VIP

Highly Efficient and Mild Copper-Catalyzed N- and C-Arylations with Aryl Bromides and Iodides

Henri-Jean Cristau,*[a] Pascal P. Cellier,[a, c] Jean-Francis Spindler,[b] and Marc Taillefer*[a]

Abstract: Mild, efficient, copper-catalyzed N-arylation procedures for nitrogen heterocycles, amides, carbamates, and C-arylation procedures for malonic acid derivatives have been developed that afford high yields of arylated products with excellent selectivity. The N-arylation of imidazole with aryl bromides or iodides was found to be greatly accelerated by inexpensive, air-stable catalyst systems, combining catalytic copper salts or oxides with a set of structurally simple chelating ligands. The reaction was shown to be compatible with a broad range of aryl halides, encompassing sterically hindered, electron-poor, and electron-rich ones, providing the arylated products under particularly mild conditions (50–82 °C). The lower limit in ligand and catalyst loading and the scope of Ullmann-type condensations catalyzed by complexes bearing those ligands with respect to the nucleophile class have also been investigated. Chelating Schiff base Chxn-Py-Al (**1c**) generates a remarkably general copper catalyst for N-arylation of pyrrole, indole, 1,2,4-triazole, amides, and carbamates; and C-arylation of diethyl malonate, ethyl cyanoacetate, and malononitrile with aryl iodides under mild conditions (50–82 °C). The new method reported here is the most successful to date with regard to Ullmann-type arylation of some of these nucleophiles.

Keywords: arylation · copper · homogeneous catalysis · N,O ligands · nucleophilic substitution

Introduction

Transition-metal-catalyzed arylation of nucleophilic compounds with aryl halides is a key tool for carbon–heteroatom or carbon–carbon bond formation in organic synthesis. Certain classes of compounds available through these processes, such as N-arylated azoles,[1] N-arylated oxazolidin-2-ones,[2,3] or C-arylated malonic acid derivatives,[4] are industrially important synthetic targets. These motifs are found in a range of pharmaceuticals, agrochemicals, and natural products. Crucial requirements for development of an industrial process giving access to the aforementioned compounds are reliability, experimental ease, and, most important, low catalyst cost. Nucleophilic aromatic substitution with aryl halides can be mediated by palladium,[5] nickel,[6] or copper catalysts.[7,8] The lower cost of copper-based catalytic systems makes them particularly attractive for large-scale industrial applications.

Copper-catalyzed arylation of amines (Ullmann condensation),[9] amides and carbamates (Ullmann–Goldberg condensation)[10] or activated methylene compounds (Ullmann–Hurtley condensation)[11] are well-documented methodologies that were discovered several decades before the palladium and nickel-catalyzed methodologies. However, these transformations have not been employed to their full potential for a long time. Until recently, they suffered from reduced synthetic scope as a result of the harsh reaction conditions often required, a limited substrate scope, and the moderate yields obtained.[7c–e] Condensations were traditionally conducted in high-boiling-point polar solvents such as *N*-methylpyrrolidone (NMP), nitrobenzene, or dimethylformamide (DMF), at temperatures as high as 210 °C, sometimes in the presence of stoichiometric amounts of copper reagents and preferentially with aryl halides activated by electron-withdrawing or *o*-carboxylic acid groups.[12,13] The economic attractiveness of copper has led to a resurgence of interest in Ullmann-type reactions in recent years and has

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 DOI: 10.1002/chem.200400582

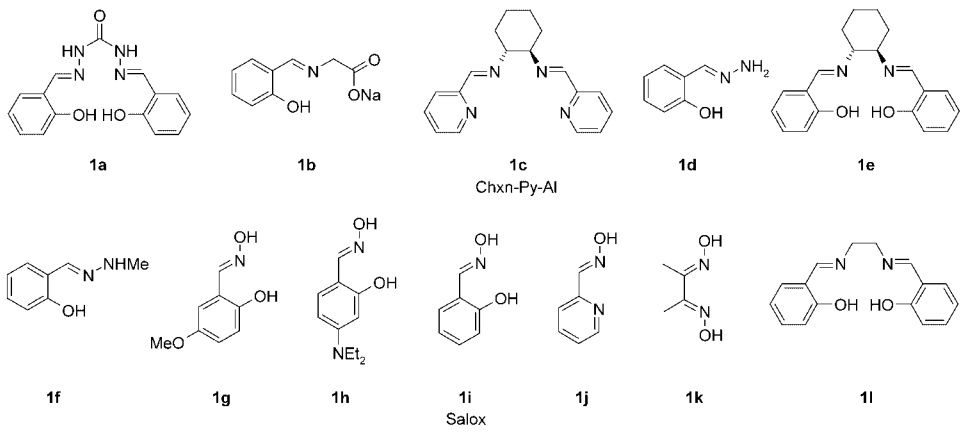
challenged synthetic chemists to devise milder synthetic methods. The development of new ligand structures for copper-catalyzed cross-coupling protocols constitutes an area of considerable interest. Indeed, pioneering work by Weingarten,[14] Takenaka,[15] Buchwald,[16] and Goodbrand[17] revealed rate accelerations when arylations were conducted in the presence of certain copper ligands. These additional compounds are thought to increase catalyst solubility, stability, and/or to prevent aggregation of the metal. This and the observation that some coupling partners with a supplementary copper-chelating group, such as 2-halogenobenzoic acids,[18] α- and β-amino acids,[19] or β-amino alcohols,[20] induced rate accelerations of Ullmann-type arylations relative to unfunctionalized parent substrates have led to a growing number of papers focusing on the deliberate use of additional ligands to facilitate the cross-coupling reactions.[7a–b] Careful choice of the promoter allows condensations to be run at relatively low temperatures, contrasting with the rather drastic experimental conditions necessitated by the traditional Ullmann-type arylations.

Starting from the idea that the presence of ancillary ligands coordinating the metal center is the most important factor in determining the efficiency of the catalyst system, we initiated a research program aimed at identifying appropriate new ligands with high binding propensity, to improve copper-catalyzed cross-couplings. A screening of forty new potential ligands led us to the discovery that simple bidentate oxime-containing compounds generate extremely effective catalysts for C–N and C–O bond formation involving pyrazoles[21] and phenols,[22] respectively. These compounds include the mixed donor salicylaldoxime **1i** and the vicinal dioxime dimethylglyoxime **1k**. Although oximes have often been used to complex copper salts,[23] there have been no reports of the use of such ligands in Cu-catalyzed aromatic substitution chemistry. Next, we tried to devise second-generation ligands and pursued our investigations on a broader structural range. We succeeded in identifying new multidentate donor compounds with nitrogen- or oxygen-binding sites, and alternatively a mixture thereof. An example is the chelating Schiff base **1c**,[24] hereafter named Chxn-Py-Al, which allowed expanding the reaction scope in a few cases. The ligands depicted here dramatically reduce temperatures required to effect pyrazole and phenol arylations (25–82 °C), while affording coupling products with excellent yields and selectivity regardless the electronic nature of substituents on aryl halides. Copper(I) oxide (Cu_2O; 5 mol %), an inexpensive ligand **1** (20 mol %) and two equivalents of Cs_2CO_3 in acetonitrile were identified as highly efficient systems to perform the couplings and brought notable improvement over previously disclosed methods.

Thus, it was a natural extension for us to investigate the generality of the coupling reaction with respect to nucleophiles, such as the other azoles (imidazoles, pyrroles, indoles, triazoles, and tetrazoles), amides, carbamates, or malonic acid derivatives. In this paper, we report a full account of our efforts toward the synthesis of arylated derivatives of these compounds and we demonstrate that Chxn-Py-Al (**1c**) is a remarkably general ligand for Ullmann-type condensation reactions.[25] While being not commercially available, **1c** is a stable, crystalline solid, which is very easily synthesized from cheap starting materials, with high yield and on a multigram scale.[22]

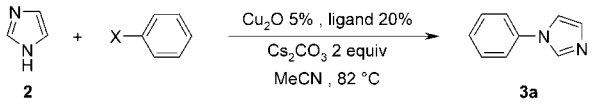
Results and Discussion

Copper-catalyzed N-arylation of azoles with aryl bromides and iodides: We first focused on the N-arylation of imidazole, since 1-arylimidazoles, which in addition to being recurrent templates in medicinal chemistry,[26] are exploited as important building blocks for the synthesis of *N*-heterocyclic carbenes,[27] a powerful class of ligands for transition-metal catalysis and for room-temperature ionic liquids,[28] which have been attracting a great deal of interest as environmentally benign solvents for organic synthesis.



It was determined during a preliminary survey of reaction conditions using bromobenzene as a model arylating agent that: 1) cuprous oxide is slightly more efficient than cuprous bromide as a precatalyst, 2) acetonitrile is a better solvent than DMF, and 3) cesium carbonate is far more efficient than any other inorganic base investigated. These are the same findings as those we have obtained for pyrazole N-arylation.[21] Copper(I) oxide is particularly interesting as a copper source owing to its low cost and insensitivity to light and air.[29] In comparison, cuprous bromide is slightly air-sensitive, while cuprous iodide is light sensitive, and both are more expensive than Cu_2O. The search for suitable ligands for imidazole N-arylation with bromobenzene was undertaken in acetonitrile at a relatively low temperature (82 °C), with cesium carbonate as a base (2 equiv), a catalytic amount of cuprous oxide (5 mol %), and 20 mol % of each ligand (based on the limiting reagent), with a reaction time fixed to 24 h. Table 1 shows the most

Table 1. Screening of ligands for the N-arylation of imidazole with bromobenzene or iodobenzene at 82 °C.[a]



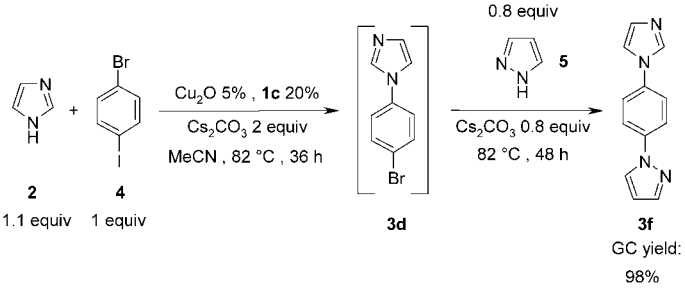
Entry	X	T [°C]	t [h]	Ligand	GC Yield [%][c]
1	Br	82	24	**1a**	55
2	Br	82	24	**1b**	49
3	Br	82	24	**1c**	48
4	Br	82	24	**1d**	48
5	Br	82	72	**1d**	91
6	Br	82	100	**1d**	>99
7	Br	82	24	**1e**	45
8	Br	82	24	**1f**	45
9	Br	82	24	**1g**	40
10	Br	82	24	**1h**	39
11	Br	82	24	**1i**	38
12	Br	82	24	**1k**	23
13	Br	82	24	**1l**	12
14[b]	I	82	24	**1j**	100
15[b]	I	82	24	**1i**	100
16[b]	I	50	24	**1i**	100

[a] Reaction conditions: imidazole (0.75 mmol), bromobenzene (0.5 mmol), Cs_2CO_3 (1.0 mmol), Cu_2O (5 mol %), ligand (20 mol %), MeCN (300 μL), under N_2. [b] Iodobenzene (0.75 mmol) and imidazole (0.5 mmol) were used. [c] Selectivity was >99 % in all cases.

significant results and reveals that many of the new ligands we recently reported for pyrazole N-arylation allowed the present Ullmann-type condensation to be efficiently performed at the lowest temperature reported to date for an aryl bromide. Our results are noteworthy compared with the 125 °C required using $Cu(OTf)_2$·PhH/1,10-phenanthroline catalytic system.[16b] Hydrazone- (entries 1,4,8) and Schiff-base-type supporting ligands (entries 2,3,7) with at least one additional phenol- or pyridine-type binding site[30] proved to be superior to oxime-type bidentate ligands (entries 9–12). It can be observed that salen-type ligand **1e** is much more efficient than parent compound **1l** in promoting Ullmann-type condensation. This result could be explained in terms of the geometry induced by the ligand around the copper catalyst. Actually, the dismutation equilibrium of the active copper(I) species into copper metal and copper(II) can be shifted toward Cu^I thanks to the use of ligands that favor a tetrahedral structure rather than a square planar one, more common with copper(II) species.[31] Moreover, rotation around the C–C bond in **1l** is expected to reduce its binding efficiency, which is restricted in **1e**. Reactions using ligands **1a–l** were totally selective with respect to imidazole and almost totally selective with respect to bromobenzene. They were never accompanied by formation of biaryl byproducts, while affording less than one percent of hydrodehalogenated arene byproduct. Moreover, bromobenzene proved to be unreactive toward NH- or OH-group-containing ligands. With commercially available and cheap ligand **1d**, a yield higher than 90 % could be obtained after 72 h heating (entry 5). The more reactive iodobenzene allowed condensation to be driven to completion in less than 24 h at temperatures ranging from 50 to 82 °C (entries 14–16). Those reaction conditions are the mildest yet reported for the N-arylation of an imidazole with a haloaromatic, whatever the metal catalyst.

The scope of the process with respect to aryl halide structure was investigated next. The catalyst systems composed of cuprous oxide and commercially available ligands **1d** or **1i** efficiently catalyzed the arylations of imidazole with electronically diverse aryl bromides at 82 °C and iodides at 50–82 °C (Table 2, reaction times are not optimized). Thus, electron-poor (entries 3,4,6,8), electron-neutral (entries 1,2), and even electron-rich (entries 5) aryl halides afforded the N-arylated products in excellent yields (generally greater than 90 %). This weak sensitivity to electronic effects is very interesting with regard to electron-rich substrates, since transition-metal-catalyzed reactions involving these arylating agents are traditionally less straightforward, particularly if the metal is palladium.[32] Lastly, the reaction was sensitive to steric hindrance near halogen atom, as usually stated in Ullmann-type condensations, being slower when starting from an *ortho*-substituted aryl iodide (entry 7).

