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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 949–953

Modification of ligand properties of phosphine ligands for C–C and C–N bond-forming reactions

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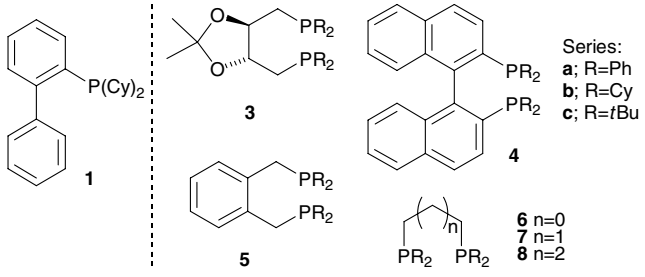
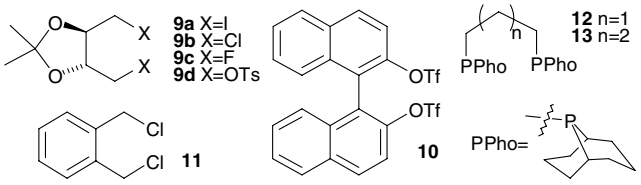
Received 6 October 2006; revised 27 November 2006; accepted 7 December 2006
Available online 26 December 2006

Abstract—A series of ligands have been prepared for use in Pd-catalysed coupling reactions to form C–C and C–N bonds; significant differences are exhibited by similar ligands containing different phosphorus substituents.

A large number of phosphine ligands have recently been reported for use in palladium-catalysed formation of C–N, C–O and C–C bonds.[1–7] The pattern of selectivity and activity, with respect to catalyst structure, is often very complex. Certain ligands, however, have emerged as being particularly effective at certain reactions. In particular, the very hindered monodonor phosphines of Buchwald and Hartwig, such as biaryl **1** and $P(tBu)_3$ **2** phosphines, are highly effective in the promotion of C–C[1,3] and C–N[2,4] bond formation, respectively.



In order to obtain a clearer idea of the factors which influence ligand activity in coupling reactions, we sought to prepare a series of derivatives of bidentate ligands containing well-established core structures. In particular, we chose to focus on the synthesis and comparative evaluation of diphenyl-, dicyclohexyl- and di(*t*-butyl)-phosphine derivatives of DIOP **3**, BINAP **4** and dibenzyl **5** phosphines in addition to the simple ethyl, propyl and butyl derivatives **6**–**8**, respectively.



The ligand selection was made on the basis of the popularity of the ligands and their structural diversity. Some of the ligands were commercially available and required no special preparative methods (**6a, 7a, 8a** and **5c**). Although some ligands in the DIOP series were available, we chose to prepare each of them through displacement reactions of the known halide precursors **9a**–**c** and the ditosylate **9d**.[8] Ligand **3a** was prepared in good yield (57% after three recrystallisations) upon reaction of diiodide **9a** with potassium diphenylphosphide. For the synthesis of **3b** and **3c**, however, it was found that the reaction of the lithium dialkylphosphide with difluoride **9c** represented a better approach.[9] Ligand **3b** was prepared in this manner using $LiPCy_2$ in dioxane over 48 h at 40 °C in a yield of 68% following recrystallisation of the CS_2 adduct from ethanol.[9a] The reaction of **9c** with $LiP(tBu)_2$ (dioxane, 24 h) gave **3c** in 56% yield after distillation.

Ligand **4a** was commercially available, but **4b** and **4c** were not. We prepared adequate samples of BINAP **4a**

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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.027

from the reaction between ditriflate **10** using the Monsanto method, in which a nickel(II) dichloride catalyst is used with Ph_2PCl and Zn dust.[10] The product was formed in 43% yield using this method, which requires careful control of the reaction temperature (110–120 °C range).

Ligand **4b** has been prepared by the reaction of a dilithiated binaphthyl with $Cy_2P(O)Cl$, followed by phosphine reduction,[11] which mirrors traditional approaches to BINAP and its derivatives.[12] However, we sought a more effective; one-step method from a resolved BINOL dimesylate. In the event, the Monsanto method,[10] using Cy_2PCl was not effective, however, a modified version of the Merck method[13] (using Cy_2PH) together with added zinc dust and DABCO gave **4b** in 34% yield after purification. This represents the first successful synthesis of this compound through a P–C bond formation from a ditriflate precursor. Despite this success, however, we were unable to prepare **4c**, which has never been reported. Although replacement of one triflate in **10** was successful using the modified Merck procedure, it was not possible to substitute both, presumably due to steric hindrance.

