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Notes

Thiazolyl Phosphine Ligands for Copper-Catalyzed Arylation and Vinylation of Nucleophiles in Organic and Aqueous Media

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Summary: A straightforward and efficient synthetic route to thiazolyl phosphines is reported. Moreover, the first application of these molecules in catalysis is described. These phosphines are excellent ligands in the copper-catalyzed arylation and vinylation of nucleophiles. The reactions could be performed in acetonitrile and various mixed aqueous/organic solvents and even in pure water in the presence of a phase transfer catalyst. In each case, coupling products are obtained with high yields at very mild temperatures.

Copper-catalyzed arylation of nucleophiles allows the formation of C−N, C−C, C−O, and C−S bonds, and it has thus been used in numerous syntheses of intermediates and targets throughout the life science and polymer industries.[1] These Ullmann-type reactions suffered from reduced scope because of the harsh conditions required (Cu stoichiometric, $T > 200$ °C).[1] However, in 2001, important breakthroughs were achieved with the discovery of very efficient copper ligands, permitting the use of catalytic amounts of metal under very mild conditions (<110 °C).[2] The best ligands for all such reactions have been chelates with nitrogen and/or oxygen binding sites, while aryl and alkyl phosphines generally confer poor catalytic activity to Cu in these coupling reactions. A reading of the literature suggests that, for other metal-catalyzed reactions, such lack of reactivity has often been overcome by using "cage-like" or heteroaryl phosphines.[3] Heterocyclic substituents can indeed confer suitable electronic and steric properties to the phosphorus coordinating atom, therefore permitting a more efficient metal-based catalysis compared to simple alkyl/aryl phosphines.[4e] Moreover, the heterocycle can provide additional binding sites for the catalytic metal center and thus enhance its efficiency.[4] We were therefore interested in testing heteroaryl phosphines as ligands in Ullmann-type reactions.

In this paper, we report the syntheses of the four original thiazolyl phosphines **2a**,**b** and **3a**,**b** (Scheme 1)[5] and the first example of their use as ligands for the catalytic reactions which have been the focus of our research in the past few years: the Cu(I)-catalyzed arylation and vinylation of nucleophiles.[6] We also demonstrate that the use of thiazolyl phosphines makes it possible to perform these reactions in aqueous media and pure water.

Thiazolyl phosphines **2a**−**c** are prepared by substitution of the formamidine-functionalized thiazole **1** by diphenylbromophosphine,[7] phenyldibromophosphine, and tribromophosphine, respectively. Hydrolyses of the corresponding formamidines in basic media led to the respective 2-aminothiazolyl phosphines **3a**−**c**.

It is worth noting that electrophilic substitution of the thiazole ring occurs at position 5,[5] the latter being activated by the

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10.1021/om800728m CCC: $40.75

Scheme 1. Synthesis of the Thiazolyl Phosphines

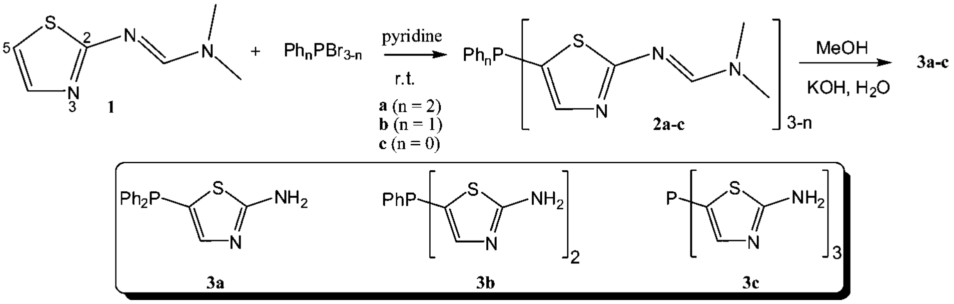
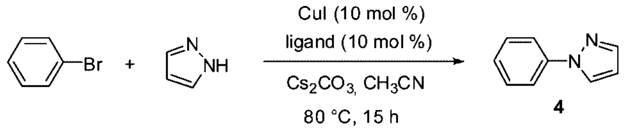


Table 1. Effect of the Ligand on the Coupling of Pyrazole with Bromobenzene[a]



entry	ligand	amt (mol %)	GC yield of **4** (%)[b]
1	**2a**	10	100 (93)[c]
2	**3a**	10	100
3	**2b**	10	70
4	**3b**	10	70
5	**2c**	10	67
6	**3c**	10	72
7	**1**	10	12
8	PPh_3	10	12

[a] Reaction conditions: 0.5 mmol of PhBr, 0.7 mmol of pyrazole, 0.7 mmol of Cs_2CO_3, 0.05 mmol of CuI, 0.05 of ligand, CH_3CN (300 μL). [b] GC yield determined using 1,3-dimethoxybenzene as internal standard (average of two runs). [c] Isolated yield.

electron-donating 2-formamidinyl substituent (σ_p[$Me_2NCH{=}N-$] = −0.25, σ_R = −0.29).[8] The regioselectivity of this reaction is confirmed, for example, by the structures of **2a** and **3a** in the solid state as determined by X-ray crystallography (Figures 1 and 2).

