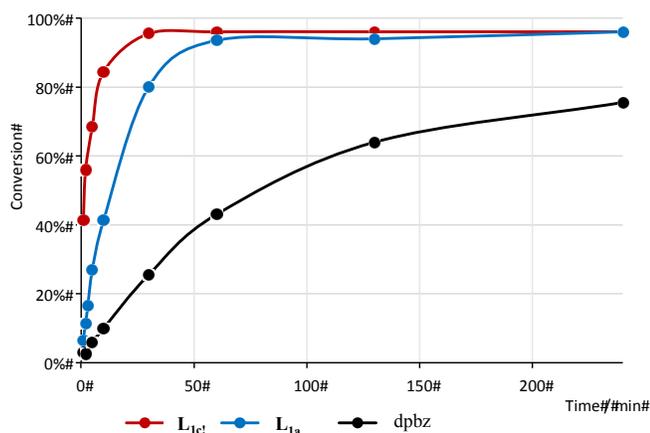
Figure 2. Conversion of 3-methoxybenzyl chloride with time for ligands **L$_{1a}$**, **L$_{1c}$** and dpbz. Aliquots of the reaction mixtures were quenched and conversions were determined from integration of the ^{1}H NMR signals for the benzylic CH$_2$ resonances for product **A** and 3-methoxybenzyl chloride. See the ESI for full details.

Conclusions

A new class of ligands for Fe-catalysed Negishi cross-coupling has been prepared featuring a thiophene backbone. The reactivity of the thiophene nucleus confers the advantages of ease and modularity of the synthesis of diphosphinothiophenes over their diphosphinobenzene analogues. In addition, it has been shown that the diphosphinothiophenes can produce Fe-catalysts that show significantly higher activity and selectivity than the dpbz analogues. Computational work is in progress that may shed light on the source of these ligand effects. In addition, thiophenes can be chemically or electrochemically polymerised to give conducting polymers and therefore the possibility of polymerising or co-polymerising the diphosphinothiophenes reported here is currently under investigation.

Notes and references

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Electronic Supplementary Information (ESI) available: synthesis and characterisation of the ligands and the method used for the catalytic runs. See DOI: 10.1039/c000000x/

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