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Nitrogen Ligands in Copper-Catalyzed Arylation of Phenols: Structure/Activity Relationships and Applications

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Abstract: In spite of the importance of ligand/copper-catalyzed arylations of nucleophiles in organic chemistry, the structural and electronic features that make a ligand efficient in these reactions have not been determined until now. In this work, several bidentate ligands involving pyridine and/or imine nitrogen binding sites such as our lead ligand **1** have been synthesized, and tested in phenol arylations with a view to highlight relationships between the structure of the chelates and their efficacy. This study allowed us to more precisely define the role of each type of N-binding site during the catalytic process, and to discover new efficient ligands. Among them, the iminopyridine **6a**, which is cheap and easy-to-prepare in high yield, is very attractive for industrial applications. Some examples of its field of application are presented here. In the future, the development of this work could allow a more rational design of efficient ligands in arylation reactions, without resorting to classical ligand screening.

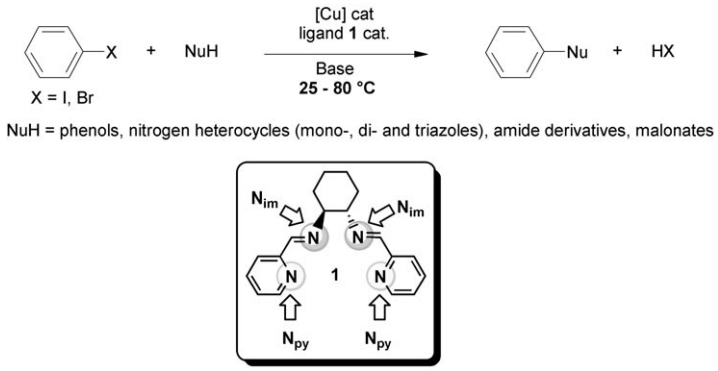
Keywords: arylation; catalysis; copper; nitrogen ligands; nucleophiles

Introduction

Copper-catalyzed arylation of nucleophiles constitutes a very attractive method for creating C–C, C–N, C–O or C–P bonds, and to access in this way to a wide range of intermediates and targets throughout the life science and polymer industries.[1] These methodologies have received intense attention over the past five years. This has led to the development of copper ligands that enable couplings to be performed under very mild conditions compared to the classical copper-mediated Ullmann and Goldberg reactions.[1a] Work in our laboratories has generated a range of multidentate donor-compounds with nitrogen-, oxygen-, or a mixture of both types of binding sites that give efficient catalysts for C–N, C–O and C–C bonds formation.[2] For instance, the tetradentate ligand **1**, which displays two imine (N_{im}) and two pyridine (N_{py}) potentially coordinating nitrogens, supports the copper-catalyzed arylations[2b–f,3] and vinylations[2a,3] of a wide range of N-, O-, C-nucleophiles, often under the mildest temperature conditions ever reported (20–80 °C) (Scheme 1).

It is worth noting that all the additional ligands mentioned in the literature play a crucial role and undoubtedly determine the performance of the copper-catalyzed arylations. However, the way they act during the catalytic process remains unknown. In this work, we attempt to find some information in order to get a better understanding of this particular question.

To this end, several ligands derived from **1** have been synthesized and tested in a model reaction, the copper-catalyzed arylation of phenols, in the hope to highlight the relationship between the structure of the chelates and their efficiency. A rationalization of the experimental data has thus permitted us to better understand the role played by each type of binding site (either imine or pyridine) during the catalytic process. These studies have also permitted us to discover new efficient ligands. One of them, easily prepared from cheap starting materials, is very attractive for applications on the industrial scale. Finally, this work also provides preliminary insights which could allow us in the future to design and choose ligands on the basis of more rational criteria.



Scheme 1. Ullmann-type condensations in very mild conditions in the presence of the tetradentate ligand **1**.

Results and Discussion

Synthesis of the Ligands Derived from 1 and Catalytic Activity they Confer to Copper in *O*-Arylation Reactions

In order to get a better understanding of the role of nitrogen binding sites, bidentate ligands involving either a diimine (**2**), or a bipyridine (**3a** and **4**) or an iminopyridine 1,4-*N,N*-pincer (**5** and **6a**) have been first considered (Scheme 2). It is worth noting that such chelators, when complexed to copper(I), are expected to give rise to five-membered chelate rings, which are known to be the most stable compared to larger chelate ring sizes.[4]

Synthesis of Bidentate Derivatives (Scheme 2)

trans-1,2-Bis(benzylidenamino)-cyclohexane **2**, resulting from the condensation of *trans*-1,2-diamine with two equivalents of benzaldehyde, differs from **1** since it has no pyridine binding sites. It was synthesized in order to evaluate the activity conferred to copper by the *diimine chelate* alone. This ligand was punctually used to promote Diels–Alder[5] and aziridination reactions[6] in combination with copper(II) and copper(I), respectively.