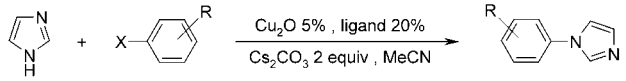
Particularly noteworthy are the reactivity differences exhibited by aryl halides toward oxidative addition. The reaction of imidazole with 4-bromoiodobenzene **4** took place on the iodine moiety with complete regioselectivity at 50 °C, when starting from a stoichiometric mixture of coupling partners (Table 2, entry 6; GC yield: 96 %). This selectivity in favor of the monosubstitution product thus allows retaining an active halide site for further functionalization. It was exploited to perform the two-step, one-pot synthesis of 1-[(4-imidazol-1-yl)phenyl]pyrazole (**3f**) starting from 4-bromoiodobenzene (**4**; Scheme 1). Compound **3f** was obtained with a remarkable 98 % GC yield (based on the default reagent, pyrazole).



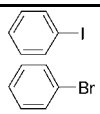
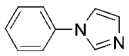
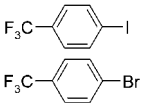
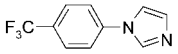
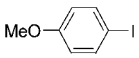
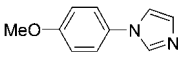
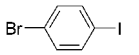
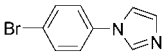
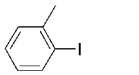
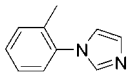
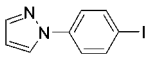
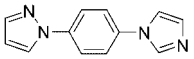
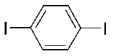
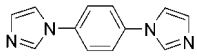
Scheme 1. One-pot synthesis of compound **3f** starting from 4-bromoiodobenzene.

In an endeavor to expand the scope of the methodology, protocols based on the use of our new catalytic systems were applied to a variety of other azoles. N-Arylation of pyrrole and indole with iodobenzene in acetonitrile was uneventful and could be driven to completion within 24 h at 82 °C by using ligands **1c** or **1i** (Table 3, entries 1,4). Both arylated products were isolated in 92–94 % yield. Condensations were also quantitative at 50 °C albeit the reaction time required was longer (74–96 h, entries 2,5). It should be pointed out that no byproduct arising from C-3 arylation of indole was observed under our reaction conditions. Such side reactions have been observed in the literature with pal-

Table 2. Copper-catalyzed N-arylation of imidazole with functionalized aryl bromides or iodides under mild conditions.[a]

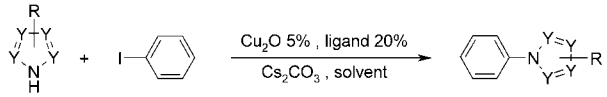


2 3

Entry	Aryl halide	Coupling product		T [°C]	t [h][l]	Ligand	Yield [%][b]
1[d]			**3a**	50	24	**1i**	100[k]
2				82	100[i]	**1d**	95
3[d]			**3b**	50	24	**1i**	100[k]
4[h]				82	72	**1d**	94
5[f]			**3c**	50	24	**1d**	97
6[c]			**3d**	50	36	**1i**	89
7			**3e**	82	36[j]	**1i**	92
8[e]			**3f**	82	24	**1i**	100[k]
9[g]			**3g**	82	48	**1i**	90

[a] Reaction conditions: imidazole (3 mmol), ArX (2 mmol), Cs_2CO_3 (4 mmol), Cu_2O (5 mol%), ligand **1d** or **1i** (20 mol%), MeCN (1.2 mL), under N_2. [b] Yield of isolated product unless otherwise noted. [c] With imidazole (2 mmol) and ArX (2 mmol). [d] With imidazole (2 mmol) and ArX (3 mmol). [e] With imidazole (2 mmol) and ArX (2.4 mmol). [f] With imidazole (2 mmol) and ArX (2.6 mmol). [g] With imidazole (5 mmol), ArX (2 mmol), and Cs_2CO_3 (6 mmol). [h] With Cs_2CO_3 (3.6 mmol). [i] GC yield was 91% after 72 h heating. [j] GC yield was 93% after 24 h heating. [k] GC yield. [l] Reaction times are unoptimized; no reaction was stopped before 24 h.

Table 3. Copper-catalyzed N-arylation of azoles with iodobenzene under mild conditions.[a]



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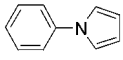
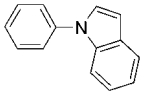
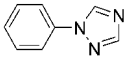
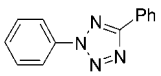
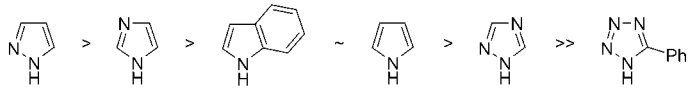
Entry	Azole	Coupling product		T [°C]	t [h]	Ligand	Solvent	Yield [%][b]	Selectivity[c]
1[d]			**6a**	82	24	**1i**	MeCN	100 (94)	97
2[d]				50	96	**1c**	MeCN	100	97
3[e]			**6b**	82	24	**1i**	MeCN	82	96
4[e]				82	24	**1c**	MeCN	>99 (92)	99
5[e]				50	74	**1c**	MeCN	99	99
6[f]			**6c**	82	24	**1i**	DMF	80	79
7[f]				82	24	**1c**	DMF	79	99
8[f]				82	48	**1c**	DMF	100 (91)	98
9			–	110	24	**1c**	DMF	0	–

[a] Reaction conditions: azole (1 equiv), iodobenzene (1.5 equiv), Cs_2CO_3 (2 equiv), Cu_2O (5 mol%), ligand **1c** or **1i** (20 mol%), solvent, [PhI] = 2.5 M, under N_2. [b] Yields refer to GC yields and yields in parentheses refer to isolated yields with >95% purity as determined by GC and ^1H NMR spectroscopy. [c] Selectivity relative to PhI. [d] With azole (1 equiv) and iodobenzene (1.2 equiv), [PhI] = 2 M. [e] With azole (1.5 equiv) and iodobenzene (1 equiv), [PhI] = 1.67 M. [f] With Cs_2CO_3 (1.6 equiv).

ladium catalysis[5j] with aryl halides or with copper catalysis[33] with triarylbismuthanes as arylating agents. 1,2,4-Triazole coupled smoothly to iodobenzene to yield a single regioisomer. N-Arylation occurred regiospecifically at the N1(2) atom, because of its enhanced nucleophilicity relative to the N4 atom, resulting from an α-effect in the corresponding anion. Reactions had to be performed in DMF due to poor solubility of cesium salt of 1,2,4-triazole (pK_{HA} = 14.75 in DMSO) in acetonitrile,[37a] which led to incomplete conversion of iodobenzene even after prolonged heating. Ligand **1c** was found more suitable than Salox **1i**, because the latter was not fully unreactive toward arylating

agent. Due to the weaker nucleophilicity of 1,2,4-triazole compared to pyrazole or imidazole, reaction of iodobenzene with Salox could actually compete with N-arylation of the substrate (Table 3, entry 6: 79% selectivity to product). Use of ligand **1c**, which cannot undergo any copper-catalyzed cross-coupling, cleanly led to a quantitative condensation within 48 h at 82 °C and 1-phenyl-1,2,4-triazole **6c** was isolated in 91% yield (entry 8). Attempts to N-arylate 5-phenyltetrazole with iodobenzene in DMF or acetonitrile at 82 °C failed, regardless of the precatalyst and nature of the supporting ligands. The arylating agent was recovered unchanged after 24 h heating. The use of more forcing reaction conditions (110 °C, DMF) was also unsuccessful (entry 9) and led to decomposition of iodobenzene to benzene (12%), phenol (8%), and diphenyl ether (38%). The two last reaction products probably arise from mono- and di-O-arylation, respectively, of cesium hydroxide generated from thermal decomposition of cesium hydrogen carbonate.[34] Analogous byproduct formation has already been observed in the literature, with carbonate[22,35] or hydroxide bases.[20a] The formation of a C–N bond is here a difficult problem to address, probably because of poor nucleophilicity of 5-phenyltetrazole anion. To our knowledge, metal-catalyzed N-arylation of tetrazole derivatives with aryl halides has never been described in the literature.[36]

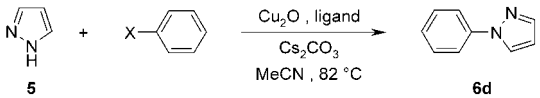
The order of reactivity in the azole series for Ullmann-type N-arylation emerging from this study is as follows:



First, we observed that imidazole proved to be less reactive than pyrazole. N-Arylation of the latter with bromobenzene was almost quantitative within 24 h at 82 °C,[21] while the same level of yield was only reached after 72 h with the former under the same reaction conditions. The weaker reactivity of imidazole does not appear to be the result of a difference in the ease of deprotonation by the base, since both substrates have comparable pK_{HA} values.[37,38b] We believe that the α-effect in pyrazolate anion is responsible for nucleophilicity enhancement, and consequently for such a rate-acceleration. Considering their better nucleophilicity and their superior ability to undergo C–N bond-forming reductive elimination, one would have expected indole and pyrrole to be more reactive than imidazole.[40a] The opposite result that we obtained can be explained by the higher acidity of imidazole and the subsequent greater ease of ionization (pK_{HA} = 18.6 in DMSO).[37a] It can also be rationalized by invoking the high copper-binding propensity of diazoles through the lone pair of their pyridine-type nitrogen atom (σ binding interaction),[38] when indole and pyrrole cannot efficiently chelate copper salts due to the electron-deficient nature of their nitrogen atoms.[39] Pyrrole (pK_{HA} = 23.0 in DMSO)[37a] and indole (pK_{HA} = 20.95 in DMSO)[37a] exhibited similar reactivity. The latter is more sterically encumbered, which is apparently counterbalanced by its greater ease of ionization. That 1,2,4-triazole was less reactive than pyrazole and imidazole could be attributed to an overall decrease in nucleophilicity when going from diazole to triazole family. As a result, two of the three elementary steps of the possible catalytic cycles depicted in Scheme 5 (see below) would be significantly slowed down: 1) nucleophilic substitution of copper-bound halide by triazolate anion and 2) C–N bond-forming reductive elimination.[40] Thus, reactivity of azoles appears to be the result of a complex balance between several parameters, including nucleophilicity, catalyst complexing ability, and acidity.[12g]

Taking into account the future large-scale industrial applications of our cross-coupling methodology, we decided to study the lower limit in ligand and catalyst loading compatible with both satisfactory reaction rates and high yields for the N-arylation of pyrazole. Though a 2:1 ligand-to-copper ratio has been used in all couplings described in our previous article,[21] it should be noted that reducing the amount of either **1i** or **1c** to a 1:1 ligand-to-copper ratio afforded almost the same yield within 24 h for condensation with bromobenzene (Table 4, entries 1–4). The exact nature of the catalytically active species is not known, albeit these results support an active species bearing one **1i** or **1c** ligand. The model reaction chosen for study of the coupling efficiency at low catalyst loading was the N-arylation of pyrazole with the more reactive iodobenzene in the presence of Cu_2O and **1i** in acetonitrile at 82 °C (Table 4). Lowering the amount of Cu_2O to 0.2 mol% led to incomplete consumption of iodobenzene after 48 h heating (71%, entry 5, L/Cu = 2:1). However, raising the ratio of L/Cu to 10:1 was of great benefit, since a quantitative yield of **6d** was obtained within the same time period (entry 6). When low catalyst loadings are employed (Figure 1), a higher ligand/catalyst ratio is thought to statistically favor formation of the active catalyst species and to disfavor competitive complexation of compounds other than the coordination of **1i** to copper. By contrast, no

Table 4. N-arylation of pyrazole at reduced catalyst and/or ligand loading.



5 **6d**

Entry	X	Ligand	Amount of Cu_2O [mol%]	Amount of ligand [mol%]	Amount of Cs_2CO_3 [equiv]	t [h]	GC Yield [%][d]
1[a,c]	Br	**1i**	5	20	2	24	96
2[a]	Br	**1i**	5	10	2	24	95
3[a,c]	Br	**1c**	5	20	2	24	93
4[a]	Br	**1c**	5	10	2	24	85
5[b]	I	**1i**	0.2	0.8	1.4	48	71
6[b]	I	**1i**	0.2	4.0	1.4	48	100
7[b]	I	**1i**	0.55	2.2	1.4	48	>99
8[b]	I	**1i**	0.55	11	1.4	48	>99
9[b]	I	**1i**	0.05	1.0	1.4	96	77
10[b]	I	**1i**	0.05	0.2	1.4	96	61

[a] Reactions conditions: Cu_2O, ligand, pyrazole (0.75 mmol), PhBr (0.5 mmol), Cs_2CO_3 (1 mmol), MeCN (300 μL), under N_2. [b] Reaction conditions: Cu_2O, Salox, pyrazole (12.5 mmol), PhI (8.3 mmol), Cs_2CO_3 (11.7 mmol), MeCN (5 mL), under N_2. [c] This entry is taken from reference [21]. [d] Selectivity was >99%.

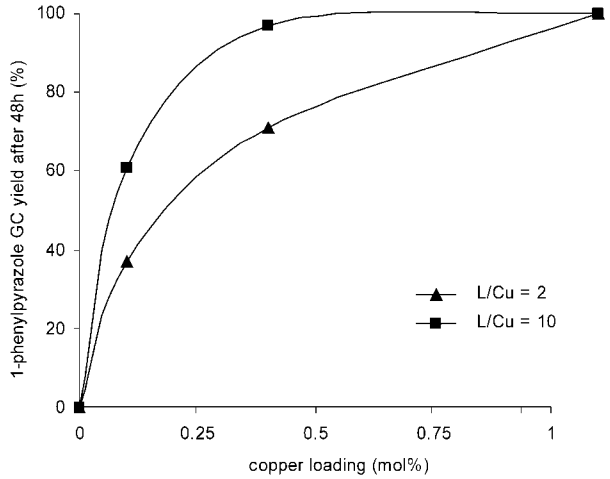


Figure 1. Beneficial use of a higher L/Cu ratio at low catalyst loading.

significant effect on reactivity was observed when shifting from a 2:1 to a 10:1 L/Cu ratio from 0.55 mol% Cu_2O loading (Table 4, entries 7,8 and Figure 1). We also checked that the catalyst suffered no deactivation after prolonged heating at 82°C: feeding a reaction mixture with additional pyrazole, iodobenzene, and cesium carbonate (0.5 equiv each) after complete conversion of starting material immediately got the reaction started again. Catalytic arylation still operates with 0.05 mol% Cu_2O and retains its complete selectivity albeit the reaction rate is very slow (entries 9,10). It is worth noting that this study, which was carried out on an 8 mmol scale, also demonstrates that this reaction has the potential to scale up to gram quantity.

