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Highly efficient and economic synthesis of new substituted amino-bispyridyl derivatives via copper and palladium catalysis

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Abstract

A convenient route for the synthesis of a variety of amino-bispyridyl compounds is introduced. Bispyridylamines were prepared in three steps from commercially available 2,6-dibromopyridine, via a copper mediated alkylation followed by two consecutive N-arylation reactions catalyzed by copper and palladium, respectively.

Nitrogen ligands are able to bind strongly to transition metal atoms and can stabilize both very low and very high oxidation states.[1–6] Even if the nitrogen donor ligands have been less extensively developed for catalytic applications compared to phosphorus, they perform equally well or better in some reactions than their phosphine analogues. On the one hand, they are often less stabilizing under catalytic conditions when coordinated to transition metals. On the other hand, neutral nitrogen donor ligands are more readily displaced from transition metal centers than anionic units or phosphine ligands and therefore may play an interesting flexible role in organometallic transformations.[7] Examples of nitrogen ligands often involve diimine ligands (heterocycles),[8–12] which have been intensively studied in asymmetric catalysis with almost all transition metals.[2–6,13] Other examples of multidentate N-donor ligands have found only limited use in catalysis.[14] Catalytic applications of mainly late transition metal complexes have been reported for trispyrazolylborate,[15,16] triazacyclononane[17] and pyridine-2,6-diimine[18] ligands. A great achievement was notably reported by Gibson and Brookhart with the discovery of highly active iron and cobalt polymerization catalysts containing bulky tridentate pyridine diimine ligands.[19]

As recently pointed out by Chelucci, the chemistry of those compounds mostly relies on the efficient formation of five-membered chelates upon metal binding. Interestingly, only a few pyridine-based ligands with the potential to form six-membered chelates with metals have been introduced. Wright's bis(pyridyl) silane,[20] Chelucci's dipyridylpropane,[21] Nájera dihydropyridylmethane,[22] and Kwong's dipyridylketone[23] are examples of those compounds. Recently, Kempe,[24] Bolm[25] and Kim[26] showed the applicability of 2,2′-dipyridylamines in transition metal-catalyzed polymerization, allylic oxidation, and transesterification, respectively. Jordan also prepared polymerization catalysts containing a neutral bidentate methylenedipyridyl.[27] Despite these interesting examples, the chemistry of 2,2′-dipyridylamines and 2,2′-methylenedipyridyl has mainly been limited to the study of their coordination behavior, and, to the best of our knowledge, no sterically hindered dipyridyl derivatives were described in the literature.

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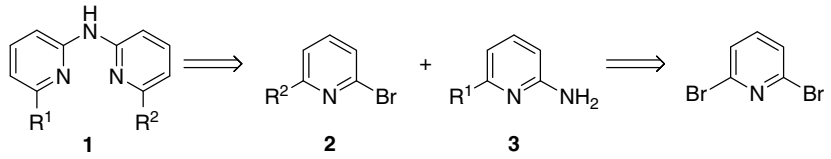
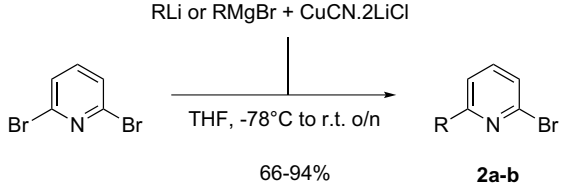


Scheme 1. Synthesis of substituted dipyridylamines.

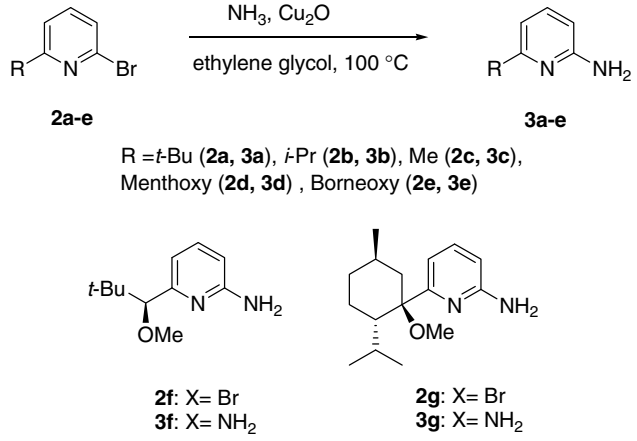
Due to the high potential of such ligands in coordination chemistry, we wish to report in this Letter first the synthesis of 6-alkyl-2-bromopyridines and 6-alkyl-2-aminopyridines, then the preparation of some new 2,2′-bispyridylamine derivatives from the commercially available 2,6-dibromopyridine, as outlined in Scheme 1. As we were looking for economic and attractive procedures for the synthesis of compounds **1**, the direct amination of pyridine halides would be a valuable transformation and will be evaluated.