Within the crystalline lattice, the phosphorus atom in both compounds is pyramidal, and the sulfur atom points in the direction opposite to that of the phosphorus free electron pair. The slightly shorter P−C bond between phosphorus and the heterocycle (1.804 Å for P−C_3H_2NS compared to 1.827−1.836 Å for P−C_6H_5 in both phosphines **2a** and **3a**) suggests the existence of a degree of conjugation between phosphorus and the thiazole moiety. Additionally, evidence for delocalization within the formamidinyl group in **2a** includes almost equal C3−N1 and C3−N2 distances (1.319 and 1.308 Å, respectively) and slow rotation around the C3−N1 bond, rendering the two NMe_2 methyl groups inequivalent in solution as seen in both ^{1}H and ^{13}C NMR. It is also noteworthy that the formamidinyl substituent exists as the more thermodynamically stable *E* isomer.[9] We suggest that the major structural features of **2a** and **3a** are likely conserved in the di- and trisubstituted analogues **2b**,**c** and **3b**,**c**.

The catalytic activity conferred by formamidinothiazolyl phosphines **2a**−**c** and aminothiazolyl phosphines **3a-c** to copper was first evaluated in the arylation of pyrazole with bromobenzene using our standard conditions (acetonitrile with Cs_2CO_3 as base, Table 1).[6] The catalytic system combines CuI (10 mol %) and the phosphine (10 mol %) (entries 1−6).

Monosubstituted thiazolyl phosphines **2a** and **3a** afford complete conversion of PhBr into phenylpyrazole **4** within 15 h at 80 °C (entries 1 and 2). However, the catalytic activity of copper decreases in the presence of phosphines involving two (**2b**, **3b**) or three (**2c**, **3c**) heteroaryl substituents under the same conditions (average yield 70%, entries 3−6). Interestingly, the performances of the reaction are the same when using the formamidinothiazolyl phosphine **2a** or aminothiazolyl phosphine **3a** (entries 1 and 2). The same behavior is observed for disubstituted (**2b** and **3b**) and trisubstituted (**2c** and **3c**) thiazolyl phosphines (entries 3−6). Therefore, the formamide moiety does not seem to play a significant role during the catalytic process.

Moreover, there is strong evidence from these data in favor of a cooperative effect between phosphorus and the thiazole ring. Thus, the coupling product was obtained in poor yield in the presence of only thiazolyl ring **1** (12%, entry 7) or only triphenylphosphine (10%, entry 8). This result could mean that the replacement of a phenyl group by a thiazolyl on the phosphorus greatly influences the electronic properties of the resulting ligand. In opposition to this proposal stand the results of voltammetric investigations on all six of these thiazolylphosphines, which indicate that the onset potential for oxidation at phosphorus is very similar to that reported previously for triphenylphosphine. This cooperative effect could also indicate

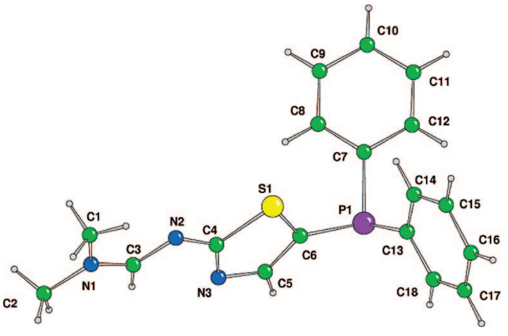


Figure 1. Crystal structure of **2a**.

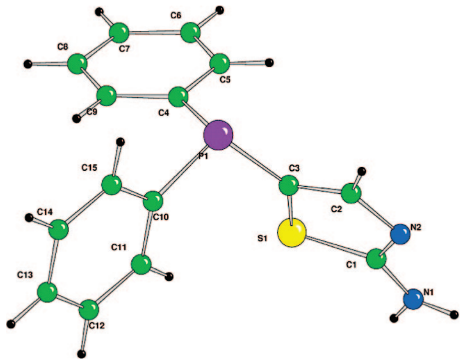


Figure 2. Crystal structure of **3a**.