It is worth noting that we have devised a general and high-yielding method for the N-arylation of monoazoles, diazoles, and triazoles. Copper-catalyzed methods with organometal or organometalloid reagents (arylbismuthanes, arylplumbanes, arylboronic acids, etc.) are generally not very successful for the N-arylation of monoazoles like indole or pyrrole,[33,41] while palladium is virtually inefficient for mediating the N-arylation of diazoles with unactivated aryl halides.[42] Besides, the present methodology is a cheap alternative to the use of sophisticated palladium–phosphine systems for the N-arylation of monoazoles.[5j,43] With regard to Ullmann condensations, the experimental conditions presented here are milder than those reported in the literature. Buchwald et al. found that CuI-catalyzed coupling reactions of aryl iodides and various azoles occurred at 110–125°C using ligands such as 1,10-phenanthroline, *N,N′*-dimethyl-1,2-ethylenediamine, racemic *trans*-1,2-diaminocyclohexane, or its *N,N′*-dimethyl analogue (only three N-arylations of indole and one N-arylation of pyrazole with aryl iodides were run at 80°C).[16b,24,44,45] Kang et al. obtained similar results for the N-arylation of indole and pyrrole with 1,2-ethylenediamine as a promoter at 110°C.[46] As a comparison, Buchwald et al. have performed the N-arylation of pyrazole (80°C), imidazole (110°C), and 1,2,4-triazole (110°C) within 24 h with iodobenzene or 5-iodo-*m*-xylene in 89–93% yield,[44c] while we have run the corresponding reactions at 50,[21] 50, and 82°C, respectively, within the same reaction time and with yields ranging from 80 to 100%. It should also be mentioned that Buchwald's system was reported to be unsuccessful[47] or low-yielding (18%)[44b] for the N-arylation of imidazole with aryl bromides at 110–112°C. The CuI–L-proline catalytic system recently described by Ma et al.[48] requires much longer reaction times than ours, temperatures 10–40°C higher, and was not reported to allow the use of aryl bromides. As a comparison, this group has performed the arylation of imidazole with 4-iodoanisole at 90°C within 36 h (91% yield), while we have succeeded to complete the same reaction at 50°C in less than 24 h (Table 2, entry 5, 97% yield).

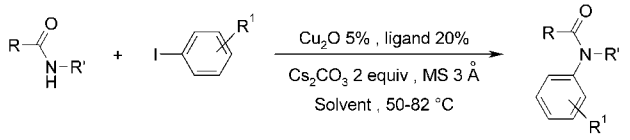
Copper-catalyzed N-arylation of amides and amide derivatives: In the hope of broadening the scope of our arylation protocol, we decided to check the efficiency of our catalyst–ligand systems on reactions that involve nitrogen nucleophiles with an α-carbonyl or an α-sulfonyl group, known as Goldberg condensations. We first focused on the N-arylation of acetamide and benzamide, which can be considered as cheap aniline precursors. A preliminary study involving both substrates has shown that condensations have to be conducted in DMF rather than in acetonitrile, in which amides are less soluble. Salicylaldoxime (**1i**) was found efficient for promoting Goldberg condensations, although substituting with **1c** improved reaction yields. We observed that acetamide, benzamide, and their N-arylated products were slightly sensitive under the basic reaction conditions employed. Small amounts of aniline and diphenylamine were detected by GC/MS (<5%). The observed hydrolysis might be caused by cesium hydroxide or water, arising from thermal decomposition of cesium hydrogen carbonate[34] produced by deprotonation of amides with Cs_2CO_3 [Eq. (1)].

$$x\ CsHCO_3 \xrightarrow{\Delta} \begin{cases} x = 2: & Cs_2CO_3 + H_2O + CO_2 \\ x = 1: & CsOH + CO_2 \end{cases} \qquad (1)$$

We were pleased to find that addition of small amounts of powdered and activated 3 Å molecular sieves to the reaction mixture had the synthetic advantage of reducing formation of these byproducts to less than 1%. Molecular sieves also limit the competitive arylation of water by iodoaromatics, producing phenols and diarylethers, to less than 2%.

Arylation of acetamide with iodobenzene occurred sluggishly at 82°C and delivered two coupling products, in spite of the use of excess amide (1.5 equiv). The expected *N*-phenylacetamide (**7a**) was obtained with 85% selectivity, along with *N,N*-diphenylacetamide (**7b**) from competitive diarylation with 8% selectivity (Table 5, entry 1). Raising the amount of amide to 2.5 equivalents did not result in an interesting increase in selectivity. As Ullmann–Goldberg arylations are sensitive to steric hindrance effects, a better selectivity for the monoarylation product was expected if starting from the more hindered benzamide. Indeed, diarylation of this substrate was not observed and *N*-phenylbenzamide (**7c**) was obtained in 96% selectivity and 91% yield within 48 h (Table 5, entry 3). The better reactivity of benza-

Table 5. Copper-catalyzed N-arylation of amides or amide derivatives with aryl iodides under mild conditions.[a]



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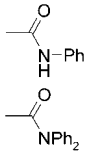
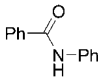
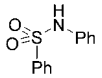
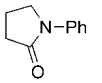
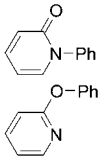
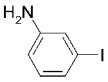
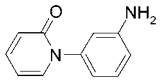
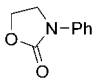
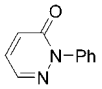
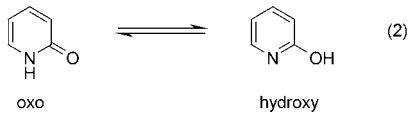
Entry	Aryl halide	Nucleophile	Coupling product		T [°C]	t [h]	Ligand	Solvent	Yield [%][b]
1[c]				**7a** **7b**	82	75	**1c**	DMF	**7a**: 81 (85) **7b**: 7 (8)
2				**7c**	82	24	**1c**	DMF	(81)
3					82	48	**1c**	DMF	91 (96)
4[c,d]				**7d**	82	24	**1c**	DMF	(86)
					82	48	**1c**	DMF	88 (94)
5[e]				**7e**	82	40	**1c**	DMF	92 (100)
6[e]				**7f** **7g**	82	24	**1c**	MeCN	**7f**: 90 (98) **7g**: 2 (2)
7[e,f]				**7h**	82	48	**1c**	MeCN	82
8[g]					82	24	**1i**	MeCN	(59)
9[g]					82	24	**1c**	MeCN	(74)
10[g]				**7i**	82	24	**1i**	DMF	(86)
11[g]					82	24	**1c**	DMF	(94)
12[c]					82	24	**1c**	DMF	97 (>99)
13[c]					50	96	**1c**	DMF	(>99)
14[d,e,g]				**7j**	82	100	**1i**	MeCN	89

[a] Reaction conditions: nucleophile (3 mmol), ArI (2 mmol), Cs_2CO_3 (4 mmol), Cu_2O (5 mol%), ligand **1c** or **1i** (20 mol%), 3 Å molecular sieves (600 mg), solvent (1.2 mL), under N_2. [b] Yields refer to isolated yields with >95% purity as determined by GC and ^{1}H NMR spectroscopy and yields in parentheses refer to GC yields. [c] With Cs_2CO_3 (3.2 mmol). [d] With MeCN (1.6 mL). [e] With nucleophile (2 mmol) and ArI (3 mmol). [f] With ligand **1c** (10 mol%). [g] Without molecular sieves.

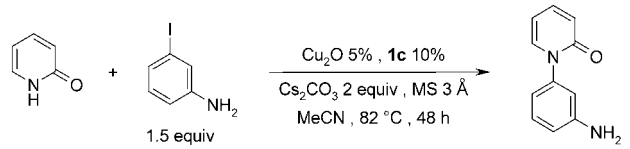
mide (pK_{HA} = 23.35 in DMSO)[37a] relative to acetamide (pK_{HA} = 25.5 in DMSO)[37a] might result from its greater ease of deprotonation. N-Arylation of benzenesulfonamide was uneventful. Only a small amount (0.5%) of benzenesulfonamide diarylation product was detected by GC/MS and identified by coaddition of a pure sample.

Given the full selectivity of the reaction with respect to pyrrolidin-2-one, the use of a moderate excess of iodobenzene allowed the coupling to be driven to completion and the corresponding *N*-phenylamide (**7e**) to be isolated in 92% yield (entry 5). Arylation of ambidentate pyridin-2-one (**8**) was also investigated. According to the literature, the more polar lactam form **8**, which is in tautomeric equilibrium with the lactim form **9** (2-hydroxypyridine) [Eq. (2)], is favored in polar solvents.[49] We only observed the polar oxo form by ^{1}H NMR spectroscopy in deuterated acetonitrile at 25°C.



8 **9** (2)

N-Arylation of this substrate with iodobenzene was found to strongly predominate over O-arylation, in acetonitrile at 82°C (N-/O-arylation = 98:2), and the reaction turned out to be quantitative within 24 h (Table 5, entry 6). Such a ratio is consistent with literature data related to Goldberg condensations.[12f,50] We took advantage of this selectivity in favor of the N-arylation product and exemplified the method developed by the synthesis of a medicinally active molecule, the sedative Amphenidone (**7h**; Scheme 2).[51] Compound **7h** was obtained in 82% isolated yield (N-/O-arylation >99:1), from pyridin-2-one (**8**) and 3-iodoaniline (**10**; Table 5,



Scheme 2. Synthesis of the sedative Amphenidone **7h** (Dornwall).

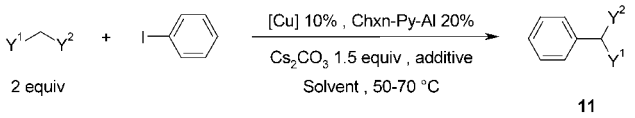
entry 7). This new mild and efficient synthetic route to Amphenidone is noteworthy compared with its previous preparation, which was carried out under traditional Goldberg conditions (heating at 180 °C in refluxing 1,2-dichlorobenzene).[51]

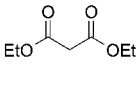
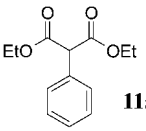
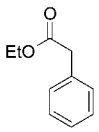
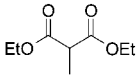
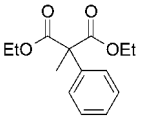
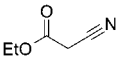
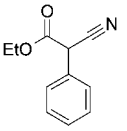
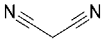
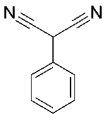
We next attempted to subject oxazolidin-2-one to arylation with iodobenzene. *N*-Aryloxazolidin-2-ones constitute an important class of therapeutic agents; this is illustrated by the drugs Linezolid (Zyvox)[2] and (*R*)-Toloxatone (Humoryl),[3] with antibiotic and antidepressant activity, respectively. *N*-Aryloxazolidin-2-ones are also precursors to *vic*-arylaminoalcohols,[52] another template in medicinal chemistry.[53] The reaction catalyzed by Cu_2O/**1c** was quantitative in DMF in less than 24 h at 82 °C, provided that molecular sieves were used and the amount of Cs_2CO_3 was reduced to 1.6 equiv (entry 12). The GC yield was still excellent without molecular sieves and with two equivalents of base (**7i**: 94 %, entry 11), albeit slightly lowered by Cs_2CO_3-promoted hydrolysis of the coupling product to 2-anilinoethanol.[52] Condensations proved to be more troublesome and sluggish in acetonitrile or when using Salox (**1i**) as supporting ligand (entries 8–10). We suspect that Salox or the Salox anion are not to be fully unreactive toward oxazolidin-2-one moieties and to contribute a few percent to their decomposition. Moreover, it is believed that deprotonations of Salox and oxazolidin-2-one produce some $CsHCO_3$, which thermally decomposes into cesium hydroxide, as mentioned earlier. This species might also be responsible for the observed decomposition. Condensations can also be carried out in a quantitative fashion at 50 °C, if reaction time is not an issue (entry 13). Lastly, N-arylation of 2H-pyridazin-3-one was performed in 89 % yield (entry 14); reactions employing Salox and acetonitrile were somewhat faster than those with Chxn-Py-Al and DMF. To the best of our knowledge, this is the first time an Ullmann-type N-arylation of pyridazin-2-one has been described. This provides a new protocol to synthesize a class of compounds with reported herbicide, insecticide,[54] or anti-inflammatory activity.[55]

Copper-catalyzed C-arylation of malonic acid derivatives: The synthesis of α-arylated malonic acid derivatives continues to attract much attention, as they represent useful precursors to two commercially important classes of nonsteroidal anti-inflammatory drugs, α-arylacetic acids (Diclofenac, Indomethacin, etc.) and α-arylpropionic acids (Ibuprofen, Naproxen, Flurbiprofen, etc.).[4] They are also used in material sciences, as precursors to electron-acceptors of the 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ) class.[56] Hurtley discovered in 1929 that C-arylation of several families of stabilized carbanions, including malonic acid derivatives, could be promoted by catalytic amounts of copper salts.[11] His protocol necessitates the use of a strong base (NaH, MeONa) and is limited to aryl halides bearing *ortho*- or pseudo-*ortho*-carboxylic acid groups.[13] Extension of the method to aryl halides lacking substituents capable of coordinating to the active Cu species is hampered by numerous restrictions, including modest yields, the requirement of at least stoichiometric amounts of copper,[56a,57] limited substrate scope,[58] or a high reaction temperature (120 °C), at which malonate esters tend to decompose.[59] Only recently was a variant of this transformation performed under mild conditions, in the presence of simultaneously catalytic copper and a weak base, allowing high functional-group tolerance. Buchwald et al. employed CuI as a precatalyst and 2-phenylphenol as ligand to mediate the C-arylation of diethyl malonate with aryl iodides in the presence of cesium carbonate at 70 °C.[8] However, this method suffers from a few drawbacks. The nature of the ligand 2-phenylphenol is problematic, since O-arylation of this compound competes with C-arylation of the substrate in a few cases. Yields are also diminished by hydrolysis followed by decarboxylation of the coupling products, affording ethyl α-arylacetates as side products (up to 10 %). Keeping these limitations in mind, we decided to devise new conditions allowing efficient Ullmann-type arylation of three malonic derivatives bearing an activated methylene group, diethyl malonate, ethyl cyanoacetate, and malononitrile, without preparation of the anions prior to coupling.