The first step of our strategy required the addition of an alkyl substituent onto 2,6-dibromopyridine. Nevertheless, two objectives have to be addressed (i) this addition must proceed without any reduction of the halopyridines and (ii) no double addition of the nucleophile must occur. As palladium and nickel complexes often led to the elimination of secondary and tertiary Grignard reagents,[28] as lithium reagents could transmetallate aryl halides, we turned our attention to copper chemistry.[29] Among the copper source, cuprates, and specifically those arising from CuI and CuCN·2LiCl,[30] provided better yields than organocopper reagents. Then the treatment of 2,6-dibromopyridine with 1.5 equiv of *t*-Bu_2CuLi or *t*-BuCuCNLi·LiCl at −78°C in THF led to compounds **2a** in 66% and 94% yields, respectively (Scheme 2). As only one *tert*-butyl group was transferred from *t*-Bu_2CuLi and because the yield was slightly lower with this copper reagent, we used the mixed cuprate for the addition of the *iso*-propyl group. Under these reaction conditions, bromopyridine **2b** was isolated in 66% yield. Neither reduction of the bromopyridine nor bis addition of the alkyl substituent was observed. Moreover, to the best of our knowledge, this is the shortest procedure to prepare **2a**.[31]

Ammonia is among the least expensive bulk chemicals and a common nitrogen source in the synthesis. Despite these, ammonia is rarely used in catalysis,[32] and primary arylamines are typically prepared from ammonia surrogates[33] such as LiHMDS,[34] benzophenone imine,[35] allylamine,[36] carbamate,[37] followed by a deprotection step.



Scheme 2. Synthesis of 2-bromo-6-alkyl pyridines **2**.



Scheme 3. Synthesis of 2-amino-6-substituted pyridines **3**.

However, the reaction of ammonia with aryl halides in the presence of a catalytic amount of palladium[38] or copper[39] has been recently reported. Following the Merck procedure in the presence of a catalytic amount of copper(I) oxide in ethylene glycol and ammonia at 100 °C,[39] aminopyridines **3** were prepared in good yields (54–82%, Scheme 3, Table 1). It is worth mentioning that other solvents than ethylene glycol led to no reaction or lower yields and that, starting from **2a–c**, higher amounts of corresponding alkoxypyridines were produced. Moreover, under these reaction conditions, neither bis aryl formation nor reduction of bromopyridines **2** was observed.

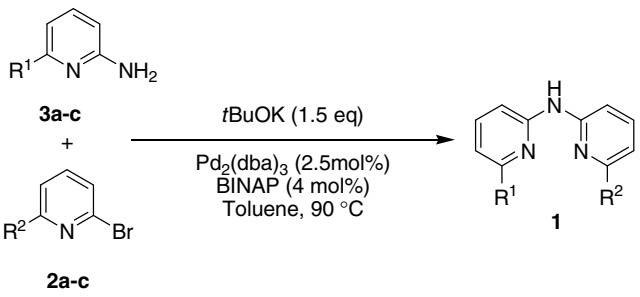
The last step in the synthesis of the new 2,2′-bispyridylamine was a second N-arylation reaction between aminopyridine **3** and bromopyridine **2**. As copper-mediated

Table 1
Copper catalyzed amination of 6-alkyl-2-bromopyridine **2**[a]

R	Compound	Yield[b] (%)
t-Bu	**3a**	75
i-Pr	**3b**	66
Me	**3c**	62
Menthoxy	**3d**	82
Borneoxy	**3e**	69
(*R*)-CH(OMe)(*t*-Bu)	**3f**	68
6-((1*R*,2*S*,5*R*)-2-*iso*-Propyl-1-methoxy-5-methylcyclohexyl)	**3g**	54

[a] 0.5 mmol of bromopyridine **2**, 2 mol % of copper(I) oxide in a 25 mL stainless steel autoclave containing 1 mL of a solution of ethylene glycol saturated with ammonia, 100°C, 24 h.