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that both the phosphorus atom and the heteroaryl substituent are involved in the coordination during the catalytic process. In this case, thiazolyl phosphines would act as multidentate ligands and the heterocycle could intervene via its soft donor sulfur atom or its harder nitrogen atoms. Potentially multidentate ligands can enhance the activity of the metal by stabilizing metal ions in a variety of oxidation states and geometries. For example, the phosphine could stabilize copper in a lower oxidation state thanks to its π character, while the nitrogen σ donor could facilitate oxidative addition.[4c] Mechanistic studies are underway to rationalize the experimental results and better understand which coordinating sites play a role during catalysis.

We also examined copper-catalyzed arylations of pyrazole with substituted aryl bromides using thiazolyl phosphine **3a** (10%) as ligand (Table 2, entries 1−7). Compound **3a** appeared to be the best choice because of its high efficacy (Table 1) and its greater stability compared to **2a**.

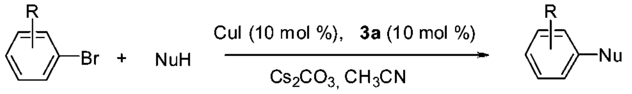
The expected aryl pyrazoles are obtained in very high to quantitative yields whatever the nature of the substituent, either electron withdrawing (CN, NO_2, Ph, and C(O)Me, entries 1−4) or electron donating (Me and OMe, entries 5−7). This synthetic method also efficiently couples heteroaryl bromides with, for example, 2-bromopyridine being quantitatively and selectively converted (entry 8). The scope of the investigation was also successfully extended to vinylations by β-bromostyrene: styrylpyrazole is indeed obtained in quantitative yield within 15 h at 50 °C or even at room temperature after 3 days (entry 9). To our knowledge, this corresponds to the mildest conditions reported to date for such reactions.[1,6b] Finally, arylation of other heterocycles (pyrrole and indole, entries 10 and 11) and of O nucleophiles such as 3,5-dimethylphenol (entry 12) is also efficient under the standard conditions.

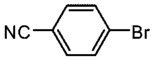
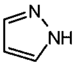
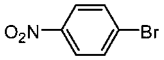
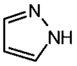
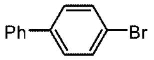
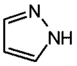
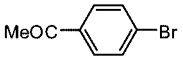
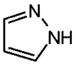
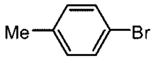
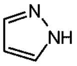
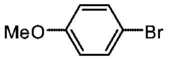
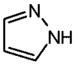
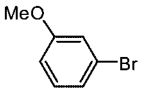
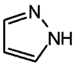
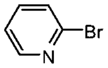
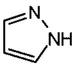
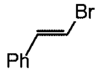
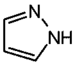
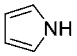
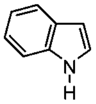
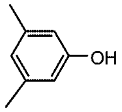
In view of the industrial importance of arylation of nucleophiles, the development of more sustainable methods is required to allow practical exploitation. In particular, the use of a nontoxic, nonpolluting, cheap, and abundant solvent such as water is considered of high practical value, especially for large-scale applications.[10] Therefore, in an additional set of experiments, several copper-catalyzed vinylations and arylations of pyrazole were performed in mixed aqueous/organic solvents as well as in pure water using **3a** as ligand (Table 3).

It is worth noting that copper-promoted couplings are often water sensitive and that, so far, few examples have been reported in mixed aqueous/organic solvents.[1,10a] In most of the known examples, the introduction of a cosolvent (DMF, DMSO) is necessary, usually in vast excess ($\geq$90%), for the reaction to occur at all.[10a,11] The few reported arylations which proceed in neat water involve high ligand loadings (200−300 mol %),[12] use high reaction temperatures ($\geq$120 °C),[13] and/or require microwave irradiation.[14]

Using **3a** as ligand, the catalytic activity is surprisingly not altered in the presence of 20% water (CH_3CN/H_2O (4:1)), since PhBr and β-bromostyrene are converted in very high to quantitative yields under mild conditions (80 °C, 18 h, entries 1 and 2). In a CH_3CN/H_2O (1:1) mixture (entries 3 and 4), the yields of phenylpyrazole (**4**) and styrylpyrazole (**5**) decrease to 25 and 56%, respectively. Interestingly, the replacement of CH_3CN by the industrial solvent methyl isobutyl ketone (MIBK) in a 1:1 mixture with water leads to a great enhancement of the reaction, both coupling products being obtained in 75 and 90% yields, respectively (entries 5 and 6).