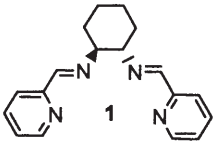
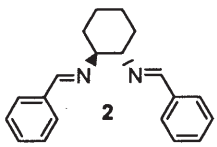
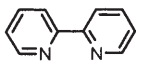
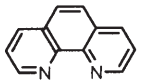
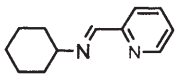
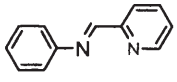
It was also of interest to study chelators involving only pyridinic sites, such as commercially available *bipyridinic pincers* **3a** and **4**, which are known for their affinity for copper(I).[7] Within the planar and rigid 1,10-phenanthroline **4**, a *cis* geometry is blocked for the pincer, whereas 2,2′-bipyridine **3a** displays more flexibility.[8]

Lastly, ligands **5** and **6a** were designed to evaluate the efficacy of an *iminopyridine pincer* in the arylation reaction. Both scaffolds represent "half of the tetradentate ligand **1**" and combine both types of N-binding sites. Compounds **5** and **6a**, very easily obtained by straightforward condensation of 2-pyridylcarboxaldehyde with an amine (cyclohexylamine and aniline, respectively), have been described but their coordinating properties towards copper have not been studied, to the best of our knowledge.[9]

The catalytic activity conferred by these derivatives of **1** has been then evaluated in the case of the copper-catalyzed arylation of phenols, reactions we previously extensively studied (Figure 1).[2b,d]

Activity Conferred to Copper by the Above-Mentioned Bidentate Ligands

Before presenting the results, it is worth noting that bipyridine ligands **3a** and **4** are known to allow this

Tetradentate	Bidentate			
Reference ligand	Diimine chelate	Bipyridine chelates		Imino-pyridine chelates
				 
1	**2**	**3a**	**4**	**5** **6a**

Scheme 2. Tetradentate ligand **1** and its potential substitutes of the 1,4-N,N-chelate-type.

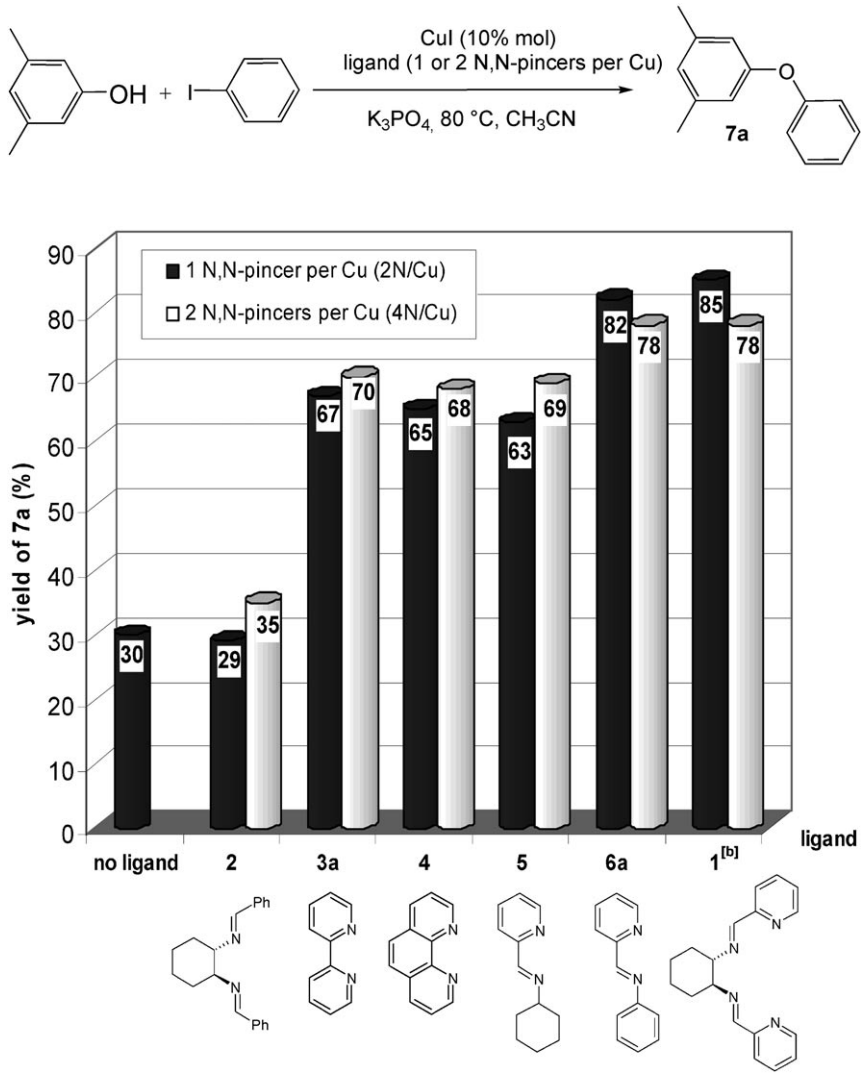
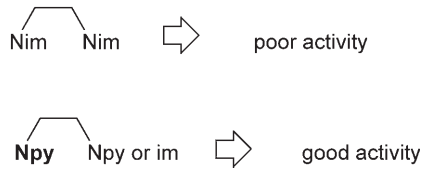