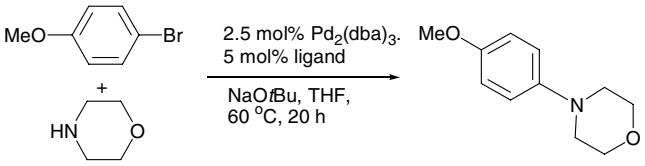
The synthesis of **5a** proved straightforward and the required ligand was isolated in 72% yield upon reaction of $KPPh_2$ with dichloride **11** in THF at rt. The synthesis of **5b** proved more elusive.[14] After some experimentation, the best results (48% yield) were obtained using the conditions of Lappert to generate the diGrignard reagent from 1,2-di(chloromethyl)benzene (Barbier-type method) followed by the reaction with $ClPCy_2$.[15]

The syntheses of **7b** and **8b** were achieved through the simple reaction of Cy_2PLi with an appropriate dihalide.[16] For the propyl bridged diphosphine, the use of 1,3-difluoropropane gave the best result (dioxane, 40 °C, 64% yield after distillation), whereas for the butyl analogue **8b**, the best result was obtained using dichlorobutane (dioxane 0 °C–rt, 54% after recrystallisation). The same sets of reaction conditions proved effective for the synthesis of **7c** and **8c** in yields of 62% and 73%, respectively, from tBu_2PLi (generated in situ from the hydride). Unfortunately, we were unable to prepare sufficient quantities of either **6b** or **6c** for characterisation and application to the coupling reactions below.

In addition to the ligands described above, we were also able to prepare the bis(phobyl)phosphines **12** and **13**, in both cases from PhoPLi and either 1,3-difluoropropane or 1,4-dichlorobutane respectively, in 57% and 55% yields. This provided two further hindered ligands for evaluation and comparison.[17]

With a diverse ligand set in hand, C–N bond formation (Scheme 1, Table 1) was first selected for a comparative investigation.[2,4,6] After initial screening using ligands **4a** and **5c**, the conditions indicated on the Scheme were selected. As can be seen, there was a dramatic difference in performance between the ligands.

It is immediately obvious that the best ligands for this application are the bis(*t*Bu) ligands, notably **3c** and **7c**.



Scheme 1.

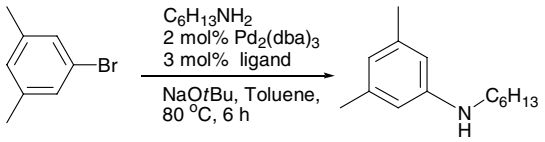
Table 1. Pd-Catalysed C–N bond formation (% conversion)

Ligand	T/h		
	2.5	5.5	20
3a	0	0	0
4a	50	50	50
5a	0	0	0
6a	0	0	0
7a	0	0	0
8a	0	<5	<5
3b	5	10	10
4b	9	24	50
5b	0	<5	6
7b	0	<5	8
8b	<5	<5	9
3c	95	95	98
5c	40	30	30
7c	70	95	98
8c	50	70	98
12	0	0	0
13	0	0	0

In addition, the *t*Bu-substituted diphosphine **8c** also performed well, although ligand **5c** was rather poor. Several of the less hindered ligands gave no conversion at all. BINAP, **4a**, performed well initially but did not catalyse the reaction to completion. These observations reflect the findings of previous researchers in this area, that is, that bulky ligands form good catalysts.[2,4] However, it is surprising that the phobyl-substituted ligands did not give better results. Ligands containing a 2-arylbenzene group have been reported to give excellent results, which were speculated to be due to the involvement of an interaction of the *ortho*-arene with the Pd metal. Although **5c** contains an arene ring in close proximity to the phosphines, it is probably not able to engage in a similar stabilising interaction as the resulting metallocycle will be too strained.

Similar results were obtained for the C–N bond formation using a primary amine and a less electron-rich arene (Scheme 2, Table 2).[2,4,6] In this case the pattern of results was rather different, and to some extent unexpected. Although BINAP has already been shown to be effective in this reaction,[6] its cyclohexyl analogue also proved to be a good ligand, and in addition, the *t*Bu propyl ligand **7c** was very effective. Homologue **8c** was somewhat less active, but still gave one of the best conversions out of all the ligands tested. These results indicate that a hindered ligand is favoured for this process, in accord with previous observations.

A study was also carried out on the C–C bond forming Suzuki reaction (Scheme 3, Table 3).[1,3] In parallel with



Scheme 2.

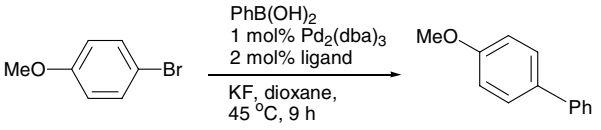
Table 2. Pd-Catalysed C–N bond formation (% conversion)

Ligand	T/h		
	2.0	4.0	6.0
3a	1	1	1
4a	96	100	100
5a	0	0	0
6a	0	0	6
7a	1	1	2
8a	8	10	17
3b	28	28	32
4b	94	96	100
5b	65	83	88
7b	18	15	43
8b	3	3	3
3c	24	60	33
5c	2	2	5
7c	100	100	100
8c	47	59	80
12	5	4	5
13	0	0	0

C–N bond formation, bulky, hindered, ligands have been shown to be particularly beneficial to this process. In the event, our *t*Bu-substituted ligands **3c**, **7c** and **8c** gave the best results, that is, the shortest reaction times and typically full conversions, for the reaction of an electron-rich bromide. Several other ligands were capable of effective catalysis, but none could match the performance of the *t*Bu substituted phosphines.