Table 2. Coupling of Aryl and Vinyl Bromides with N and O Nucleophiles[a]



entry	aryl or vinyl bromide	nucleophiles	yield (%)[b]
1			98 (94)
2			99 (92)
3			99 (98)
4			99 (95)
5			87 (80)
6			86 (82)
7			98 (93)
8			99 (94)
9			98 [c] (90)
10	PhBr		97 (93)
11	PhBr		82 (78)
12	PhBr		73 (70)

[a] Reaction conditions: 0.5 mmol of ArBr/β-bromostyrene, 0.7 mmol of nucleophile, 0.7 mmol of Cs_2CO_3, 0.05 mmol of CuI and **3a**, CH_3CN, 80 °C, 15 h. [b] GC yield determined using 1,3-dimethoxybenzene as internal standard. Isolated yields are given in brackets. [c] Temperature 50 °C for 15 h or 25 °C for 72 h.

However, in pure water, both couplings revealed very sluggish performance (4% yield from PhBr or PhI and 10% from

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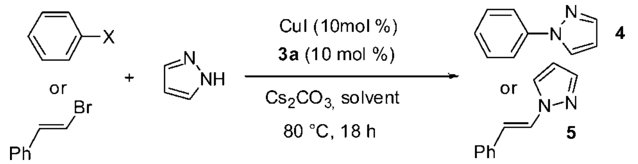
Table 3. Arylation and Vinylation of Pyrazole in Aqueous Media[a]



entry		solvent	GC yield (%)[b]
1	PhBr	CH_3CN/H_2O (4:1)	90 (85)
2	β-bromostyrene	CH_3CN/H_2O (4:1)	100 (96)
3	PhBr	CH_3CN/H_2O (1:1)	25
4	β-bromostyrene	CH_3CN/H_2O (1:1)	56
5	PhBr	MIBK[c]/H_2O (1:1)	75 (71)
6	β-bromostyrene	MIBK[c]/H_2O (1:1)	90 (85)
7	PhBr or PhI	H_2O	4
8	β-bromostyrene	H_2O	10
9	PhBr	H_2O[d]	30
10	PhI	H_2O[d]	40
11	PhI	H_2O[d]	70[e] (67)
12	β-bromostyrene	H_2O[d]	65
13	β-bromostyrene	H_2O[d]	90[e] (86)

[a] Reaction conditions: 0.5 mmol of PhBr or β-bromostyrene, 0.7 mmol of pyrazole, 0.7 mmol of Cs_2CO_3, 0.05 mmol of CuI and **3a**, CH_3CN/degassed H_2O (300 μL). [b] GC yield determined using 1,3-dimethoxybenzene as internal standard (average of two runs). Isolated yields are given in parentheses. [c] Methyl isobutyl ketone, solvent currently used in the industry. [d] Hexadecyltriethylammonium bromide, 20%. [e] Time 50 h.

β-bromostyrene, entries 7 and 8), probably because of the low solubility of the reactants in this solvent. Indeed, we were pleased to find that the addition of hexadecyltriethylammonium bromide as phase transfer catalyst allows greatly improved yields of **4** and **5** (30% from PhBr, 40% from PhI and 65% from β-bromostyrene, entries 9, 10, and 12). Also noteworthy is that, with a longer reaction duration (50 h instead of 18), **4** and **5** can be obtained in 70 and 90% yields, respectively (entries 11 and 13). To our knowledge, these encouraging preliminary results constitute the first examples of intermolecular copper-catalyzed couplings in neat water under such mild conditions.[10a,13]

In conclusion, we have shown the versatility of a new class of thiazolyl phosphine ligands readily accessible via electrophilic phosphorylation of thiazole **1** with Ph_2PBr, $PhPBr_2$, or PBr_3 (ligands **2a**−**c**) and subsequent base hydrolysis of the protecting and activating formamidinyl group (ligands **3a**−**c**). Among this group of ligands, **3a** turns out to be an excellent ligand for promoting copper-catalyzed arylation and vinylation of nucleophiles in CH_3CN. Even more interestingly, **3a** allows these reactions to be performed in mixed aqueous/organic solvents and in pure water if a phase transfer catalyst is used. Work is now in progress to expand the scope of Ullmann-type couplings in neat water and to identify the copper intermediates involved in the catalytic process.

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Supporting Information Available: Text, figures, and CIF files giving experimental procedures, full characterization data of new compounds, NMR spectra, and crystallographic data of **2a** (CCDC 679655) and**3a** (CCDC 679654). This material is available free of charge via the Internet at http://pubs.acs.org.

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