Our initial exploration of reaction conditions focused on the coupling of diethyl malonate (2 equiv) with iodobenzene (1 equiv). The results are compiled in Table 6. Chxn-Py-Al **1c** was preferred to Salox **1i** as a ligand, since previous work in our laboratory has shown that the latter, due to its nucleophilic nature, was not fully unreactive toward base-sensitive functional groups.[21] The beneficial use of **1c** in this case probably arose from its aprotic nature and chemical inertness toward ester moieties. Cuprous iodide as a precatalyst afforded an excellent yield (95 %) of cross-coupling product **11a** in THF or acetonitrile at 70 °C, using Cs_2CO_3 as a base, and proved to be more efficient than cuprous oxide (Table 6, entries 1–3). Ethyl α-phenylacetate (**11b**) was also obtained with 3–4 % GC yield through decarboxylation of the product. Since water or cesium hydroxide generated from $CsHCO_3$ [Eq. (1)] probably contribute to decomposition through ester hydrolysis, water removal could deliver an even cleaner condensation. Indeed, we found that addition of small amounts of finely ground and activated 3 Å molecular sieves almost completely inhibited this side reaction (< 0.5 %), while leading to only a slight decrease in the reaction rate. In the presence of this additive, acetonitrile was superior to THF as solvent (entries 4,5). Quantitative consumption of iodobenzene was attained by employing a slightly longer reaction time, which provided diethyl α-phenylmalonate (**11a**) in 93 % isolated yield (entry 6). It is important to note that no iodobenzene was consumed by reaction with **1c**, contrary to the literature with 2-phenylphenol as ligand.[8] Although **11a** is more acidic than diethylmalonate, no diarylated byproduct arising from phenylation of **11a** was formed under our conditions. We also observed

Table 6. Copper-catalyzed C-arylation of malonic acid derivatives with iodobenzene under mild conditions.[a]



Entry	Cu	Nucleophile	Coupling product			T [°C]	t [h]	Additive	Solvent	Yield [%][b]
1	Cu_2O		 **11a**		**11b**	70	24	–	THF	**11a**: 59/**11b**: 3
2	CuI						24	–	THF	**11a**: 95/**11b**: 4
3	CuI						24	–	MeCN	**11a**: 95/**11b**: 3
4	CuI						24	MS 3 Å	THF	**11a**: 88[c]
5	CuI						24	MS 3 Å	MeCN	**11a**: 95[c]
6	CuI						30	MS 3 Å	MeCN	**11a**: 98 (93)[c]
7	CuI				**11c**	70	24	MS 3 Å	MeCN	<1
8	CuI				**11d**	70	28	MS 3 Å	MeCN	98 (92)
9	CuI				**11e**	50	72	–	MeCN	69 (62)[d]

[a] Reaction conditions: nucleophile (4 mmol), PhI (2 mmol), Cs_2CO_3 (3 mmol), Cu (10 mol%), ligand **1c** (20 mol%), 3 Å molecular sieves (600 mg, if needed), solvent (1.2 mL), under N_2. [b] Yields refer to GC yields and yields in parentheses refer to isolated yields with >95% purity as determined by GC and ^{1}H NMR spectroscopy. [c] GC yield in **1b** was <0.5%. [d] Conversion of PhI was 88% and GC yield of benzene was 15%.

that a reversal of the stoichiometry of the reaction, that means using a twofold excess of iodobenzene relative to diethyl malonate, was detrimental to the yield, which decreased to about 70%.

With optimized conditions in hand, the scope of this catalytic process was examined with various malonic derivatives, and the results are summarized in Table 6. Diethyl 2-methylmalonate did not participate in the copper-catalyzed arylation process under conditions permitting a quantitative arylation of the unsubstituted parent compound (entry 7). It is unclear whether this lack of reactivity arises because of steric hindrance or is due to decreased acidity of the substrate ($pK_{HA}=18.7$ in DMSO)[60] relative to diethyl malonate ($pK_{HA}=16.4$ in DMSO).[37a] Poor results were also obtained in the literature for that kind of coupling using copper[57i,58b] or palladium[5e] catalysts. In fact, catalytic intermolecular arylation of 2-alkyl-substituted diethylmalonates with aryl halides was only reported to be successful under Hurtley's conditions.[61] However, diethyl 2-methyl-2-arylmalonates, precursors to profen drugs, could be accessed easily by sequential one-pot arylation and alkylation of diethyl malonate.[5e] Arylation of ethyl cyanoacetate with iodobenzene proceeded in a chemoselective fashion and **11d** was isolated in a remarkable 92% yield (entry 8). The reaction time required was similar to that of diethyl malonate. Again, molecular sieves reduced the extent of decarboxylation to less than 0.5% and diarylation was not observed.

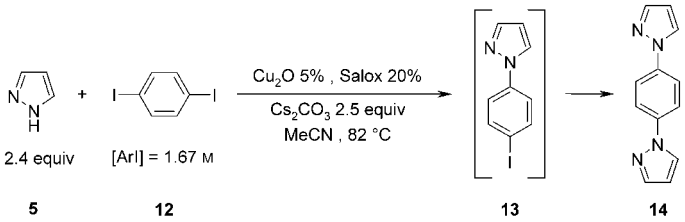
Careful choice of reaction conditions proved of value in the synthesis of 2-phenylmalononitrile (**11e**), the formation of which is significantly hampered by hydrodehalogenation of iodobenzene. We found that reducing temperature to 50°C had a beneficial impact on selectivity in favor of the desired reaction and that the use of molecular sieves was unnecessary. Condensation proceeded to 88% conversion of iodobenzene within 72 h at this relatively low temperature. Compound **11e** was obtained with 79% selectivity and was isolated in decent yield (62%, entry 9). This yield is noteworthy compared with the 55% reported by Miura[59] for the same coupling performed at 120°C without additional ligand, and with the 42–61% yields obtained using stoichiometric amounts of copper salts.[56a,57g–57h] Malononitrile is prone to decomposition under our coupling conditions, which leads to formation of benzonitrile in small amounts, from cyanide ion arylation (4%). Such a side reaction has already been observed in the literature in the course of a copper-catalyzed dicyanomethyl anion arylation.[57e]

Thus, the three targeted malonic acid derivatives have been monoarylated with iodobenzene under mild conditions (50–70°C, 62–93% yield), by using the same catalytic system, CuI/**1c**. The experimental conditions employed have no equivalent in the literature from the standpoint of cost and performance with regard to ethyl cyanoacetate arylation.

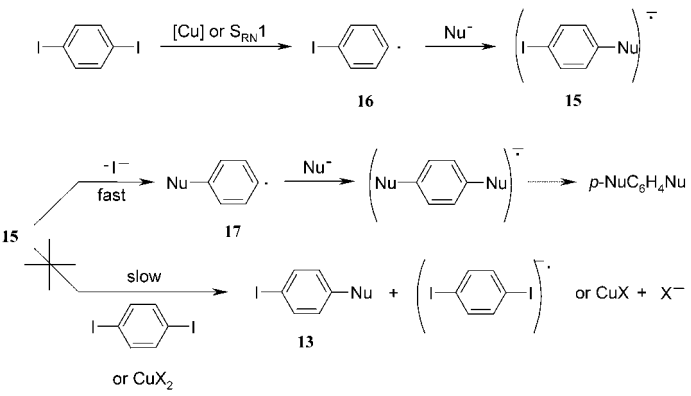
Mechanism of the copper-catalyzed nucleophilic aromatic substitution with aryl halides: The results we obtained provided valuable information with respect to the mechanism of the reaction. Uncatalyzed pathways, such as S_NAr[62] or $S_{RN}1$[63] (thermal or photochemical) could be discarded, since control experiments involving either bromobenzene or

iodobenzene conducted without the copper source did not allow the cross-coupling products to be formed. Elimination–addition via aryne intermediates[62] was also ruled out considering the regioselectivity of the reaction with respect to substituted aryl halides. As a consequence, arylations described in this article proceed according to a copper-catalyzed pathway. Among the classes of mechanisms that have been proposed in the literature[7c] for such Ullmann-type condensations, two conceivable ones are those involving 1) radical intermediates and 2) oxidative addition/reductive elimination.

Intervention of radicals or radical anions is contradicted by several experiments that we have carried out. Nucleophilic aromatic substitutions were inhibited neither by electron-acceptors (nitroarenes) nor by radical scavengers such as THF[64] or BHT. Supplementary evidence excluding the participation of radical anion intermediates under our reaction conditions was obtained by using a classical diagnostic technique, the study of the behavior of a dihalobenzene and its substitution products during a nucleophilic substitution reaction.[65] Pyrazole was chosen as the model nucleophile for that experiment. We observed that coupling of 1,4-diiodobenzene (**12**) to excess pyrazole initially gave rise to monosubstituted product **13**, which underwent subsequent substitution to afford **14** (Scheme 3). Mechanisms involving formation of radical anion intermediates would lead to the disubstitution product **14** without significant intermediacy of monosubstitution product **13**. According to the literature,[66] the aforementioned processes lead to quasi-exclusive disubstitution, even at short reaction times, because radical anion **15**, generated by reaction of the nucleophile with halo-aryl radical **16**, does not undergo bimolecular electron transfer (to copper(II) or 1,4-diiodobenzene) to give monosubstitution product **13**, but instead loses the second iodide ion to form aryl radical **17**. This unimolecular pathway is indeed much faster (Scheme 4). Additionally, a radical pathway would not have led to a ratio of $E/Z = 99{:}1$ for the configuration of the double-bond geometry in the 1-styrylpyrazole that we have recently synthesized through alkenylation of pyrazole with β-bromostyrene using the present method.[21] Since vinyl radicals are known to undergo rapid inversion of configuration,[67] a substantial loss of stereochemistry would have been observed. This result seems to rule out intervention of radicals, even briefly, free, or tightly held in a solvent cage or in the form of undissociated complex with copper.[18,66b]



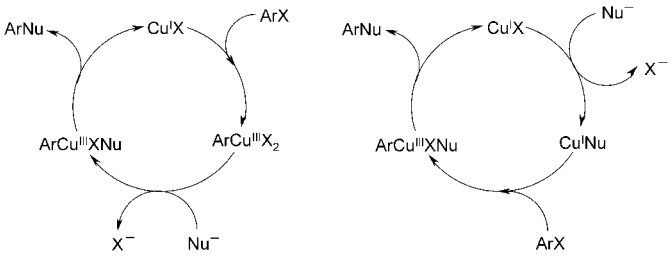
Scheme 3. Test for intermediacy of radical anion intermediates in Ullmann-type condensations.



Scheme 4. Expected behavior of 1,4-diodobenzene if mechanism would involve radical anion intermediates.

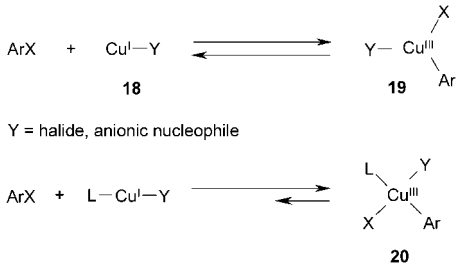
The intervention of the oxidative addition/reductive elimination mechanism in Ullmann condensations was first proposed by Cohen in 1974.[68] This mechanism was next substantiated by several literature reports[64,66b,69] indicating Cu^{I} and Cu^{III} intermediates. It appears to be a possible explanation for the Ullmann condensations described here, since it accommodates the following experimental facts:[21] 1) the reactivity sequence in such processes ($ArI > ArBr \gg ArCl$) parallels the leaving-group ability of the halide ions, 2) couplings are slightly favored by electron-withdrawing groups on aryl halides and slightly disfavored by electron-releasing ones, 3) steric hindrance on either coupling partner is rate-depressing, and 4) unactivated aryl halides do not react in the absence of the copper catalyst. A copper(I)-catalyzed nucleophilic substitution mechanism would thus parallel that of the corresponding palladium(0) and nickel(0) reactions; this would not be surprising, since copper(I) is a d_{10} transition metal, isoelectronic to the two aforementioned species. This mechanism involves the three following elementary steps: oxidative addition of the aryl halide to copper(I) generating a transient Cu^{III} species, nucleophilic substitution of copper-bound halide by pyrazole anion, and reductive elimination of the coupling product, thereby regenerating the active catalyst. Although we have assumed that copper complexes are monomeric and undergo oxidative addition to a single metal center, a dinuclear oxidative addition process could also occur. Uncertainty remains as to whether nucleophilic substitution step precedes or follows the oxidative addition step. Both possibilities are depicted on Scheme 5.

A possible role played by the additional ligands in the present Ullmann condensation is to promote oxidative addi-



Scheme 5. The two alternative oxidative addition/reductive elimination mechanistic pathways for copper-catalyzed nucleophilic aromatic substitutions with aryl halides.

tion to the Cu^{I} complex. Indeed, oxidative addition of cuprous halides to aryl halides would be a reversible process according to the literature.[64] The well-documented copper-catalyzed halogen exchange in aryl halides is a further indication of this reversibility,[64,70] seeing that the reverse reaction is equivalent to reductive elimination of aryl halide from Cu^{III}. Our best ligands are hard donor ligands (Lewis bases with nitrogen or oxygen binding sites), which display a higher affinity toward hard copper(III) than soft copper(I).[31b,71] Due to their suitable σ-donor and π-acceptor properties, as well as their chelating nature, they might exhibit a superior ability to stabilize the oxidative addition product **20**, thus shifting to the right the position of the equilibrium in Scheme 6.



Scheme 6. Hypothesis of stabilization of the Cu^{III} oxidative addition product by the use of an appropriate supporting ligand L.