Figure 1. Influence of the type of N,N-pincer on the outcome of arylation[a] of 3,5-dimethylphenol with PhI.[a] *Reaction conditions:* iodobenzene (0.5 mmol), 3,5-dimethylphenol (0.6 mmol), K_3PO_4 (0.6 mmol), CuI (0.05 mmol), ligand **2** to **6** [0.05 mmol (2N/Cu) or 0.10 mmol (4N/Cu)], CH_3CN (300 μL), 24 h. GC Yields determined with 1,3-dimethoxybenzene as internal standard. Selectivity (yield of expected product divided by conversion of PhI) $\geq$ 96% ; only by-product: benzene resulting from dehydrohalogenation of PhI.[b] In the case of **1**, one N,N-pincer per Cu (black histogram) is obtained for a **1**/Cu ratio of 0.5 (5 mol% of **1**). Two N,N-pincers per Cu (white histogram) are obtained for a **1**/Cu ratio of 1 (10 mol% of **1**).

type of coupling, but in relatively harsh conditions and only if associating to triphenylphosphine.[10] On the other hand, diimine **2** and iminopyridine ligands **5** and **6a** have never been used in such coupling reactions.

Arylation of 3,5-dimethylphenol with iodobenzene was performed in the presence of the bidentate compounds **2**–**6a** for two different ligand-to-Cu ratios: **L**/Cu = 1 or 2 (i.e., for 1 or 2 N,N-pincers per Cu).

In the first case (**L**/Cu = 1, Figure 1, black histogram), we observed that the diimine pincer alone (ligand **2**) does not enable any acceleration of the reaction, diaryl ether **7a** being obtained in about 30% yield as in the absence of ligand. On the other hand, the yield of **7a** can significantly be increased when using either the bipyridinic pincers **3a** and **4**, which display comparable efficiency, or the mixed chelators **5** and **6a** that combine both types of binding sites (63–82%). The results also highlight the importance of the *N*-imino substituent, the yield of **7a** increasing from 63 to 82% when replacing the cyclohexanyl of **5** by a phenyl group. In these conditions, ligand **6a** was even able to promote the coupling reaction as efficiently as our tetradentate lead ligand **1** (Figure 1: comparison made in both cases with 1 N,N-pincer per Cu).



Scheme 3. Relationships between nature of the N,N-chelator and activity in phenol arylations.

Interestingly, when doubling the amount of ligand (**L**/Cu = 2, Figure 1, white histogram), the outcome of the reaction gets very weakly affected in all the cases. This last feature shows that the second equivalent of ligand is not necessary during the catalytic process, which could be in accordance with the existence of key intermediates incorporating only one chelator per catalytic site.

Hence this preliminary study indicates that, to confer a good catalytic activity to copper, the dinitrogen pincer has to involve at least one pyridine-type binding site (Scheme 3), the best results being obtained for **6a**, the mixed ligand involving also an aromatic imine (some examples of application for this ligand are reported in the last paragraph). Moreover, it is interesting to note that associating only one 1,4-N,N-chelator to the copper(I) precursor is sufficient to efficiently promote the arylation of phenols.

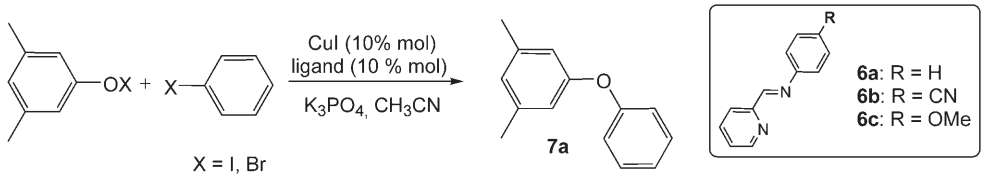
At this stage of the study, we have performed a finer tuning in modifying the electronic density on both nitrogen coordinating sites (either imine or pyridine) and in evaluating the effects of this parameter on the outcome of the reaction. For that purpose, two model ligands have been chosen: the chelate **6a** and the bipyridine **3a**.

Variation of the Electronic Density on the Imine and Pyridine Binding Sites: Influence on the Copper-Catalyzed Arylation of Phenols

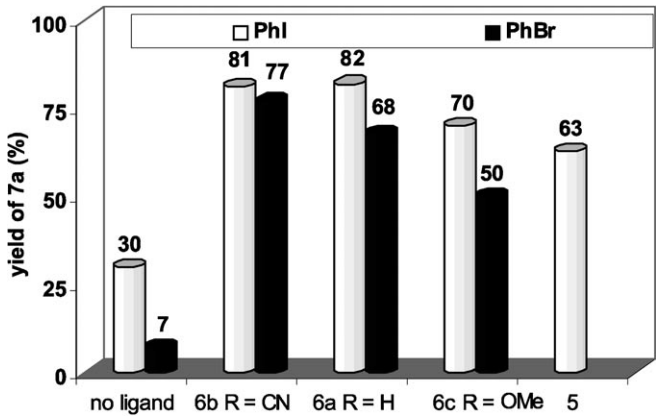
Case of the Imine Binding Sites

We first modulated the electron density on the imine-type binding site, in introducing on **6a** various substituents in the *para* position of the imino-nitrogen. Iminopyridine ligands **6b** and **6c** have thus been obtained by condensation of 2-pyridylcarboxaldehyde with *p*-cyanoaniline and *p*-methoxyaniline, respectively. Both have then been tested in the arylation of 3,5-dimethylphenol for a ligand-to-Cu ratio: **L**/Cu = 1 (i.e., for 1 N,N-pincer per Cu) (Table 1).

