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Homogeneous Catalysis (1)

Copper-Catalyzed Arylation of Nucleophiles by Using Butadienylphosphines as Ligands: Mechanistic Insight

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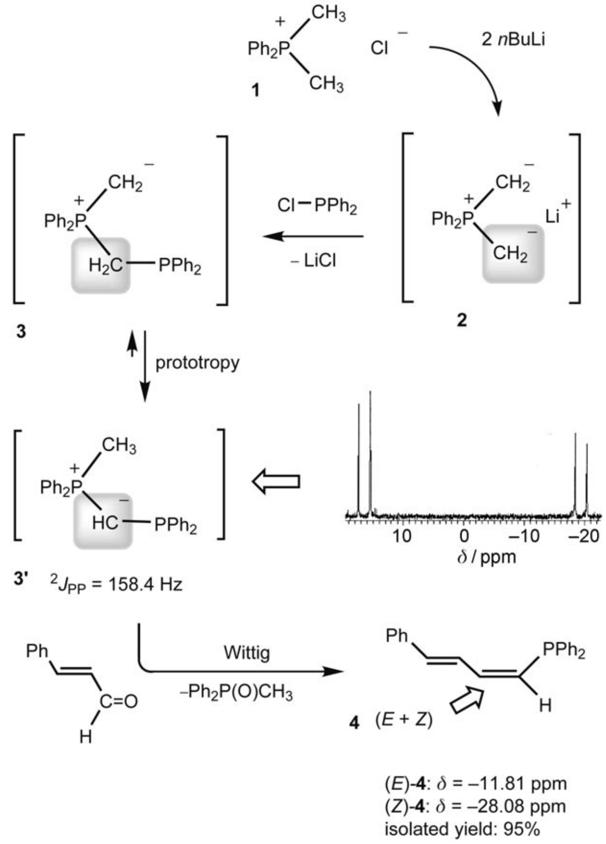
Butadienylphosphines are interesting molecules in coordination chemistry and catalysis since they combine two very well-known ligands: phosphines and conjugated dienes. However,

these molecules have never been used in catalysis, probably because existing synthetic routes are neither general nor efficient.[1]

There are very few examples of butadienylphosphines described in the literature. During our studies on highly nucleophilic metalated ylides, we recently discovered a new, general, one-pot synthetic route to prepare these potential ligands.[2] Herein we describe the first example of a catalytic reaction with butadienylphosphines. We found that 4-phenyl-1,3-butadienyldiphenylphosphine (**4**; Scheme 1) is indeed an excellent ligand for Ullmann-type copper-catalyzed arylations of N and O nucleophiles (Table 1). Moreover, by following the reactions by ^{31}P NMR spectroscopy, we are also able to propose a working mechanism.

Our general protocol for the synthesis of butadienylphosphines, applied here for the preparation of **4**, is based on the following sequence (Scheme 1): In the first step, phosphonium diylid **2**, generated in situ from the corresponding phosphonium salt **1**,[3] reacts with chlorodiphenylphosphine to give monoylid **3** by nucleophilic substitution. The latter species is transformed instantaneously into monoylid **3′** through intramolecular prototropy. For the second step, the in situ addition of cinnamaldehyde leads to butadienylphosphine **4** through a Wittig reaction. The yield of **4** is almost quantitative, with the *Z* and *E* isomers being isolated in yields of 75 and 20%, respectively. As expected, the *Z* isomer ((*Z*)-**4**) is the major product because ylide **3′** is not stabilized.[4]



Scheme 1. One-pot synthesis of butadienylphosphine **4** and its ^{31}P NMR spectrum in CDCl$_3$.