Conclusion

In conclusion, we have shown that the catalytic systems we have recently described for Ullmann-type arylation of pyrazoles and phenols offer a straightforward entryway into a variety of other copper-catalyzed reactions. Catalysts generated from catalytic cuprous oxide or iodide and a catalytic amount of a multidentate donor compound **1**, combining oxygen- and/or nitrogen-binding sites, such as potentially bidentate oxime ligand Salox **1i**, hydrazone ligand **1d** or potentially tetradentate Schiff base ligand **1c**, allowed the high-yielding arylation of a broad spectrum of nitrogen and carbon nucleophiles at relatively low temperatures (50–82 °C), in acetonitrile or DMF, in the presence of the mild base cesium carbonate. A variety of substituted aryl bromides and iodides were readily coupled with a number of azoles (with the exception of tetrazoles), amides, carbamates, pyridazin-2-one, diethyl malonate, ethyl cyanoacetate, and malononitrile. The experimental conditions described in this work represent a new landmark in the field of Ullmann-type arylation of imidazole, 1,2,4-triazole, pyrrole, and ethyl cyanoacetate. Our conditions proved to be just as efficient as those already reported for indole,[44a] diethyl malonate,[8] and malononitrile[59] arylation. With regard to amides and carbamates, our catalytic systems were particularly efficient for condensations with oxazolidin-2-one and pyridin-2-one.[72] The synthetic use of the method was demonstrated by an efficient preparation of the sedative Amphenidone. Reactions were somewhat slower with sulfonamides and other carboxylic amides investigated. Their scope did not exceed that of the best Ullmann–Goldberg-type process, reported by Buchwald and co-workers, using 1,2-diamines as ligands.[73] Compared to other Ullmann-type nucleophilic aromatic substitution methods described in the literature, the present one is unique in terms of versatility, since a single catalyst, generated from ligand **1c**, can be used for the first time in C–N, C–O, and C–C bond-forming reactions. The attractiveness of this general and reliable synthetic tool is further enhanced by its absence of reactivity toward aryl halides. This is an advantage over some of the ligands recently reported by others for analogous copper-catalyzed reactions.[8,20b,24,44a,48,73,74] Mildness, low-cost, experimental simplicity, and the ability to work at low catalyst loading are features of our methodology that make it particularly well suited for industrial-scale syntheses, for which financial and environmental issues are of greater concern. Consequently, it should find applications very soon.[75] Efforts to expand the utility of our new catalyst systems to other cross-coupling and related reactions, along with mechanistic studies, are in progress in our laboratory and will be reported in due course.

Experimental Section

General: Flash column chromatography was performed with SDS 60 ACC silica gel (35–70 μm or 70–200 μm). Thin-layer chromatography was carried out with Merck silica gel $60F_{254}$ plates. All products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and GC/MS. IR spectra were recorded on a Nicolet 210 FT-IR instrument (neat or thin film for liquid products, and KBr pellets or in dichloromethane for solid products). ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were recorded at room temperature on a Bruker AC 200 MHz or a Bruker Avance 250 MHz instrument with chemical shifts reported in ppm relative to the residual deuterated solvent peak. $^{19}F\{^{1}H\}$ NMR spectra were recorded at room temperature on a Bruker Avance 250 MHz instrument with chemical shifts reported in ppm relative to $CFCl_3$. The peak patterns are indicated as s, singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; m, multiplet. Gas chromatographic analysis were performed on a Delsi Nermag DI-200 instrument with an FID detector, a Delsi Nermag Enica 31 integrator and a SGE BPX5 25 m × 0.53 mm semicapillary apolar column (stationary phase: 5% phenylpolysil-phenylenesiloxane film, 1 μm). 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 and GC/MS method: initial temperature: 50 °C; initial time: 3 min; ramp: 10 °C min^{-1}; final temperature: 250 °C; final time: 10 min. FAB+ mass spectra were recorded on a JEOL JMS-DX300 spectrometer (3 Kev, xenon) in a *m*-nitrobenzylalcohol (NBA) matrix. Melting points were determined using a Büchi B-540 apparatus and are uncorrected.

Materials: All reactions were carried out under a pure and dry nitrogen atmosphere with standard Schlenk techniques. All solvents were distilled and stored under a nitrogen atmosphere. Acetonitrile was distilled from P_2O_5 and stored on 3 Å activated molecular sieves.[76] DMF was distilled under vacuum from $MgSO_4$ and stored protected from light on 4 Å activated molecular sieves. All solid materials were stored in the presence of P_2O_5 in a bench-top desiccator under vacuum at room temperature and weighed in the air. Of special note is that Cs_2CO_3 (Aldrich) was ground to a fine powder prior to drying. Copper(I) iodide was purified according to a reported procedure[77] and stored protected from light. Copper(I) oxide was used without further purification. Ligands **1a**,**b**,**e–h** were synthesized as we have previously reported.[21] Ligands **1d**,**i–l** were purchased from commercial sources. Salicylaldoxime (**1i**) was recrystallized in petroleum ether before use. The synthesis of ligand Chxn-Py-Al (**1c**) is described below. All aryl halides and nucleophiles were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). If

solids, they were recrystallized in an appropriate solvent.[78] If liquids, they were distilled under vacuum and stored under an atmosphere of nitrogen. Pyrrole was distilled immediately before use. Special care was taken with aryl iodides: liquid samples were regularly distilled over copper powder to remove iodine and stored protected from light. Solid samples were stored protected from light. Molecular sieves were activated and stored under vacuum at 100 °C in the presence of P_2O_5. Formation of the two byproducts *N*,*N*-diphenylbenzamide[79] and *N*,*N*-diphenylbenzenesulfonamide[80] was determined by GC by coaddition of authentic samples, synthesized under Schotten–Baumann conditions according to or by adapting reported procedures. GC yield of compound **3f** (Table 2) was determined by obtaining the correction factor by using an authentic sample that we had previously synthesized.[21]

General procedure for the N- or C-arylation of nucleophiles: After standard cycles of evacuation and back-fill with dry and pure nitrogen, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with Cu_2O (0.1 mmol, 10 mol %) or CuI (0.2 mmol, 10 mol %), ligand **1** (0.4 mmol, 20 mol %), the nucleophile (2 mmol), if a solid, Cs_2CO_3 (4.0 mmol), and the aryl halide (3.0 mmol), if a solid. The tube was evacuated, back-filled with nitrogen and capped with a rubber septum. If liquids, the nucleophile and the aryl halide were added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed acetonitrile or DMF (1.2 mL). The septum was removed; the tube was sealed under a positive pressure of nitrogen and stirred in an oil bath (preheated to the required temperature), for the required time period. The reactions were generally carried out for 24 h for convenience, but do not necessarily require such extended reaction time. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane and filtered through a plug of Celite, the filter cake being further washed with dichloromethane (~20 mL). The filtrate was concentrated in vacuo to yield a residue that was dissolved in dichloromethane (50 mL). The resulting organic layer was washed sequentially with water (2×20 mL) and brine (2×20 mL), and then dried over $MgSO_4$. The solvent was removed in vacuo to yield the crude product, which was purified by flash column chromatography on silica gel. In a few cases (pointed out below), the extraction sequence was skipped and the crude residue was directly adsorbed onto silica gel.

General procedure for reactivity comparisons or screening of reaction conditions: The above procedure was applied on a 0.5 mmol scale instead of a 2 mmol scale. After heating for the required time period, the reaction mixture was allowed to cool to room temperature and was diluted with dichloromethane (5 mL). 1,3-Dimethoxybenzene (65 μL, internal standard) was 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.

1-Phenyl-1*H*-imidazole (3a): Following the general procedure (82 °C, 100 h), imidazole (204 mg, 3 mmol) was coupled with bromobenzene (211 μL, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1d** (54 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.2 mL). The crude yellow oil was purified by flash chromatography on silica gel (gradient CH_2Cl_2/AcOEt 100:0 to 50:50) to provide 274 mg (95 % yield) of the desired product as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ[81] = 7.84 (dd, ^4J = 1.3 Hz, ^4J = 1.0 Hz, 1H), 7.43–7.53 (m, 2H), 7.32–7.41 (m, 3H), 7.28 (t, ^3J = 1.3 Hz, ^4J = 1.3 Hz, 1H), 7.19 ppm (dd, ^3J = 1.3 Hz, ^4J = 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (50 MHz, [D$_6$]Acetone): δ = 138.5 (C$_q$), 136.4 (CH), 131.2 (CH), 130.8 (2CH), 127.9 (CH), 121.7 (2CH), 118.8 ppm (CH); GC/MS (EI): t_R = 14.76 min; *m/z*: 144; R_f = 0.17 (CH_2Cl_2/AcOEt 1:1).

1-(4-Trifluoromethylphenyl)-1*H*-imidazole (3b): Following the general procedure (82 °C, 72 h), imidazole (1.02 g, 15 mmol) was coupled with 4-bromotrifluoromethylbenzene (1.40 mL, 10 mmol) by using Cu_2O (72 mg, 0.5 mmol), ligand **1d** (272 mg, 2 mmol), cesium carbonate (5.86 g, 18 mmol), and acetonitrile (6 mL). The crude residue was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 100:0 to 0:100) to provide 1.99 g (94 % yield) of the desired product as a pale yellow solid. M.p. 70 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90 (brs, 1H), 7.72 (m, 2H), 7.49 (m, 2H), 7.31 (brs, 1H), 7.22 ppm (s, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 140.0 (C$_q$), 135.5 (CH), 131.2 (CH), 129.5 (q, $^2J_{CF}$ = 33.2 Hz, C$_q$), 127.2 (q, $^3J_{CF}$ = 3.8 Hz, 2 CH), 123.6 (q, $^1J_{CF}$ = 272.1 Hz, CF_3), 121.3 (2CH), 118.3 ppm (CH); ^{19}F{^{1}H} NMR (235 MHz, $CDCl_3$): δ = −62.9 ppm (s); GC/MS (EI): t_R = 14.82 min; *m/z*: 212; R_f = 0.20 (CH_2Cl_2).

1-(4-Methoxyphenyl)-1*H*-imidazole (3c): Following the general procedure (50 °C, 24 h), imidazole (136 mg, 2 mmol) was coupled with 4-iodoanisole (608 mg, 2.6 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1d** (54 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.2 mL). The crude residue was purified by flash chromatography on silica gel (gradient CH_2Cl_2/AcOEt 100:0 to 50:50) to provide 338 mg (97 % yield) of the desired product as a pale brown solid. M.p. 60–61 °C (Lit.:[82] 61–63 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (brs, 1H), 7.28 (m, 2H), 7.18 (m, 2H), 6.96 (m, 2H), 3.82 ppm (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 158.9 (C$_q$), 135.8 (CH), 130.6 (C$_q$), 130.0 (CH), 123.1 (2CH), 118.8 (CH), 114.9 (2CH), 55.6 ppm (CH_3); GC/MS (EI): t_R = 17.96 min; *m/z*: 174; R_f = 0.27 (CH_2Cl_2/AcOEt 1:1).

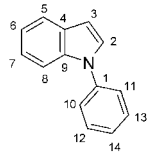
1-(4-Bromophenyl)-1*H*-imidazole (3d): Following the general procedure (50 °C, 36 h), imidazole (136 mg, 2 mmol) was coupled with 4-bromoiodobenzene (566 mg, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1i** (55 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.2 mL). The crude residue was purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2 1:1) to provide 397 mg (89 % yield) of the desired product as a colorless solid. Colorless crystals were obtained following recrystallization in aqueous ethanol. M.p. 120–121 °C (EtOH/H_2O) (Lit.:[82] 119–120 °C); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 8.27 (brs, 1H), 7.74 (t, ^3J = 1.3 Hz, ^4J = 1.3 Hz, 1H), 7.54–7.70 (m, 4H), 7.12 ppm (m, 1H); ^{13}C{^{1}H} NMR (50 MHz, [D$_6$]DMSO): δ = 136.1 (C$_q$), 135.5 (CH), 132.5 (2CH), 130.0 (CH), 122.2 (2CH), 119.2 (C$_q$), 117.8 ppm (CH); GC/MS (EI): t_R = 18.35 min; *m/z*: 222, 224; R_f = 0.30 (AcOEt).

1-(2-Tolyl)-1*H*-imidazole (3e): Following the general procedure (82 °C, 36 h), imidazole (204 mg, 3 mmol) was coupled with 2-iodotoluene (255 μL, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1i** (55 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.2 mL). The crude yellow oil was purified by flash chromatography on silica gel (gradient AcOEt/CH_2Cl_2 0:100 to 25:75) to provide 291 mg (92 % yield) of the desired product as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ[83] = 7.57 (brs, 1H), 7.27–7.34 (m, 2H), 7.21–7.25 (m, 2H), 7.19 (brs, 1H), 7.04 (brs, 1H), 2.17 ppm (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 137.5 (CH), 136.6 (C$_q$), 133.8 (C$_q$), 131.3 (CH), 129.4 (CH), 128.8 (CH), 126.9 (CH), 126.5 (CH), 120.5 (CH), 17.6 ppm (CH_3); GC/MS (EI): t_R = 14.99 min; *m/z*: 158; R_f = 0.23 (AcOEt/CH_2Cl_2 1:1).

1-[4-(1*H*-Imidazol-1-yl)phenyl]-1*H*-imidazole (3g): Following the general procedure (82 °C, 48 h), imidazole (340 mg, 5 mmol) was coupled with 1,4-diiodobenzene (660 mg, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1i** (55 mg, 0.4 mmol), cesium carbonate (1.95 g, 6.0 mmol), and acetonitrile (1.2 mL). The extraction sequence was skipped and the crude yellow solid was directly purified by flash chromatography on silica gel (gradient diethyl ether/MeOH 100:0 to 90:10) to provide 378 mg (90 % yield) of the desired product as a colorless solid. M.p. 216–217 °C (Lit.:[84] 202–204 °C); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 8.34 (s, 1H), 7.82 (m, 3H), 7.14 ppm (s, 1H); ^{13}C{^{1}H} NMR (50 MHz, [D$_6$]DMSO): δ = 135.5 (CH), 135.3 (C$_q$), 121.4 (CH), 120.0 (2CH), 118.0 ppm (CH); GC/MS (EI): t_R = 23.90 min; *m/z*: 210; R_f = 0.23 (AcOEt/MeOH 9:1).