Table 1. Influence of the electron density of the imine binding site on the outcome of the arylation of 3,5-dimethylphenol with PhI and PhBr.[a]



X	Ligand	Yield [%][b,c]
I	no ligand	30
I	**6b**	81
I	**6a**	82
I	**6c**	70
Br	no ligand	7
Br	**6b**	77
Br	**6a**	68
Br	**6c**	50



[a] *Reaction conditions:* aryl halide (0.5 mmol), 3,5-dimethylphenol (0.6 mmol), K_3PO_4 (0.6 mmol), CuI (0.05 mmol), ligand (0.05 mmol), ligand-to-copper ratio = 1 (2N/Cu), CH_3CN (300 μL), 80 °C, 24 h.
[b] GC yields determined with 1,3-dimethoxybenzene as internal standard.
[c] Selectivity ≥ 97%.

With iodobenzene (Table 1, white histogram), the outcome of the reaction is not affected when changing the electron-neutral H-substituent by an electron-withdrawing *p*-cyano group (yield of **7a**: 81–82%). However, an imine nitrogen electronically enriched by the electron-releasing *p*-methoxy group (R = OMe) appears to disfavour the coupling reaction, yield of diaryl ether **7a** decreasing to 70%. Performing the arylation with the less reactive bromobenzene enables us to discriminate ligands **6a** and **6b**, and to confirm and even amplify the electronic effect observed in the case of iodobenzene. Indeed, the yield of **7a** progressively and significantly decreases when the electron-donating ability of the *para*-substituent increases (Table 1, black histogram). Hence the lower efficiency of iminopyridine ligand **5** (Table 1), in which the imine nitrogen is bound to a cyclohexanyl group, could be due to the fact that this alkyl substituent is more electron-rich than the phenyl one present instead within ligand **6a**.

Case of the Pyridinic Binding Sites

We then investigated the case of pyridinic binding sites and chose the versatile 2,2′-bipyridine as model. A series of bipyridines disubstituted in positions 4 and 4′ by electron-withdrawing (NO_2, Cl) or electron-releasing groups (Me, OMe, NEt_2) were thus synthesized,[11] and tested in the arylation of phenol with PhI (Table 2).

Contrary to the case of imines, the efficiency of the system progressively increases when the electron-donating ability of the *para*-substituent increases.[12] Therefore, the yield of the expected diaryl ether **7a** ranges from 57 to 81% when changing the withdrawing *nitro*-substituent into a strong releasing *diethylamino* group.

In other words, the highest activity is observed for electronically enriched copper(I) as checked by cyclic voltammetry, which shows that the donor properties of the substituted bipyridines are transferred to the metal.

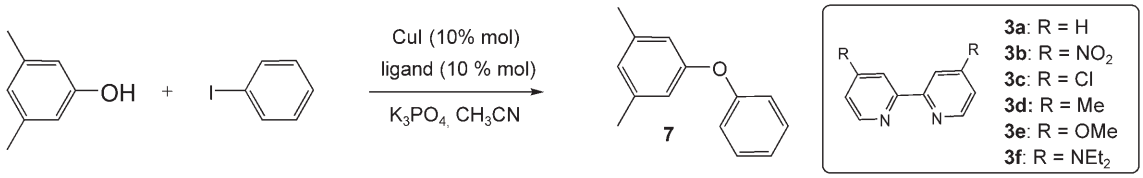
To perform these electrochemical studies, stoichiometric amounts of copper(I) and 4,4′-disubstituted bipyridines were dissolved in acetonitrile (conditions close to those taking place in arylations), and the Cu(I/II) oxidation potential of the Cu(I) complexes was determined (Scheme 4).

We first observed that, whatever the nature of the substituent, copper(I) is electronically enriched when associated to bipyridine ligands. Indeed, the Cu(I/II) oxidation peak potential in the absence of additional ligand {E[Cu(I)→Cu(II)]: +1.21 V *vs.* SCE} is always higher than those measured in the presence of bipyridines {E[Cu(I)→Cu(II)]: −0.16 to 0.62 V *vs.* SCE}.

A correlation between the electron-donating ability of the *para*-substituent, the oxidation potential of the copper(I) complex and its efficiency in the arylation reaction could thus be highlighted: the more electron-releasing the substituent, the lower the oxidation peak potential Cu(I/II) and the better the activity of the corresponding complex in arylation.