^{31}P NMR spectroscopy was used to monitor the formation of **3′** (two doublets, see Scheme 1) and of both the *Z* and *E* isomers of **4**. In this study, the (*Z*)-**4** butadienyl phosphine, readily prepared on a gram scale, has been employed as a ligand in copper-catalyzed arylations of nucleophiles, a type of reaction which has recently been the focus of research in our group.[5] These reactions involve the formation of C−N, C−C, C−O, and C−S bonds, and are thus important for the production of both intermediates and target molecules of interest to the life sciences and polymer industries.[6] Until 2000, the reactions were of limited scope because of the harsh conditions required (stoichiometric Cu, $T > 210\,°C$).[6] However, since 2001,[7] important breakthroughs have been achieved with the discovery of very efficient ligands for the copper center which permit the use of catalytic quantities of metal under much milder conditions.[5,6b–d]

The efficiency of butadienylphosphine (*Z*)-**4** as a ligand in arylation reactions was investigated. A first set of experiments

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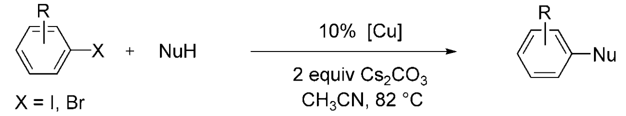
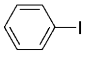
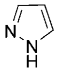
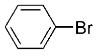
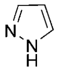
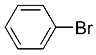
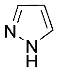
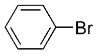
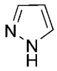
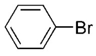
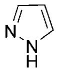
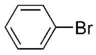
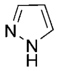
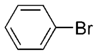
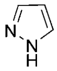
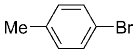
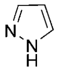
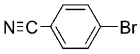
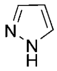
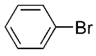
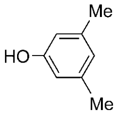
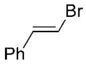
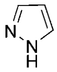
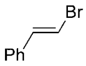
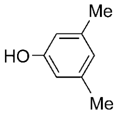
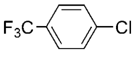
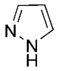
Supporting information for this article (synthetic and characterization data of (*Z*)-**4**, (*E*)-**4**, and **5**; crystallographic data of **5**; and general procedure for the catalytic reactions) is available on the WWW under http://dx.doi.org/10.1002/anie.200800688.

was carried out using CuI (10%), (*Z*)-**4** (20%), pyrazole as the nucleophile, and iodo- and bromobenzenes as the substrates (Table 1, entries 1 and 2). We were pleased to find that the catalytic system achieves quantitative conversion of PhI into phenylpyrazole within only 3 h at reflux in acetonitrile (entry 1). Much more interestingly, the same performance is obtained using less-reactive and less-expensive PhBr (100% yield in 4 h; entry 2). The unusually short time required to complete these reactions demonstrates the high activity conferred to the copper center by (*Z*)-**4**. It is noteworthy that without additional ligand (except for the solvent, which can also play this role), CuI (10%) is not able to promote the reaction so readily from PhBr (entry 3). With these conditions, a maximum of 78% yield can be reached from PhBr only after 26 h,[8] and this yield is not augmented by a longer reaction time.

Table 1: Copper-catalyzed arylations.



Entry	ArX or vinylBr	NuH	Catalytic system[a]	*t* [h]	Yield [%][b]
1			CuI + 2 L	3	100
2			CuI + 2 L	4	100
3			CuI	4	5[e]
4			CuI + 2 Ph$_3$P	4 10	8 10
5			CuI + 2 Ph$_2$PMe	4	10
6			CuI + 2 Ph$_2$PCH=CH$_2$	4	16
7			**5**	4	98
8			**5**	4	97
9			**5**	4	98
10			**5**	10	91[c]
11			**5**	4	100
12			**5**	10	95
13			**5**	24	70[d]

[a] L = (*Z*)-**4**; **5** = [CuIL$_2$] (Figure 1). [b] GC yield determined using 3,5-dimethoxybenzene as an internal standard; after work-up, yields of isolated products reach 90–95% of these values. [c] Base: K$_3$PO$_4$. [d] DMF, 140°C. [e] Maximum yield after 26 h: 78%.