1-Phenyl-1*H*-pyrrole (6a): Following the general procedure (82 °C, 24 h), freshly distilled pyrrole (208 μL, 2 mmol) was coupled with iodobenzene (269 μL, 2.4 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1i** (55 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.2 mL). The crude residue was purified by flash chromatography on silica gel (hexanes) to provide 269 mg (94 % yield) of the desired product as a pale brown solid. M.p. 62 °C (Lit.:[85] 62 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.60 (m, 4H), 7.38 (m, 1H), 7.26 (m, 2H), 6.54 ppm (m, 2H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ[86] = 141.0 (C$_q$), 129.7 (2CH), 125.7 (CH), 120.6 (2CH), 119.4 (2CH), 110.7 ppm (2CH); GC/MS (EI): t_R = 12.75 min; *m/z*: 143; R_f = 0.33 (hexanes).

6b



1-Phenyl-1*H*-indole (6b): Following the general procedure (82 °C, 24 h), indole (351 mg, 3 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by

using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.2 mL). The crude red oil was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 100:0 to 50:50) to provide 355 mg (92% yield) of the desired product as a green-yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74–7.80 (m, 1H; H5), 7.62–7.68 (m, 1H; H8), 7.51–7.58 (m, 4H; H10–13), 7.34–7.47 (m, 1H; H14), 7.40 (d, ^3J = 3.3 Hz, 1H; H2), 7.20–7.33 (m, 2H; H6,7), 6.76 ppm (dd, ^3J(H3,H2) = 3.3 Hz, ^5J(H3,H8) = 0.9 Hz, 1H; H3); assignment was based on a COSY H-H experiment; $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ[86] = 139.9 (C1), 135.9 (C9), 129.7 (C10,11), 129.4 (C4), 128.0 (C2), 126.5 (C14), 124.4 (2CH), 122.4 (C7), 121.2 (C5), 120.4 (C6), 110.6 (C8), 103.7 ppm (C3); GC/MS (EI): t_R = 19.08 min; *m/z*: 193; R_f = 0.23 (hexanes).

1-Phenyl-1*H*-[1,2,4]triazole (6c): Following the general procedure (82 °C, 48 h), 1,2,4-triazole (138 mg, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.043 g, 3.2 mmol), and DMF (1.2 mL). The crude residue was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 100:0 to 50:50) to provide 264 mg (91% yield) of the desired product as a dark yellow solid. Pale yellow needles were obtained following recrystallization in chloroform. M.p. 46 °C ($CHCl_3$) (Lit.:[87] 46–47 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.52 (brs, 1H), 8.04 (brs, 1H), 7.53–7.65 (m, 2H), 7.26–7.51 ppm (m, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 152.6 (CH), 140.9 (CH), 137.0 (C_q), 129.7 (2CH), 128.2 (CH), 120.0 ppm (2CH); GC/MS (EI): t_R = 14.02 min; *m/z*: 145; R_f = 0.21 (CH_2Cl_2/AcOEt 9:1).

***N*-Phenylacetamide (7a) and *N*,*N*-diphenylacetamide (7b)**: Following the general procedure (82 °C, 75 h), acetamide (177 mg, 3 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.043 g, 3.2 mmol), activated and powdered 3 Å molecular sieves (600 mg), and DMF (1.2 mL). The crude residue was purified by flash chromatography on silica gel (gradient CH_2Cl_2/AcOEt 100:0 to 60:40) to provide 219 mg (81% yield) of **7a** as a colorless solid and 15 mg (7% yield) of **7b** as a colorless solid.

*Data for **7a***: M.p. 115 °C (Lit.:[88] 114 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.35 (brs, 1H, NH), 7.49–7.54 (m, 2H), 7.24–7.32 (m, 2H), 7.04–7.12 (m, 1H), 2.13 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ[89] = 169.2 (C_q), 138.1 (C_q), 128.9 (2CH), 124.3 (CH), 120.3 (2CH), 24.4 ppm (CH_3); GC/MS (EI): t_R = 14.06 min; *m/z*: 135; R_f = 0.30 (CH_2Cl_2/AcOEt 3:2).

*Data for **7b***: M.p. 102 °C (Lit.:[90] 101 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.12–7.45 (m, 10H), 2.07 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ[89] = 170.4 (C_q), 143.1 (2C_q), 129.4 (4 CH), 128.3 (2CH), 127.6 (2CH), 126.7 (2CH), 23.9 ppm (CH_3); GC/MS (EI): t_R = 19.66 min; *m/z*: 211; R_f = 0.14 (CH_2Cl_2).

***N*-Phenylbenzamide (7c)**: Following the general procedure (82 °C, 48 h), benzamide (363 mg, 3 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), activated and powdered 3 Å molecular sieves (600 mg), and DMF (1.2 mL). The crude residue was purified by flash chromatography on silica gel (gradient CH_2Cl_2/hexanes 50:50 to 100:0) to provide 359 mg (91% yield) of the desired product as a colorless solid. M.p. 164 °C (Lit.:[91] 163 °C, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (brs, 1H, NH), 7.86 (m, 2H), 7.64 (m, 2H), 7.32–7.58 (m, 5H), 7.15 ppm (m, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 165.8 (C_q), 138.0 (C_q), 135.0 (C_q), 131.8 (CH), 129.1 (2CH), 128.8 (2CH), 127.0 (2CH), 124.6 (CH), 120.3 ppm (2CH); GC/MS (EI): t_R = 20.76 min; *m/z*: 197; R_f = 0.45 (CH_2Cl_2).

***N*-Phenylbenzenesulfonamide (7d)**: Following the general procedure (82 °C, 48 h), benzenesulfonamide (472 mg, 3 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.043 g, 3.2 mmol), activated and powdered 3 Å molecular sieves (600 mg), and DMF (1.6 mL). The reaction mixture was diluted with CH_2Cl_2/MeOH (25 mL, 1:1) before being filtered through a plug of Celite. The crude brown oil was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 9:1 to 5:95) to provide 411 mg (88% yield) of the desired product as a colorless solid. M.p. 109–110 °C (Lit.:[92] 110 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.88 (m, 2H, H), 7.79 (brs, 1H, NH), 7.35–7.50 (m, 3H), 7.07–7.25 ppm (m, 5H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 138.9 (C_q), 136.6 (C_q), 133.1 (CH), 129.3 (2CH), 129.1 (2CH), 127.3 (2CH), 125.3 (CH), 121.6 ppm (2CH); GC/MS (EI): t_R = 21.54 min; *m/z*: 233; R_f = 0.36 (CH_2Cl_2).

1-Phenylpyrrolidin-2-one (7e): Following the general procedure (82 °C, 40 h), pyrrolidin-2-one (152 μL, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), activated and powdered 3 Å molecular sieves (600 mg), and DMF (1.2 mL). The crude residue was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2/AcOEt 50:50:0 to 0:100:0, then 0:100:0 to 0:95:5) to provide 297 mg (92% yield) of the desired product as a colorless solid. Alternatively, the crude residue can be purified by recrystallisation in ethanol instead of flash column chromatography, to provide 265 mg (82% yield) of the desired product as an off-white solid. M.p. 69–70 °C (EtOH) (Lit.:[12f] 70 °C, diisopropyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.58–7.63 (m, 2H), 7.32–7.40 (m, 2H), 7.13–7.18 (m, 1H), 3.87 (m, 2H), 2.61 (m, 2H), 2.08–2.23 ppm (m, 2H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 174.2 (C_q), 139.4 (C_q), 128.8 (2CH), 124.5 (CH), 120.0 (2CH), 48.8 (CH_2), 32.8 (CH_2), 18.0 ppm (CH_2); GC/MS (EI): t_R = 17.38 min; *m/z*: 161; R_f = 0.53 (CH_2Cl_2/AcOEt 4:1).

1-Phenyl-1*H*-pyridin-2-one (7f) and 2-phenoxypyridine (7g): Following the general procedure (82 °C, 24 h), 2-hydroxypyridine (951 mg, 10 mmol) was coupled with iodobenzene (1.68 mL, 15 mmol) by using Cu_2O (72 mg, 0.5 mmol), ligand **1c** (584 mg, 2 mmol), cesium carbonate (6.52 g, 20 mmol), activated and powdered 3 Å molecular sieves (3 g), and acetonitrile (6 mL). The crude residue was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2/AcOEt 100:0:0 to 0:100:0, then 0:100:0 to 0:80:20). Elution with CH_2Cl_2/AcOEt 9:1 gave 34 mg (2% yield) of **7g** as a yellowish oil (which can be crystallized in a few hours if left at 0 °C), and elution with CH_2Cl_2/AcOEt 8:2 gave 1.54 g (90% yield) of **7f** as a yellow solid.

*Data for **7f***: M.p. 127 °C (Lit.:[12f] 129 °C, diisopropyl ether); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.59–7.66 (m, 1H), 7.36–7.56 (m, 6H, H), 6.48 (m, 1H), 6.31 ppm (m, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 162.4 (C_q), 140.97 (C_q), 139.9 (CH), 138.0 (CH), 129.3 (2CH), 128.5 (CH), 126.5 (2CH), 121.9 (CH), 105.9 ppm (CH); GC/MS (EI): t_R = 18.11 min; *m/z*: 171; R_f = 0.14 (CH_2Cl_2/AcOEt 9:1).

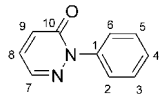
*Data for **7g***: M.p. 39 °C (Lit.:[93] 41.5–43.5 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.19–8.22 (m, 1H, H), 7.63–7.73 (m, 1H, H), 7.36–7.45 (m, 2H), 7.12–7.24 (m, 3H), 6.96–7.02 (m, 1H), 6.88–6.92 ppm (m, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 163.8 (C_q), 154.2 (C_q), 147.8 (CH), 139.4 (CH), 129.7 (2CH), 124.7 (CH), 121.2 (2CH), 118.5 (CH), 111.5 ppm (CH); GC/MS (EI): t_R = 15.15 min; *m/z*: 171; R_f = 0.43 (CH_2Cl_2/AcOEt 9:1).

1-(3-Aminophenyl)-1*H*-pyridin-2-one (Amphenidone, 7h): Following the general procedure (82 °C, 48 h), 2-hydroxypyridine (190 mg, 2 mmol) was coupled with 3-iodoaniline (361 μL, 3 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (58 mg, 0.2 mmol), cesium carbonate (1.303 g, 4 mmol), activated and powdered 3 Å molecular sieves (600 mg), and acetonitrile (1.2 mL). The extraction sequence was skipped and the crude brown oil was directly purified by flash chromatography on alumina gel (gradient hexanes/CH_2Cl_2/AcOEt 50:50:0 to 0:100:0, then 0:100:0 to 0:25:75) to provide 305 mg (82% yield) of the desired product as a colorless solid. M.p. 179 °C (Lit.:[51] 182.5–184.5 °C); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.43–7.56 (m, 2H), 7.11 (m, 1H), 6.60 (m, 1H), 6.41–6.50 (m, 3H), 6.25 (m, 1H), 5.34 ppm (brs, 2H, NH_2); $^{13}C\{^1H\}$ NMR (50 MHz, [D$_6$]DMSO): δ = 161.0 (C_q), 149.4 (C_q), 141.7 (C_q), 140.2 (CH), 139.0 (CH), 129.3 (CH), 120.4 (CH), 113.4 (2CH), 111.8 (CH), 105.1 ppm (CH); GC/MS (EI): t_R = 22.11 min; *m/z*: 186; R_f = 0.33 (AcOEt/CH_2Cl_2 4:1, alumina).

3-Phenyloxazolidin-2-one (7i): Following the general procedure (82 °C, 24 h), oxazolidin-2-one (263 mg, 3 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (1.043 g, 3.2 mmol), activated and powdered 3 Å molecular sieves (600 mg), and DMF (1.2 mL). The crude residue was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 50:50 to 0:100) to provide 316 mg (97% yield) of the desired product as a colorless solid. M.p. 120 °C (Lit.:[94] 120–121 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.48–7.53 (m, 2H), 7.30–7.38 (m, 2H), 7.07–7.15 (m, 1H), 4.40 (m, ^3J = 8.0 Hz, 2H), 3.97 ppm (m, ^3J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ = 155.3 (C_q), 138.3 (C_q), 129.0 (2CH),

124.0 (CH), 118.2 (2CH), 61.4 (CH_2), 45.1 ppm (CH_2); GC/MS (EI): t_R = 18.25 min; *m/z*: 163; R_f = 0.20 (CH_2Cl_2/hexanes 4:1).

2-Phenyl-2*H*-pyridazin-3-one (7j): Following the general procedure (82 °C, 100 h), 2H-pyridazin-3-one (192 mg, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by using Cu_2O (14.4 mg, 0.1 mmol), ligand **1i** (55 mg, 0.4 mmol), cesium carbonate (1.303 g, 4 mmol), and acetonitrile (1.6 mL). The crude residue was purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 50:50 to 0:100) to provide 306 mg (89% yield) of the desired product as a colorless solid. Colorless crystals were obtained following recrystallization in petroleum ether/$CHCl_3$. M.p. 106–108 °C (petroleum ether/$CHCl_3$) (Lit.:[95] 102 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.89 (dd, ^4J = 1.7 Hz, ^3J = 3.8 Hz, 1H; H7), 7.57–7.63 (m, 2H; H2,6), 7.35–7.52 (m, 3H; H3–5), 7.24 (dd, ^3J = 3.8 Hz, ^3J = 9.5 Hz, 1H; H8), 7.05 ppm (dd, ^4J = 1.7 Hz, ^3J = 9.5 Hz, 1H; H9); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 160.1 (C10), 141.5 (C1), 136.7 (C7), 131.3 (CH), 131.2 (CH), 128.8 (2CH), 128.4 (C4), 125.3 ppm (2CH); GC/MS (EI): t_R = 17.83 min; *m/z*: 172; R_f = 0.20 (CH_2Cl_2).

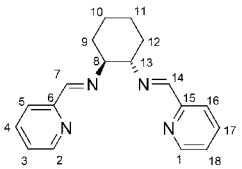
7j 

Diethyl phenylmalonate (11a): Following the general procedure (70 °C, 30 h), diethyl malonate (607 μL, 4 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using CuI (38 mg, 0.2 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (977 mg, 3 mmol), activated and powdered 3 Å molecular sieves (600 mg), and acetonitrile (1.2 mL). The reaction mixture was neutralized with aqueous hydrochloric acid (6 mL, 1 N) before being filtered through a plug of Celite, extracted with CH_2Cl_2 (~20 mL) and concentrated in vacuo. The crude residue was directly purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 100:0 to 80:20) to provide 439 mg (93% yield) of the desired product as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.42 (m, 5H), 4.62 (s, 1H), 4.22 (m, 4H), 1.26 ppm (t, ^3J = 7.1 Hz, 6H); the protons of each methylene group were diastereotopic (second order signal)—consequently, multiplicities given in the literature[8] for such proton signals are not correct; ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 168.2 (2C_q), 132.9 (C_q), 129.3 (2CH), 128.6 (2CH), 128.2 (CH), 61.8 (2CH_2), 58.0 (CH), 14.0 ppm (2CH_3); GC/MS (EI): t_R = 16.77 min; *m/z*: 236; R_f = 0.27 (hexanes/CH_2Cl_2 7:3).