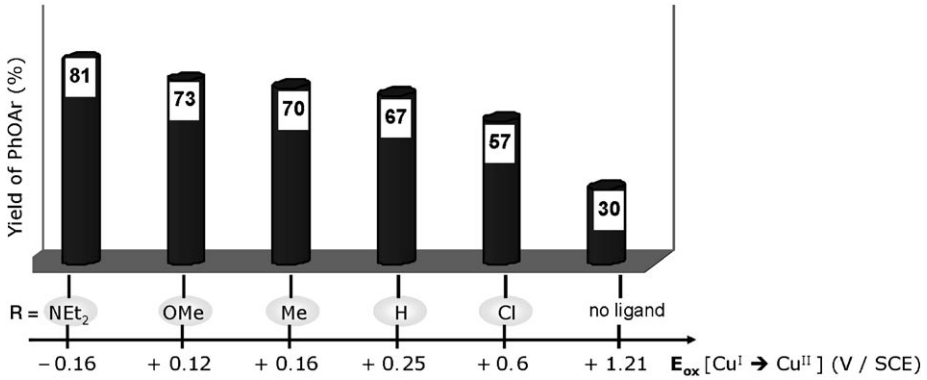
In an endeavour to rationalize these results, we focused on the mechanism involved in copper-catalyzed arylation reactions.

Table 2. Influence of the electron density of the pyridinic binding site on the outcome of the arylation of 3,5-dimethylphenol with iodobenzene.[a]



Ligand	R	Hammett σ of R	E[Cu(I)→Cu(II)] [V]	Yield [%][b,c]
3a	H	0	1.21	67
3b	NO_2	0.77	0.62	54
3c	Cl	0.23	0.25	57
3d	Me	−0.17	0.16	70
3e	OMe	−0.29	0.12	73
3f	NEt_2	−0.63	−0.16	81

[a] *Reaction conditions:* iodobenzene (0.5 mmol), 3,5-dimethylphenol (0.6 mmol), K_3PO_4 (0.6 mmol), CuI (0.05 mmol), ligand (0.05 mmol), ligand-to-copper ratio = 1 (2N/Cu), CH_3CN (300 μL), 80 °C, 24 h.
[b] GC yields determined with 1,3-dimethoxybenzene as internal standard.
[c] Selectivity ≥ 97%.



Scheme 4. Yield of diaryl ether **7a** as a function of the oxidation potential of Cu(I) into Cu(II) in the presence of one equivalent of 4,4′-disubstituted pyridine. The oxidation potentials were measured by cyclic voltammetry in CH_3CN at 20 °C ([Cu] = 2 mM, *n*-Bu_4NBF_4, 0.3 M) at a stationary carbon disk electrode (Ø 2 mm) with a scan rate of 0.5 $V s^{-1}$.

Attempts to Rationalize the Results of the Structure/Activity Studies

In this type of reaction, the mechanism commonly proposed involves oxidative addition of the aryl halide to a copper(I) catalyst, nucleophilic substitution and subsequent reductive elimination of the coupling product.[2a,c,f,13] The corresponding proposed catalytic cycle (Scheme 5a), represented for the efficient bidentate iminopyridine ligand **6a**, aims to take into account the results obtained in this study.

We demonstrated that, for the substitutes of **1**, the coupling reaction was all the more efficient that the pyridine nitrogen was more electron-rich and the imine one more electron-poor (Scheme 5b). Within mixed ligand **6a**, the respective role of both binding sites is thus probably different, but also complementary. Hence the pyridine site could intervene in a step requiring an electron-rich copper centre: it would be the case for the putative oxidative addition of the aryl halide to the copper(I) complex (Scheme 5a, OA). On the other hand, the imine site would rather be involved in steps for which a more electrophilic copper centre is needed. Therefore, it could make the nucleophilic substitution (NS) of the phenate on copper easier, or facilitate the reductive elimination step (RE) in making the copper(III) centre electron-poor enough to favour the liberation of the expected coupling product (Scheme 5b). The synergy of both binding sites within the same molecule could then explain the high efficiency of ligand **6a**.

Additionally, it is reasonable to suggest that, in order to keep coordination sites free, the intermediates of the cycle involve one 1,4-N,N-chelate per copper, this last proposition being in accordance with the results presented in Figure 1.

Lastly, the iminopyridine pincer involved in mixed ligand **6a** displays a good balance between electron-releasing and electron-withdrawing properties. Its efficiency is illustrated below in the case of some coupling reactions.

Some Applications of the Imino-Pyridine Ligand 6a in Copper-Catalyzed Arylations and Vinylations

O-Arylation of Phenols

The application field of iminopyridine ligand **6a** has been extended to the coupling of various phenols and aryl bromides, the latter being cheaper and consequently more challenging than their iodide counterparts (Table 3).[14]