Interestingly, PPh$_3$ (in which the phenylbutadienyl moiety of **4** is replaced by a phenyl group) was found to be inefficient under the same conditions (entry 4). Although no explanation can be provided yet, it is clear that the difference in the reactivity between the two ligands is not due to the structure of the copper precursor. Indeed, complex **5**, prepared from CuI and (*Z*)-**4** (Figure 1), displays the same structure and a very similar steric hindrance around the metal center as that in [CuI(PPh$_3$)$_2$], both complexes being obtained under the conditions of the arylations.[9] In these [CuIL$_2$] complexes, the copper atom, iodine, and both phosphorus atoms are all coplanar. It is also worth noting that the catalytic system was also found to be inefficient when the phenylbutadienyl moiety of **4** was replaced by either a methyl or a vinyl group (Table 1, entries 5 and 6).

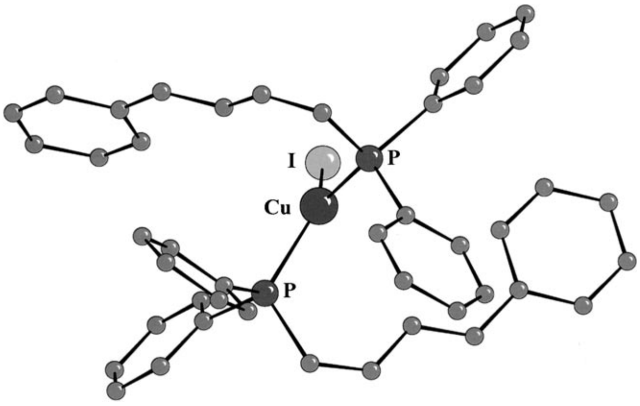
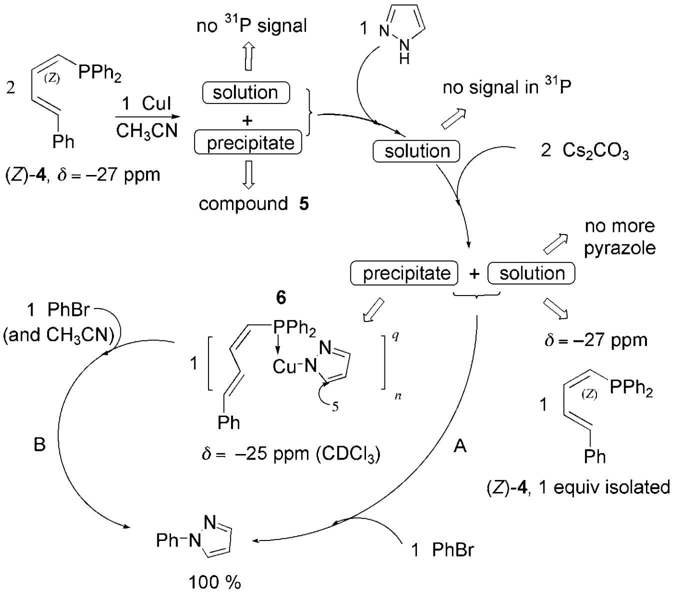


Figure 1. X-ray structure of complex **5**.

The isolated complex of **5** also displays good catalytic activity, with phenylpyrazole being obtained quantitatively, similar to when the complex is formed in situ (entries 2 and 7, under the same conditions). Complex **5** is also able to promote successfully the coupling of aryl bromides substituted by electron-donating (Me) or electron-withdrawing (CN) groups (entries 8 and 9). The efficiency of **5** was also illustrated in the case of O nucleophiles: the coupling of 3,5-dimethylphenol with PhBr occurred quantitatively within 10 h (entry 10). The scope of the reaction could also be extended to N- and O-vinylations by using bromostyrene (entries 11 and 12). Moreover, our system enables arylation with normally unreactive aryl chlorides at 140°C (entry 11). As far as we know, the conditions used for all these reactions are among the mildest reported.[5,6,10]

The use of butadienylphosphines enabled us to investigate the mechanism of these catalytic Ullmann reactions by ^{31}P NMR spectroscopy (Scheme 2). It is noteworthy that the mechanisms of palladium-catalyzed arylations are much