2-Phenylethylcyanoacetate (11d): Following the general procedure (70 °C, 28 h), ethyl cyanoacetate (427 μL, 4 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using CuI (38 mg, 0.2 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (977 mg, 3 mmol), activated and powdered 3 Å molecular sieves (600 mg), and acetonitrile (1.2 mL). The reaction mixture was neutralized with aqueous hydrochloric acid (6 mL, 1 N) before being filtered through a plug of celite, extracted with CH_2Cl_2 (~20 mL) and concentrated in vacuo. The crude residue was directly purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 100:0 to 75:25) to provide 348 mg (92% yield) of the desired product as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.45 (m, 5H), 4.71 (s, 1H), 4.25 (q, ^3J = 7.1 Hz, 2H), 1.28 ppm (t, ^3J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 165.0 (C_q), 130.0 (C_q), 129.3 (2CH), 129.2 (CH), 127.9 (2CH), 115.7 (CN), 63.3 (CH_2), 43.7 (CH), 13.9 ppm (CH_3); GC/MS (EI): t_R = 15.24 min; *m/z*: 189; R_f = 0.22 (hexanes/CH_2Cl_2 3:1).

Phenylmalononitrile (11e): Following the general procedure (50 °C, 72 h), malononitrile (132 mg, 4 mmol) was coupled with iodobenzene (224 μL, 2 mmol) by using CuI (38 mg, 0.2 mmol), ligand **1c** (117 mg, 0.4 mmol), cesium carbonate (977 mg, 3 mmol), and acetonitrile (1.2 mL). The reaction mixture was neutralized with aqueous hydrochloric acid (6 mL, 1 N) before being filtered through a plug of celite, extracted with CH_2Cl_2 (~20 mL) and concentrated in vacuo. The black residue was directly purified by flash chromatography on silica gel (gradient hexanes/CH_2Cl_2 100:0 to 60:40) to provide 176 mg (62% yield) of the desired product as a colorless solid. M.p. 64–65 °C (Lit.:[57g] 66–68 °C, hexanes/diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51 (m, 5H), 5.08 ppm (s, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 130.4 (C_q), 130.1 (2CH), 127.2 (CH), 126.2 (2CH), 111.8 (2CN), 28.1 ppm (CH); GC/MS (EI): t_R = 12.96 min; *m/z*: 142; R_f = 0.32 (hexanes/CH_2Cl_2 1:1).

Chxn-Py-Al (1c): Anhydrous magnesium sulphate (12.65 g, 105.1 mmol) and rac-*trans*-1,2-diaminocyclohexane (4.2 mL, 35.0 mmol) were successively added to a solution of 2-pyridylaldehyde (6.66 mL, 70.0 mmol) in absolute EtOH (50 mL). The mixture was stirred for 20 h at room temperature, heated at reflux for 2.5 h, and filtered through a frit while still hot. The solid was discarded and the filtrate was concentrated in vacuo. The residue was recrystallized in EtOH to provide 8.2 g (80% yield) of the desired product as pale yellow crystals. Only the (1*S*,2*S*)-stereoisomer of compound **1c** is known in the literature.[96] M.p. 140–141 °C (EtOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.54 (ddd, ^3J = 4.9 Hz, ^4J = 1.7 Hz, ^5J = 1.0 Hz, 2H; H1,2), 8.30 (s, 2H; H7,14), 7.87 (ddd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, ^5J = 1.0 Hz, 2H; H5,16), 7.63 (dddd, ^3J = 7.9 Hz, ^3J = 7.5 Hz, ^4J = 1.7 Hz, ^5J = 0.6 Hz, 2H; H4,17), 7.22 (ddd, ^3J = 7.5 Hz, ^3J = 4.9 Hz, ^4J = 1.5 Hz, 2H; H3,18), 3.50 (m, 2H; H8,13), 1.83 (m, 6H), 1.40–1.55 ppm (m, 2H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ = 161.4 (C7,14), 154.6 (C6,15), 149.2 (C1,2), 136.4 (C4,17), 124.4 (C3,18), 121.3 (C5,16), 73.5 (C8,13), 32.7 (C9,12), 24.3 ppm (C10,11); IR (KBr): ν = 3273, 3071, 3055, 3050, 2941, 2934, 2925, 2865, 2857, 2850, 1644, 1586, 1566, 1467, 1449, 1433, 1372, 1338, 991, 934, 867, 839, 771, 743 cm^{-1}; MS (FAB+, NBA): *m/z* (%): 293 (100) [M^++H], 107 (52), 92 (38), 119 (25), 294 (23) [M^++2H], 204 (22), 79 (21), 187 (20), 585 (1) [2M^++H].

1c (racemic) 

Acknowledgement

P.P.C. thanks RHODIA Organique Fine for a Ph.D. grant, and the Laboratoire de Chimie Organique is grateful to the same company for financial support of this work. Prof. A. Fruchier is gratefully acknowledged for helpful discussions and assistance with the NMR analyses.

[1] a) I. Sircar, B. L. Duell, G. Bobowski, J. A. Bristol, D. B. Evans, *J. Med. Chem.* **1985**, *28*, 1405–1413; b) T. Güngör, A. Fouquet, J.-M. Teulon, D. Provost, M. Cazes, A. Cloarec, *J. Med. Chem.* **1992**, *35*, 4455–4463; c) N.-X. Hu, S. Xie, Z. Popovic, B. Ong, A.-M. Hor, S. Wang, *J. Am. Chem. Soc.* **1999**, *121*, 5097–5098; d) K. R. Justin Thomas, J. T. Lin, Y.-T. Tao, C.-W. Ko, *J. Am. Chem. Soc.* **2001**, *123*, 9404–9411; e) S. Yu, J. Saenz, J. K. Srirangam, *J. Org. Chem.* **2002**, *67*, 1699–1702.

[2] a) S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, G. E. Zurenko, *J. Med. Chem.* **1996**, *39*, 673–679; b) J. Gallego, G. Varani, *Acc. Chem. Res.* **2001**, *34*, 836–843.

[3] F. Moureau, J. Wouters, D. P. Vercauteren, S. Collin, G. Evrard, F. Durant, F. Ducrey, J. J. Koenig, F. X. Jarreau, *Eur. J. Med. Chem.* **1994**, *29*, 269–277.

[4] G. C. Lloyd-Jones, *Angew. Chem.* **2002**, *114*, 995–998; *Angew. Chem. Int. Ed.* **2002**, *41*, 953–956.

[5] a) D. Prim, J.-M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041–2075; b) J. F. Hartwig in *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2000**, pp. 195–262; c) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146; d) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; e) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541–555; f) Kat N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566; g) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048; h) G. Mann, J. F. Hartwig, M. S. Driver, C. Fernandez-Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827–828; i) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575–5580; j) D. W. Old, M. C. Harris, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1403–1406; k) G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729–7737; l) I. P. Beletskaya, D. V.

Davydov, M. Moreno-Mañas, *Tetrahedron Lett.* **1998**, *39*, 5617–5620; m) M. Watanabe, M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **2000**, *41*, 481–483.

[6] a) R. T. Baker, S. S. Kristjansdottir (E. I. DuPont de Nemours), WO 98/00399, **1998** [*Chem. Abstr.* **1998**, *128*, 114574]; b) J. B. Arterburn, M. Pannala, A. M. Gonzalez, *Tetrahedron Lett.* **2001**, *42*, 1475–1477; c) H.-J. Cristau, R. Vogel, M. Taillefer, A. Gadras, *Tetrahedron Lett.* **2000**, *41*, 8457–8460; d) S. L. Buchwald, J. P. Wolfe, *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058; e) C. Desmarets, R. Schneider, Y. Fort, *J. Org. Chem.* **2002**, *67*, 3029–3036; f) S. Tasler, B. H. Lipshutz, *J. Org. Chem.* **2003**, *68*, 1190–1199.

[7] a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439; c) J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456; d) M. A. Khan, *Rec. Chem. Prog.* **1970**, *31*, 43–50; e) R. G. R. Bacon, H. A. O. Hill, *Q. Rev. Chem. Soc.* **1965**, *19*, 95–125.

[8] E. J. Hennessy, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 269–272.

[9] a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; b) F. Ullmann, E. Illgen, *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 380–383.

[10] a) I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691–1692; b) I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 4541–4546.

[11] W. R. H. Hurtley, *J. Chem. Soc.* **1929**, 1870–1873.

[12] For N-arylation of azoles, see: a) L. M. Sitkina, A. M. Simonov, *Chem. Heterocycl. Compd.* **1966**, *2*, 103–105; b) A. F. Pozharskii, B. K. Martsokha, A. M. Simonov, *Zh. Obshch. Khim.* **1963**, *33*, 994–995; c) T. Sugaya, Y. Mimura, N. Kato, M. Ikuta, T. Mimura, M. Kasai, S. Tomioka, *Synthesis* **1994**, 73–76; d) M. A. Khan, J. B. Polya, *J. Chem. Soc. C* **1970**, 85–91; e) C. Tironi, R. Fruttero, A. Garrone, *Farmaco* **1990**, *45*, 473–478.For N-arylation of amides, see: f) M. Sugahara, T. Ukita, *Chem. Pharm. Bull.* **1997**, *45*, 719–721; g) T. Yamamoto, Y. Kurata, *Can. J. Chem.* **1983**, *61*, 86–91.

[13] For C-arylation of malonic acid derivatives, see: a) K. A. Cirigottis, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **1974**, *27*, 2209–2228; b) R. G. R. Bacon, J. C. F. Murray, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1267–1272; c) A. Bruggink, A. McKillop, *Tetrahedron* **1975**, *31*, 2607–2619; d) A. Bruggink, A. McKillop, *Angew. Chem.* **1974**, *86*, 349; *Angew. Chem. Int. Ed.* **1974**, *13*, 340–341; e) G. J. Quallich, T. W. Makowski, A. F. Sanders, F. J. Urban, E. Vazquez, *J. Org. Chem.* **1998**, *63*, 4116–4119.

[14] H. Weingarten, *J. Org. Chem.* **1964**, *29*, 3624–3626.

[15] R. Oi, C. Shimakawa, S. Takenaka, *Chem. Lett.* **1988**, 899–900.

[16] a) J.-F. Marcoux, S. Doye, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540; b) A. Kiyomori, J.-F. Marcoux, S. L. Buchwald, *Tetrahedron Lett.* **1999**, *40*, 2657–2660.

[17] H. B. Goodbrand, N.-X. Hu, *J. Org. Chem.* **1999**, *64*, 670–674.

[18] *o*-Carboxylate substitution in aryl halides provides a strong accelerating effect, whereas *p*-carboxylate substitution has no effect: C. Couture, A. J. Paine, *Can. J. Chem.* **1985**, *63*, 111–120.

[19] a) D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467; b) D. Ma, C. Xia, *Org. Lett.* **2001**, *3*, 2583–2586.

[20] a) G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703–3706; b) Z. Lu, R. J. Twieg, S. D. Huang, *Tetrahedron Lett.* **2003**, *44*, 6289–6292; c) S. Arai, Y. Takamichi, S. Ototake, M. Hida, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547–548.

[21] H.-J. Cristau, P. P. Cellier, J.-F. Spindler, M. Taillefer, *Eur. J. Org. Chem.* **2004**, 695–709.

[22] H.-J. Cristau, P. P. Cellier, J.-F. Spindler, M. Taillefer, *Org. Lett.* **2004**, *6*, 913–916.

[23] a) V. M. Hultgren, I. M. Atkinson, R. L. Beddoes, D. Collison, C. D. Garner, M. Helliwell, L. F. Lindoy, P. A. Tasker, *Chem. Commun.* **2001**, 573–574; b) A. W. Ashbrook, *Coord. Chem. Rev.* **1975**, *16*, 285–307.

[24] Buchwald et al. had not reported the use of rac-*trans*-1,2-diaminocyclohexane as ligand for copper-catalyzed N-arylation reactions at the time we designed Chxn-Py-Al: A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.

[25] These results, obtained more than two years ago, appear only now in the literature, due to the regular time required for patent protection.

[26] a) C. Jacobs, M. Frotscher, G. Dannhardt, R. W. Hartmann, *J. Med. Chem.* **2000**, *43*, 1841–1851; b) P. Cozzi, G. Carganico, D. Fusar, M. Grossoni, M. Menichincheri, V. Pinciroli, R. Tonani, F. Vaghi, P. Salvati, *J. Med. Chem.* **1993**, *36*, 2964–2972; c) J. Ohmori, M. Shimizu-Sasamata, M. Okada, S. Sakamoto, *J. Med. Chem.* **1996**, *39*, 3971–3979; d) Y. S. Lo, J. C. Nolan, T. H. Maren, J. Welstead, W. J. , D. F. Gripshover, D. A. Shamblee, *J. Med. Chem.* **1992**, *35*, 4790–4794.

[27] a) V. C. Vargas, R. J. Rubio, T. K. Hollis, M. E. Salcido, *Org. Lett.* **2003**, *5*, 4847–4849; b) M. C. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113–123.

[28] R. E. Baltus, B. H. Culbertson, S. Dai, H. Luo, D. W. DePaoli, *J. Phys. Chem. B* **2004**, *108*, 721–727.

[29] The stabilized form commercialized by Aldrich was used.

[30] Note that the unfunctionalized analogue of Schiff base **1c** in which 2-pyridyl group was replaced by a phenyl ring inhibits the catalytic reaction.