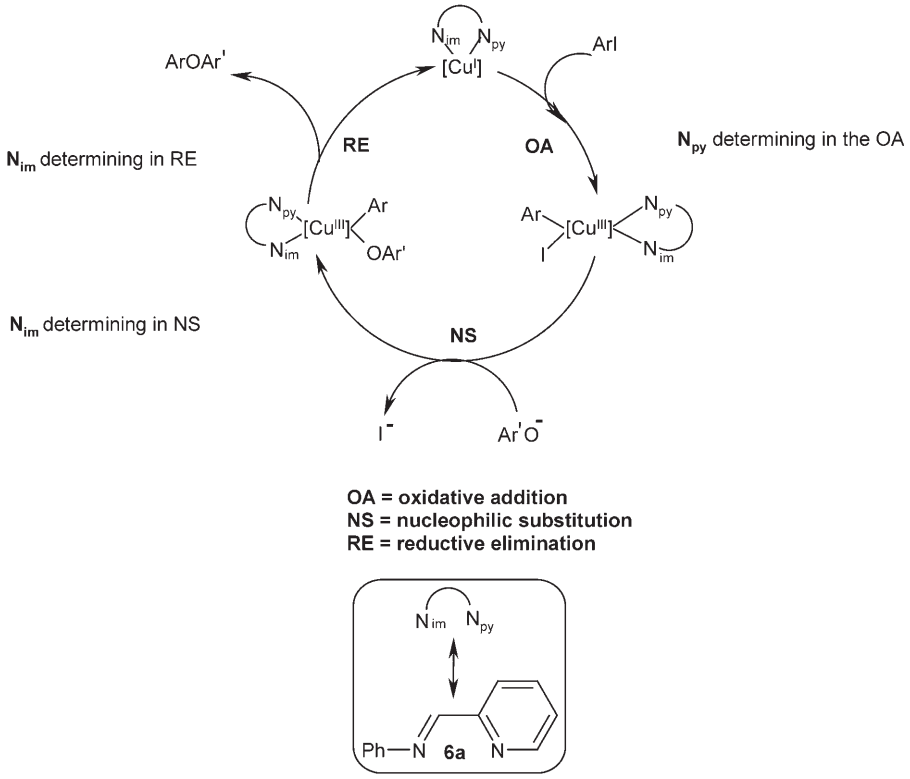
The expected diaryl ethers are obtained in good yields whatever the nature of the substituent on the aryl bromide, either electron-withdrawing (carbon trifluoride, cyano or nitro groups, entries 2, 3, 4) or electron-donating (methoxy group, entry 5). This synthetic method also efficiently couples heteroaryl bromides with 2-bromopyridine, for example, being quantitatively and selectively converted into **7f** (entry 6).

The reactivity of various phenol derivatives has also been evaluated using bromobenzene as the arylating agent (Table 3, entries 1, 7 to 9): electron-neutral and electron-rich substrates gave the corresponding diaryl ethers in high yields. Moreover, the 2,4-dichlorophenyl phenyl ether **7i** has been obtained in good yield from the corresponding hindered and electron-poor 2,4-dichlorophenol (entry 9).

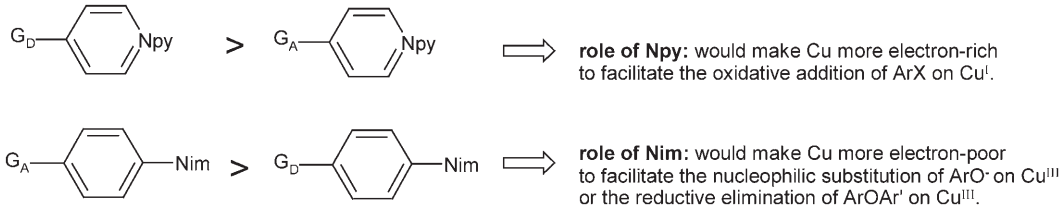
In all these examples, the reaction is totally selective with respect to phenols and the only by-products detected by GC are reduced arenes resulting from hydrodehalogenation of the corresponding aryl bromides (less than 4% yield).

The new ligand **6a** is thus able to promote efficiently the arylation of phenols with aryl bromides, with an efficiency that is comparable to our tetradentate

Scheme 5a



Scheme 5b



Scheme 5. Proposition for the respective roles of the imine and pyridine sites during the catalytic process.

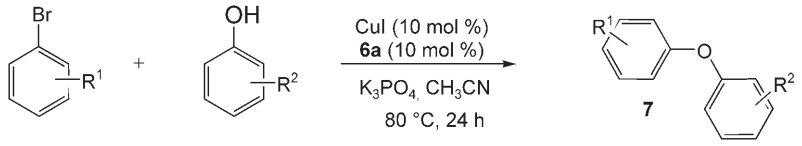
ligand **1**.[2b] To the best of our knowledge, the temperature conditions used in coupling reactions involving these two ligands, are the mildest ever reported.[2b] However, ligand **6a** obtained directly from the aniline is more attractive for industrial applications because it is cheaper to prepare than ligand **1**, which is derived from the more expensive *trans*-diaminocyclohexane.[15]

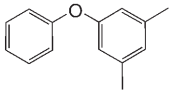
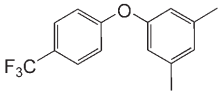
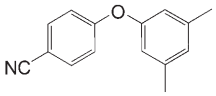
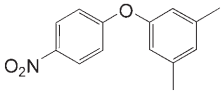
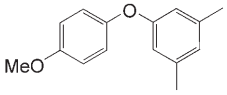
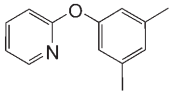
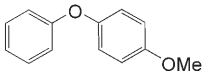
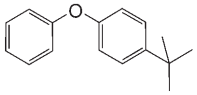
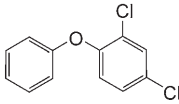
We next evaluated the potential of bidentate ligand **6a** in the *N*- and *O*-vinylation reactions of nucleophiles with hindered trisubstituted vinylating agents.