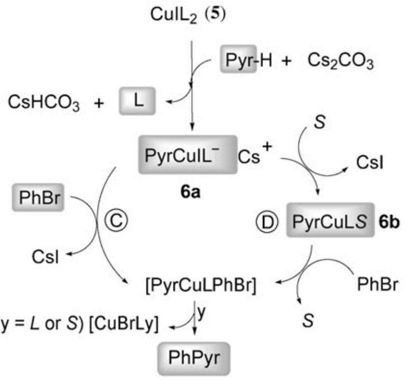
Scheme 2. Copper-catalyzed arylation of pyrazole as determined by ^{31}P NMR spectroscopic analysis of the reaction.

better understood than those catalyzed be copper, for which comparatively few studies have been performed.[5c,11] Elucidating the mechanism thus constitutes one of the most exciting challenges in Ullmann reactions. By following the reactions by ^{31}P NMR spectroscopy, we found a standard coupling between PhBr and pyrazole (or phenol) when using one equivalent of copper precatalyst.

In the first step, the addition of CuI to two equivalents of (*Z*)-**4** ligand results in the quantitative formation of complex **5** as a white precipitate (no phosphorus product is present in solution). The further addition of pyrazole (1 equiv) does not induce any change in either the precipitate or filtrate (^{31}P NMR). In contrast, the subsequent introduction of base (Cs_2CO_3, 2 equiv) provokes the release of one equivalent of butadienylphosphine (*Z*)-**4** ($\delta = -27$ ppm in CH_3CN) into the solution, in which pyrazole could no longer be detected.[12] Therefore, one equivalent of ligand (*Z*)-**4** at the copper center has likely been substituted by one pyrazolate group. The corresponding green precipitate **6** might thus be a copper complex in which the metal atom is bound to one pyrazole and one butadienylphosphine group. ^{13}C NMR spectroscopic analysis of the precipitate confirmed this proposal since the signal for C5 of the pyrazole ring appears as a doublet ($^3J_{CP} = 10.25$ Hz). Moreover, the ^{31}P NMR spectrum indicates the presence of one compound ($CDCl_3$, $\delta = -25$ ppm) which is different from **5** ($CDCl_3$, $\delta = -21$ ppm) and from (*Z*)-**4** ($CDCl_3$, $\delta = -28.08$ ppm). Finally, according to the NMR spectra, the complex does not involve coordinated acetonitrile. However, these data do not allow us to determine the exact structure of complex **6**, for which an X-ray structure would be very helpful. If in a final step one equivalent of PhBr is added to the mixture, the expected coupling product is obtained in 100% yield (path A). Even more interestingly, the addition of PhBr (1 equiv) to isolated precipitate **6** also leads quantitatively to phenylpyrazole, which confirms the presence of one pyrazole ring at the copper center (path B).

It is noteworthy that no change occurs in the ^{31}P NMR spectra (solution and precipitate) if PhBr is first added to **5**. The further addition of pyrazole and base are required for the reaction to take place, again quantitatively. A similar general behavior is observed in the case of phenols.

We can thus propose a pathway involving precoordination of the nucleophile at the copper center as the first step (Scheme 3). The corresponding anionic complex **6a** could then undergo oxidative addition of PhBr with release of CsI (path C). Alternatively, CsI could also be released from the complex **6a** as a consequence of a stabilizing intervention of the solvent before oxidative addition occurs on the neutral Cu^I complex **6b** (path D). This latter pathway could contribute to an explanation of the crucial role of the solvent in copper-catalyzed reactions.[11] In both pathways, the resulting intermediate would be probably a copper(III) complex ([PyrCuLPhBr], undetermined structure) from which the cross-coupling product is expelled and the catalytically active species reformed by reductive elimination.



Scheme 3. Possible catalytic cycle with a first ligand/pyrazolate exchange followed by oxidative addition on an anionic or neutral Cu^I intermediate ($S = CH_3CN$).

In conclusion, we have reported the first known application of a butadienylphosphine as a ligand in a catalytic reaction. Phosphine **4**, available on a large scale from a recently developed general synthetic method, was found to be a very efficient ligand in Ullmann-type copper-catalyzed arylation reactions. This ligand also provided us with some insight into this reaction, whose mechanism has been little studied until now. Work is now in progress to explore potential fields of application of these ligands in catalysis and also as dienes in Diels–Alder reactions.

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[10] (*E*)-**4** gives the same performances as (*Z*)-**4**.

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