[31] a) F. A. Cotton, G. Wilkinson in *Advanced Inorganic Chemistry 5th ed.*, Wiley-Interscience, New York, **1988**, pp. 757–758 and 767–768; b) B. J. Hathaway in *Comprehensive Coordination Chemistry 1 st ed.*, *Vol. 5* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon, Oxford, **1987**, pp. 536–537; c) X. Li, J. Yang, M. C. Kozlowski, *Org. Lett.* **2001**, *3*, 1137–1140.

[32] a) R. T. Skerlj, Z. Wang, G. J. Bridger, *Tetrahedron Lett.* **1999**, *40*, 3543–3546; b) G. Mann, J. F. Hartwig, *Tetrahedron Lett.* **1997**, *38*, 8005–8008.

[33] D. H. R. Barton, J.-P. Finet, J. Khamsi, *Tetrahedron Lett.* **1988**, *29*, 1115–1118.

[34] A. Greiner, *Synthesis* **1989**, 312–313.

[35] I. P. Beletskaya, D. V. Davydov, M. S. Gorovoi, S. V. Kardashov, *Russ. Chem. Bull.* **1999**, *48*, 1533–1536.

[36] a) I. P. Beletskaya, D. V. Davydov, M. S. Gorovoy, *Tetrahedron Lett.* **2002**, *43*, 6221–6223; b) D. V. Davydov, I. P. Beletskaya, B. B. Semenov, Y. I. Smushkevich, *Tetrahedron Lett.* **2002**, *43*, 6217–6219.

[37] a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463; b) J. A. Joule, K. Mills, G. F. Smith, *Heterocyclic Chemistry 3rd ed.*, Stanley Thornes, Cheltenham, **1995**.

[38] a) M. Inoue, M. Kishita, M. Kubo, *Inorg. Chem.* **1965**, *4*, 626–628; b) J. Reedijk in *Comprehensive Coordination Chemistry 1st ed.*, *Vol. 2* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon Press, Oxford, **1987**, pp. 73–79.

[39] J. K.-C. Lau, C. H. S. Wong, P. S. Ng, F. M. Siu, N. L. Ma, C. W. Tsang, *Chem. Eur. J.* **2003**, *9*, 3383–3396.

[40] Palladium-catalyzed C–N bond-forming reductive elimination with azoles and aryl halides as substrates has been studied by Hartwig. See: reference [5h]; b) J. F. Hartwig, *Pure Appl. Chem.* **1999**, *71*, 1417–1423.

[41] a) D. H. R. Barton, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, W. B. Motherwell, M. T. B. Papoula, S. P. Stanforth, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2667–2675; b) P. Lopez-Alvarado, C. Avendano, J. C. Menendez, *J. Org. Chem.* **1995**, *60*, 5678–5682; c) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944; d) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, D. M. T. Chan, A. Combs, *Synlett* **2000**, 674–676.

[42] Reference 6b; b) Y. D. Ward, V. Farina, *Tetrahedron Lett.* **1996**, *37*, 6993–6996; c) B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 5274–5275. N-arylation of imidazole has been reported to occur in the presence of palladium catalysts only with very activated aryl halides, prone to react under uncatalyzed S_NAr pathway: d) M. B. Andrus, S. N. Mettah, C. Song, *J. Org. Chem.* **2002**, *67*, 8284–8286; e) Y. Wan, M. Alterman, A. Hallberg, *Synthesis* **2002**, 1597–1600.

[43] a) A. Y. Lebedev, V. V. Izmer, D. N. Kazyul'kin, I. P. Beletskaya, A. Z. Voskoboynikov, *Org. Lett.* **2002**, *4*, 623–626; b) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655, 10767.

[44] a) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688; b) C. Enguehard, H. Allouchi, A. Gueiffier, S. L. Buchwald, *J. Org. Chem.* **2003**, *68*, 5614–5617. c) J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, ASAP.

[45] Buchwald also reported N-arylation of monoazoles with aryl bromides at 100–112 °C. See reference [44] and: F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793–796.

[46] S.-K. Kang, D.-H. Kim, J.-N. Park, *Synlett* **2002**, 427–430.

[47] Y.-J. Wu, H. He, A. L'Heureux, *Tetrahedron Lett.* **2003**, *44*, 4217–4218.
[48] D. Ma, Q. Cai, *Synlett* **2004**, 128–130.
[49] C. Reichardt in *Solvent and Solvent Effects in Organic Synthesis 2nd ed.*, VCH, Weinheim, **1988**, pp. 98–99.
[50] B. Renger, *Synthesis* **1985**, 856–860.
[51] J. V. Scudi, D. B. Reisner, S. J. Childress, L. A. Walter (Wallace & Tiernan), US 2947755, **1960** [*Chem. Abstr.* **1961**, *55*, 59559].
[52] S. J. Katz, S. C. Bergmeier, *Tetrahedron Lett.* **2002**, *43*, 557–559.
[53] a) J.-J. Liu, A. Dermatakis, C. Lukacs, F. Konzelmann, Y. Chen, U. Kammlott, W. Depinto, H. Yang, X. Yin, Y. Chen, A. Schutt, M. E. Simcox, K.-C. Luka, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2465–2468; b) H. Bader, J. F. Hoops, J. H. Biel, H. N. Koelling, R. G. Stein, T. Singh, *J. Med. Chem.* **1969**, *12*, 709–711.
[54] a) *The Pesticide Manual 10th ed.* (Ed.: C. Tomlin), Crop Protection Publications, Farnham, Surrey, UK, **1994**; b) A. Becker, *Inventory of Industrial Fluoro-Biochemicals*, Editions Eyrolles, Paris, **1996**.
[55] S. L. Colletti, J. L. Frie, E. C. Dixon, S. B. Singh, B. K. Choi, G. Scapin, C. E. Fitzgerald, S. Kumar, E. A. Nichols, S. J. O'Keefe, E. A. O'Neill, G. Porter, K. Samuel, D. M. Schmatz, C. D. Schwartz, W. L. Shoop, C. M. Thompson, J. E. Thompson, R. Wang, A. Woods, D. M. Zaller, J. B. Doherty, *J. Med. Chem.* **2003**, *46*, 349–352.
[56] a) B. Rosenau, C. Krieger, H. A. Staab, *Tetrahedron Lett.* **1985**, *26*, 2081–2084; b) J. Zauhar, A. D. Bandrauk, K. D. Truong, A. Michel, *Synthesis* **1995**, 703–706; c) S. Yamaguchi, K. Nagareda, T. Hanafusa, *Synth. Met.* **1989**, *30*, 401–402.
[57] a) J.-I. Setsune, K. Matsukawa, H. Wakemoto, T. Kitao, *Chem. Lett.* **1981**, 367–370; b) J.-I. Setsune, K. Matsukawa, T. Kitao, *Tetrahedron Lett.* **1982**, *23*, 663–666; c) J.-I. Setsune, T. Ueda, K. Shikata, K. Matsukawa, T. Ida, T. Kitao, *Tetrahedron* **1986**, *42*, 2647–2656; d) Y. Gao, J. Burke, T. R. , *Synlett* **2000**, 134–136; e) H. Suzuki, T. Kobayashi, Y. Yoshida, A. Osuka, *Chem. Lett.* **1983**, 193–194; f) A. Osuka, T. Kobayashi, H. Suzuki, *Synthesis* **1983**, 67–68; g) H. Suzuki, T. Kobayashi, A. Osuka, *Chem. Lett.* **1983**, 589–590; h) H. Suzuki, H. Koide, T. Ogawa, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 501–504; i) S. Pivsa-Art, Y. Fukui, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2039–2042; j) R. Ugo, P. Nardi, R. Psaro, D. Roberto, *Gazz. Chim. Ital.* **1992**, *122*, 511–514.
[58] a) J. P. Konopelski, J. M. Hottenroth, H. M. Oltra, E. A. Véliz, Z.-C. Yang, *Synlett* **1996**, 609–611; b) H. C. Hang, E. Drotleff, G. I. Elliott, T. A. Ritsema, J. P. Konopelski, *Synthesis* **1999**, 398–400; c) O. Meyer, R. Eisenacht (American Cyanamid Company), US 6156925, **2000** [*Chem. Abstr.* **2000**, *134*, 17314].
[59] K. Okuro, M. Furuune, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 7606–7607.
[60] F. G. Bordwell, J. A. Harrelson, Jr., A. V. Satish, *J. Org. Chem.* **1989**, *54*, 3101–3105.
[61] A. McKillop, D. P. Rao, *Synthesis* **1977**, 759–760.
[62] J. F. Burnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273–412.
[63] R. A. Rossi, R. H. de Rossi in *Aromatic Substitution by the $S_{RN}1$ Mechanism* (Ed.: M. C. Caserio), ACS Monograph 178, American Chemical Society, Washington, **1983**, pp. 1–10.
[64] T. Cohen, I. Cristea, *J. Am. Chem. Soc.* **1976**, *98*, 748–753.
[65] J. F. Bunnett, X. Creary, *J. Org. Chem.* **1974**, *39*, 3611–3612.
[66] a) A. J. Paine, *J. Am. Chem. Soc.* **1987**, *109*, 1496–1502; b) W. R. Bowman, H. Heaney, P. H. G. Smith, *Tetrahedron Lett.* **1984**, *25*, 5821–5824; c) R. A. Rossi, R. H. de Rossi in *Aromatic Substitution by the $S_{RN}1$ Mechanism* (Ed.: M. C. Caserio), ACS Monograph 178, American Chemical Society, Washington, **1983**, pp. 26–29, 68–70, and 93–94.
[67] a) G. M. Whitesides, C. P. Casey, J. K. Krieger, *J. Am. Chem. Soc.* **1971**, *93*, 1379–1389; b) T. Cohen, I. Cristea, *J. Org. Chem.* **1975**, *40*, 3649–3651; c) C. Galli, Z. Rappoport, *Acc. Chem. Res.* **2003**, *36*, 580–587.
[68] T. Cohen, J. Wood, A. G. Dietz, Jr., *Tetrahedron Lett.* **1974**, *15*, 3555–3558.
[69] G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.
[70] a) A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845; b) S. Zhang, D. Zhang, L. S. Liebeskind, *J. Org. Chem.* **1997**, *62*, 2312–2313.
[71] H. Deng, P. Kebarle, *J. Am. Chem. Soc.* **1998**, *120*, 2925–2931.
[72] N-arylation of both substrates was reported under Buchwald's conditions at a higher temperature, 110°C: a) B. Mallesham, B. M. Rajesh, P. R. Reddy, D. Srinivas, S. Trehan, *Org. Lett.* **2003**, *5*, 963–965; b) C. S. Li, D. D. Dixon, *Tetrahedron Lett.* **2004**, *45*, 4257–4260.
[73] A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
[74] C. Enguehard, H. Allouchi, A. Gueiffier, S. L. Buchwald, *J. Org. Chem.* **2003**, *68*, 4367–4370.
[75] Rights to the commercial use of the catalytic systems presented in this work are held by Rhodia Recherches under WO and FR patents: a) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, FR 2833947, **2003** [*Chem. Abstr.* **2003**, *139*, 69290]; b) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, WO 03/050885, **2003**; c) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, FR 2840303, **2003** [*Chem. Abstr.* **2004**, *140*, 16744]; d) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, A. Ouali, WO 03/101966, **2003**; e) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, Patent priority number FR 03 10253, **2004**.
[76] D. R. Burfield, *J. Org. Chem.* **1977**, *42*, 3060–3065.
[77] R. K. Dieter, L. A. Silks, III, J. R. Fishpaugh, M. E. Kastner, *J. Am. Chem. Soc.* **1985**, *107*, 4679–4692.
[78] D. D. Perrin, W. L. F. Armarego, D. R. Perrin, *Purification of Laboratory Chemicals 3rd ed.*, Pergamon, New-York, **1985**.
[79] I. Datta, T. K. Das, S. Ghosh, *Tetrahedron* **1990**, *46*, 6821–6830.
[80] P. Ruosteuso, A.-M. Haekkinen, T. Mattila, *Magn. Reson. Chem.* **1987**, *25*, 189–193.
[81] J. P. Collman, M. Zhong, *Org. Lett.* **2000**, *2*, 1233–1236, Supporting Information.
[82] L. Wang, Z.-C. Chen, *J. Chem. Res. Synop.* **2000**, 367–369.
[83] J. P. Collman, M. Zhong, L. Zeng, S. Costanzo, *J. Org. Chem.* **2001**, *66*, 1528–1531.
[84] A. L. Johnson, J. C. Kauer, D. C. Sharma, R. I. Dorfman, *J. Med. Chem.* **1969**, *12*, 1024–1028.
[85] H. Dumoulin, S. Rault, M. Robba, *J. Heterocycl. Chem.* **1995**, *32*, 1703–1707.
[86] M. Begtrup, J. Elguero, R. Faure, P. Camps, C. Estopa, D. Ilavsky, A. Fruchier, C. Marzin, J. de Mendoza, *Magn. Reson. Chem.* **1988**, *26*, 134–151.
[87] R. G. Micetich, P. Spevak, T. W. Hall, B. K. Bains, *Heterocycles* **1985**, *23*, 1645–1649.
[88] A. Guy, J.-P. Guette, G. Lang, *Synthesis* **1980**, 222–223.
[89] E. Ragg, G. Fronza, R. Mondelli, G. Scapini, *J. Chem. Soc. Perkin Trans. 2* **1983**, 1289–1292.
[90] R. Annunziata, M. Cinquini, F. Cozzi, F. Montanari, A. Restelli, *Tetrahedron* **1984**, *40*, 3815–3822.
[91] B. N. Goswami, N. Borthakur, A. C. Ghosh, *J. Chem. Res. Synop.* **1998**, 268–269.
[92] D. Hellwinkel, M. Supp, *Chem. Ber.* **1976**, *109*, 3749–3766.
[93] D. J. de Geest, B. J. O'Keefe, P. J. Steel, *J. Organomet. Chem.* **1999**, *579*, 97–105.
[94] E. Gulbins, K. Hamann, *Chem. Ber.* **1966**, *99*, 55–61.
[95] M. Beljean, M. Pays, *Bull. Soc. Chim. Fr.* **1973**, 3324–3330.
[96] Y. N. Belokon, M. North, T. D. Churkina, N. S. Ikonnikov, V. I. Maleev, *Tetrahedron* **2001**, *57*, 2491–2498.

Received: June 9, 2004
Published online: September 30, 2004