N- and *O*-Vinylation Reactions (Table 4)

We have previously studied the copper-catalyzed *N*- and *O*-vinylation reactions of nucleophiles.[2a] The combination of tetradentate ligand **1** and copper salts was found to generate a very powerful catalyst for the coupling of *E*-β-bromostyrene with numerous nitrogen heterocycles and phenol derivatives. Indeed, the corresponding *E*-β-styrylazoles and *E*-β-styryl aryl ethers could be obtained in high yields in the mildest temperature conditions to date (50–80 °C). However, for the usual **1**/Cu ratio of 0.5 corresponding to the introduction of one N,N-pincer per copper (2N/Cu), the coupling of more hindered 1-bromo-2-methylpropene failed in the case of pyrazole, and was very sluggish

Table 3. Couplings of aryl bromides with phenols in the presence of CuI/**6a**.[a]



Entry	R^1	R^2	Product		Yield [%][b,c] with **6a**	Yield [%][b,c] with **1**[d]
1	H	3,5-Me_2		**7a**	82	86
2	4-CF_3	3,5-Me_2		**7b**	90	89
3	4-CN	3,5-Me_2		**7c**	93	89
4	4-NO_2	3,5-Me_2		**7d**	83	84
5	4-OMe	3,5-Me_2		**7e**	70	72
6	2-Br-Py	3,5-Me_2		**7f**	100	100
7	H	4-OMe		**7g**	86	92
8	H	4-*t*-Bu		**7h**	70	75
9	H	2,4-Cl_2		**7i**	74	68

[a] *Reaction conditions:* aryl bromide (0.5 mmol), phenol (0.75 mmol), K_3PO_4 (1 mmol), CuI (0.05 mmol), ligand **6a** (0.05 mmol, "2N/Cu"), CH_3CN (300 μL), 24 h.

[b] Yields refer to GC yields (using 1,3-dimethoxybenzene as internal standard); yields are based on the default reagents (aryl bromides).

[c] Selectivity $\geq$ 96%: the only by-product is the arene resulting from hydrodeshalogenation of the corresponding aryl bromide; by-products derived from biaryl coupling were never observed.

[d] Yields obtained with tetradentate ligand **1** (5 mol% corresponding also to "2N/Cu") in the same conditions (results previously reported[2b]).

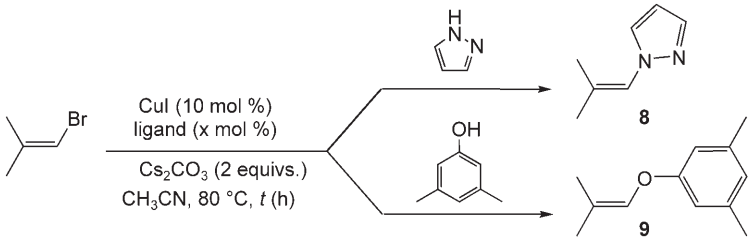
for phenols (Table 4, entries 1, 4). On increasing the ligand loading (Table 4, entries 2, 5), the outcome of the coupling was improved, but still not really satisfactory. Finally, we were pleased to find that, when replacing ligand **1** with the bidentate iminopyridine ligand **6a**, the yield of *E*-β-styrylpyrazole **8** and *E*-β-styryl 3,5-dimethylphenyl ether **9** could significantly be improved: from 40 to 75% for **8** and from 29 to 100% for **9** (Table 4).

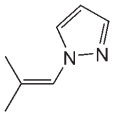
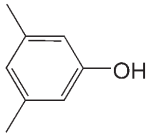
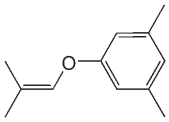
A possible explanation could be that ligand **6a**, being less sterically encumbered, enables the coordination of more bulky substrates (in this case: trisubstituted vinyl bromides) at the copper centre.

Conclusions

In spite of the great importance of copper/ligand-catalyzed arylations of nucleophiles, the role played by li-

Table 4. Vinylation of pyrazole and 3,5-dimethyphenol by 1-bromo-2-methylpropene.[a,b]



Entry	Nucleophile	Ligand [mol%]	N/Cu	Product[a]	Yield [%][c]
1		**1** (5)	**2**		8
2		**1** (10)	**4**		40
3		**6a** (20)	**4**		75 (*70*)
4		**1** (5)	**2**		21
5		**1** (10)	**4**		29
6		**6a** (20)	**4**		100 (*89*)

[a] *Reaction conditions for isolated yield:* nucleophile (2 mmol), 1-bromo-2-methylpropene (3 mmol), Cs_2CO_3 (4 mmol), CuI (0.2 mmol), ligand **6a** (0.4 mmol), CH_3CN (1.2 mL); *reaction conditions for GC yields:* nucleophile (0.5 mmol), 1-bromo-2-methylpropene (0.75 mmol), Cs_2CO_3 (1 mmol), CuI (0.05 mmol), ligand **1** (0.025 or 0.05 mmol) or **6a** (0.10 mmol), CH_3CN (300 μL). Reaction time: 24 h for the phenol and 36 h for the pyrazole.