[b] Isolated yields, all new compounds were characterized by ^1H and ^{13}C NMR, mass analysis.



Scheme 4. Synthesis of 6,6′-substituted-2,2′-dipyridylamine **1**.

Ullmann coupling is now an active field of research and as a great number of catalytic system for the synthesis of bi- or tri-arylamines has been reported, we have carried out some of these procedures. However, until now, no copper catalytic system provided the desired nitrogen compounds **1**. The bispyridylamine derivatives **1** were finally prepared via a palladium-catalyzed Buchwald–Hartwig coupling reaction.[40] In the presence of 2.5 mol % of $Pd_2(dba)_3$, 4 mol % of *rac*-BINAP, and 1.5 equiv of *t*-BuOK in toluene at 90 °C, compounds **1** were isolated in high yields (74–98%, Scheme 4). This procedure allowed the synthesis of C_2-symmetrical or C_1-symmetrical ligands and opened the route to a library of such nitrogen ligands (Scheme 4, Table 2).

In conclusion, we have described a short, simple, and flexible access to functionalized bispyridylamine compounds via copper and palladium catalysis. For this purpose, a new alkylation reaction of 2,6-dibromopyridine and a general amination reaction with ammonia, as an economic alternative to ammonia surrogate, were developed. These ligand syntheses offer the possibility of altering the nature of the two pyridine groups and the central *N*-donor atom. Applications of these derivatives as ligands in catalysis are under active progress in our group.

Table 2
Palladium catalyzed synthesis of bispyridylamines **1**[a]

R^1	R^2	Compound	Yield[b] (%)
Me	Me	**1a**	91
i-Pr	*i*-Pr	**1b**	82
t-Bu	*t*-Bu	**1c**	98
Me	Menthoxy	**1d**	79
i-Pr	Menthoxy	**1e**	93
t-Bu	Menthoxy	**1f**	84
H	(*R*)-CH(OMe)(*t*-Bu)	**1g**	90
H	6-((1*R*,2*S*,5*R*)-2-*iso*-Propyl-1-methoxy-5-methylcyclohexyl)	**1h**	89
t-Bu	6-((1*R*,2*S*,5*R*)-2-*iso*-Propyl-1-methoxy-5-methylcyclohexyl)	**1i**	83
Menthoxy	Menthoxy	**1j**	95
Borneoxy	Borneoxy	**1k**	85
6-((1*R*,2*S*,5*R*)-2-*iso*-Propyl-1-methoxy-5-methylcyclohexyl)	6-((1*R*,2*S*,5*R*)-2-*iso*-Propyl-1-methoxy-5-methylcyclohexyl)	**1l**	74
(*R*)-CH(OMe)(*t*-Bu)	(*R*)-CH(OMe)(*t*-Bu)	**1m**	89

[a] 1 mmol of bromopyridine **2**, 1.1 mmol of aminopyridine **3** and 1.5 mmol of *t*-BuOK were warmed in the presence of 2.5 mol % of $Pd_2(dba)_3$ and 4 mol % of *rac*-BINAP in toluene at 90 °C overnight.

[b] Isolated yields, all new compounds were characterized by ^1H and ^{13}C NMR, mass analysis.

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7. Ligands containing sp^2-hybridized nitrogen atoms, especially when the N atom is part of an aromatic system, have an extensive coordination chemistry, in particular when they are multidentate ligands. In contrast to the phosphorous atom, the nitrogen atom has no low-lying d orbitals available, so that nitrogen-containing ligands have only σ-donor (and no π-acceptor) properties. Therefore, the metal–nitrogen bond has a more pronounced ionic character than the metalphosphorous bond. Furthermore, as M–N bonds are more affected by steric effects than M–P bonds, stable complexes with nitrogen-containing ligands can be expected for multidentate ligands making use of the chelating effect.
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