In the related reaction of an electron-poor reagent system, several of the ligands proved to be effective (Scheme 4, Table 4), presumably reflecting a more reactive system.[1,3] Again, however, the *t*Bu-substituted phosphine ligands[1,3] gave the product in full conversion in the shortest reaction times, as did triphenylphosphine.

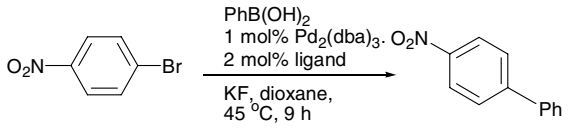
An investigation was carried out into the use of the ligands in Sonogashira reactions (Scheme 5, Tables 5 and 6).[18] Both an electron-rich and an electron-poor iodide were used as the substrates. In the synthesis of electron-rich **14**, the phenyl-substituted phosphines, with the exception of **5a**, gave excellent results; full conversion within 1 h. The Cy-substituted ligands were also effective, although the *t*Bu ligands were rather slower and the phobyl ligands ineffective. Ligands **3b** and **7b**



Scheme 3.

Table 3. Pd-Catalysed C–C bond formation (% conversion)

Ligand	T/h		
	3.0	6.0	9.0
3a	24	33	38
4a	35	41	47
5a	33	40	50
6a	13	7	19
7a	12	11	11
8a	25	24	22
3b	63	78	81
4b	45	71	79
5b	75	93	100
7b	48	53	57
8b	58	80	80
3c	100	100	100
5c	47	42	45
7c	100	100	100
8c	100	100	100
12	25	29	37
13	21	23	23
PPh_3	24	38	38

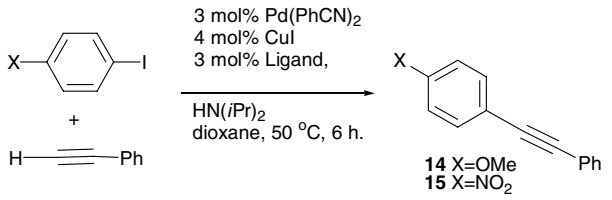


Scheme 4.

also gave full conversion within 1 h. In the case of electron-poor **15**, all of the *t*Bu and phenyl-substituted ligands proved to be the most effective, all giving full conversions within 6 h and most within 4 h. Cy-BINAP **4b** gave full conversion within 4 h but the other Cy-substituted ligands gave products in low conversions. The Pho-substituted ligands were again ineffective for this application. In previous studies, hindered phosphines such as $P(tBu)_3$ have given excellent results in this class of bond-forming reactions, particularly at very low

Table 4. Pd-Catalysed C–C bond formation (% conversion)

Ligand	T/h		
	3.0	6.0	9.0
3a	96	100	100
4a	97	100	100
5a	96	100	100
6a	55	66	78
7a	63	79	86
8a	68	80	89
3b	100	100	100
4b	66	81	95
5b	44	47	60
7b	100	100	100
8b	100	100	100
3c	100	100	100
5c	56	58	60
7c	100	100	100
8c	100	100	100
12	78	89	95
13	68	81	90
PPh_3	100	100	100



Scheme 5.

Table 5. Pd-Catalysed Sonogashira reaction to form **14** (% conversion)

Ligand	T/h		
	2.0	4.0	6.0
3a	100	100	100
4a	100	100	100
5a	<1	<1	<1
6a	—	—	—
7a	100	100	100
8a	100	100	100
3b	100	100	100
4b	65	85	92
5b	52	76	76
7b	100	100	100
8b	93	97	99
3c	100	100	100
5c	21	47	33
7c	75	83	90
8c	93	99	100
12	<1	<1	<1
13	0	0	0
PPh_3	100	100	100

catalyst loadings.[18] This study indicates that, at higher catalyst loadings, a greater range of ligands are compatible with the reaction.

In conclusion, we have described methods for a number of new diphosphines of value in organometallic catalysis of coupling reactions. The results show that relatively accessible ligands can be effective in coupling reactions, and that the structure of the ligand has a dramatic effect on its performance in the reactions investigated.

Table 6. Pd-Catalysed Sonogashira reaction to form **15** (% conversion)

Ligand	T/h		
	2.0	4.0	6.0
3a	79	100	100
4a	65	93	99
5a	93	97	100
6a	—	—	—
7a	94	100	100
8a	100	100	100
3b	1	2	5
4b	82	100	100
5b	0	0	0
7b	0	0	<1
8b	2	21	39
3c	100	100	100
5c	74	96	100
7c	100	100	100
8c	86	94	100
12	0	0	<1
13	0	0	0
PPh_3	100	100	100

Acknowledgements

We thank Rhodia Consumer Specialities Ltd for generous financial support of this project (to D.J.M.), the use of the EPSRC Chemical Database Service at Daresbury[19] and J. C. Bickerton of the Warwick MS service. We also acknowledge the generous gift of palladium reagents by Johnson-Matthey limited.

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