[b] Results with the ligand **1** were previously reported for phenol vinylations.[2a]

[c] Yields refer to GC yields (using 1,3-dimethoxybenzene as internal standard) and yield in brackets refers to isolated yields after purification by column chromatography on silica gel or alumina; yields are based on nucleophile.

gands and the structural and electronic characteristics that make them efficient have not been well-established until now. However, in the absence of these additional chelators, it would not be possible to perform the coupling reactions in mild conditions, a requirement for industrial application.

The present study deals with various nitrogen ligands bearing imine and/or pyridine binding atoms present on our lead chelate **1**, which displays one of the broadest fields of application in the literature.[2] The activity conferred to copper by these counterparts of **1** has been compared in the case of phenol arylations, in order to emphasize the structure of the ligand/efficiency relationships. The results highlight the crucial presence of a pyridinic site, and the advantages to combine the latter with an imino-nitrogen within the same ligand. Indeed, both are complementary because they are likely determining in distinct steps of the catalytic cycle. According to our results, the pyridine would rather be involved in the oxidative addition step, whereas the imine might play an important role in the nucleophilic substitution and/or in the reductive elimination.

In addition, this work has allowed us to identify new powerful ligands such as the iminopyridine **6a** whose features and advantages are: low-cost, straightforward and high-yielding (95%) synthesis from cheap and commercially available reagents. In the framework of a close collaboration with industry, the discovery of such chelate scaffolds is of great interest.

Finally, this study should provide some tools useful for designing ligands able to perform a given reaction, according to the structural and electronic features of the involved coupling partners. Hence, making a pyridine site more electron-rich could facilitate the oxidative addition of less reactive electron-rich and/or bulky aryl halides. Respectively, reducing the electronic density of an imine site by introducing electron-withdrawing groups, may make the nucleophilic substitution and the reductive elimination of electron-poor and/or less hindered substrates easier.

Analogous studies are presently underway for oxygen-containing ligands in order to understand the way oxygen binding sites are involved during the catalytic process. Finally work is also in progress to extend this study to the case of other *N*- or *C*-nucleophiles.

Experimental Section

General Remarks

All reactions were carried out in 35-mL Schlenk tubes or in Carousel "reaction stations RR98030" Radley tubes, under a pure and dry nitrogen atmosphere. Acetonitrile was dis-

tilled from P_4O_{10} and was stored over 4 Å activated molecular sieves under a nitrogen atmosphere. Cesium carbonate (Aldrich) and tripotassium phosphate (Riedel-de Haën) were ground to a fine powder and stored under vacuum in the presence of P_4O_{10}. All other solid materials were stored in the presence of P_4O_{10} in a bench-top desiccator under vacuum at room temperature and weighed in the air. Copper(I) iodide was purified according to literature procedures[16] and stored protected from light. The synthesis of ligand **1** was reported in our previous papers.[2f] Iodobenzene, aryl bromides, β-bromostyrene and nucleophiles (phenols or pyrazole) were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). If solids, they were recrystallized in an appropriate solvent.[17] If liquids, they were distilled under vacuum and stored under an atmosphere of nitrogen. Special care was taken with liquid iodobenzene, which was regularly distilled and stored protected from light. All phenols were also stored protected from light.

Materials and Instrumentation

All products were characterized by their NMR, GC/MS and IR spectra. NMR spectra were recorded at 20 °C on DRX-250 and DRX-400 spectrometers working respectively at 250.13 and 400.13 MHz for ^{1}H and at 62.90 and 100.61 MHz for ^{13}C. Gas chromatography-mass spectra (GC/MS) were recorded on an Agilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and a HP5-MS 30 m × 0.25 mm capillary apolar column (Stationary phase: 5 % diphenyldimethylpolysiloxane film, 0.25 μm).

GC/MS method: Initial temperature: 45 °C; initial time: 2 min; ramp: 2 °C min^{-1} until 50 °C then 10 °C min^{-1}; final temperature: 250 °C; final time: 10 min. IR spectra were recorded on a Nicolet 210 FT-IR instrument (KBr pellet). Melting points were determined using a Büchi B-540 apparatus and are uncorrected.

General Procedure for Copper-Catalyzed Coupling Reaction of Phenols

After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar (12 × 4.5 mm) was charged with CuI (9.5 mg, 0.05 mmol), the ligand, the phenol (73.3 mg, 0.6 mmol) and K_3PO_4 (127.3 mg, 0.6 mmol). The tube was evacuated, back-filled with nitrogen. The aryl halide (0.5 mmol) was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed acetonitrile (300 μL). The tube was sealed under a positive pressure of nitrogen, stirred and heated to the required temperature for 24 h. The reaction mixture was allowed to cool to room temperature and diluted with dichloromethane (5 mL). 65 μL of 1,3-dimethoxybenzene (internal standard) were added. A small sample of the reaction mixture was taken and filtered through a plug of Celite®, the filter cake being further washed with dichloromethane. The filtrate was washed three times with water and analyzed by gas chromatography. The GC yields were determined by obtaining the correction factors using authentic samples of the expected products.

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