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A practical synthesis of *N,N*-dimethyl-(6-arylpyrid-2-yl)alkylamines

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ABSTRACT

Described is a multigram synthesis of pyridyl amine ligands, which are being studied for their potential use in commercial processes. A practical scale-up was hindered by benzotriazole byproducts of a Grignard addition. With an improved purification to remove these byproducts and a strategic re-ordering of synthetic steps, an array of *N,N*-dimethyl-(6-arylpyrid-2-yl)alkylamines was made efficiently on large scales.

Catalysts made of Group IV metals containing pyridyl amines have attracted attention for their applications in olefin polymerization.[1] These single site catalysts have an advantage over heterogeneous catalysts in that their reactivity can be tuned by ligand variations, and they can provide polymers with greater stereoregularity.[2] Recently, pyridyl amine complexes have been employed for selective ethylene oligomerization.[3] Mechanistic studies suggest that metallocyclic intermediates are responsible for the unparalleled oligomer selectivity.[4]

The synthesis of pyridyl amines for oligomerization catalysts has been of interest in our laboratory. Our original synthetic procedure to make pyridyl amines, shown in Figure 1, started with Suzuki coupling of an aryl boronic acid to 6-bromo-2-pyridine carboxaldehyde (**1**).[5] After purification by column chromatography, the aldehyde was condensed with dimethylamine and benzotriazole to give a stabilized iminium salt (**2**). Grignard addition to the condensation adduct installed the aliphatic or aromatic substituent.[6] Chromatography was needed to purify the final product, separating it from the benzotriazole byproduct prior to metallation with an appropriate metal precursor.

Preparation of an array of ligands in small (100 mg) quantities was achieved employing the synthesis in Figure 1. However, gram quantities of the most promising ligands were required for further study. The Suzuki coupling and amine condensation steps scaled up well with a combined yield of over 80% on a 20 g scale. Unfortunately, the benzotriazole generated during the Grignard addition proved exceedingly difficult to remove, requiring a disproportionately large silica gel or alumina column, and often multiple purification steps. Although this synthesis allowed rapid diversification of R′, attempts to purify more than 5 g of ligand at one time could not be achieved with more than 90% purity.

During the course of the Grignard addition, a white or yellow precipitate was observed that dissolved upon aqueous ammonium chloride quench. It was hypothesized that this precipitate was a benzotriazole-magnesium salt and removal before workup would simplify purification. Filtration of the crude reaction mixture over alumina did indeed remove most of the impurities. Analysis of the condensed filtrate by ^{1}H NMR indicated that benzotriazole constituted only 10–15% of the product. A silica gel plug eluted with ethyl acetate was sufficient to purify the resulting pyridyl amine. Grignard addition yields following this protocol are moderate, as seen in Table 1. Fortunately, use of 1.5 equiv of Grignard reagent resulted in improved yields.

It was later found that filtering the reaction mixture through Celite using diethyl ether to wash the filtrand was as effective as filtration through alumina and/or silica gel. Other solvents, such as ethyl acetate or THF, have a tendency to dissolve the benzotriazole-magnesium salt, allowing it to contaminate the product.

To facilitate diversification of ligand synthesis, the sequence of steps from the original preparation was rearranged (Fig. 2). This change provided a convenient route for introducing aromatic variations in the 6-position of the pyridine ring. Thus, after Grignard addition to a benzotriazole-activated substrate, bromopyridinyl compound **3** was made in about 90% yield from 2-bromo-6-pyridine carboxaldehyde. After filtration through Celite, NMR analysis indicated that amine **3** was sufficiently clean, and no further purification was required. With the Suzuki coupling now as the last step, an advanced intermediate was created and analogues with varying aryl groups were made efficiently. A few examples of these ligands are shown in Figure 2. In addition to the benefit of facile

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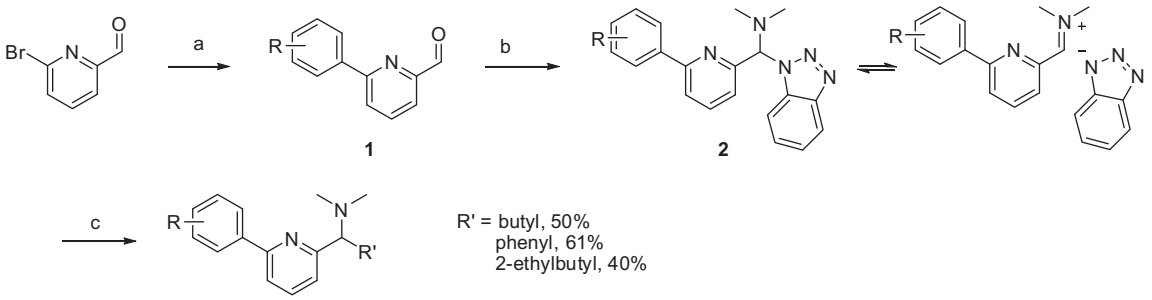
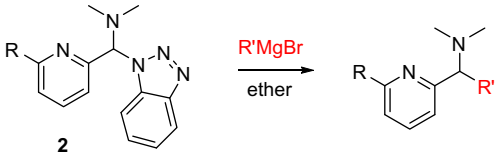


Figure 1. Original pyridyl amine synthetic protocol. Reagents and conditions: (a) $ArB(OH)_2$, $Pd(PPh_3)_4$ Na_2CO_3, H_2O, MeOH, tol, reflux, silica gel chromatography, 72–82%; (b) benzotriazole, Me_2NH, $MgSO_4$, CH_2Cl_2, 82%—quant.; (c) R′MgX, diethyl ether, chromatography.

Table 1
Grignard addition results



Entry	Grignard reagent	Equiv	Scale (g)	Yield[a] (%)
1	Neopentylmagnesium bromide	1.0	2.7	36
2	Decylmagnesium bromide	1.0	2.5	54
3	(3,7-Dimethyloctyl)magnesium bromide	1.0	2.5	57
4	(Cyclohexylmethyl)magnesium bromide	1.5	3.9	84
5	(2-Ethylbutyl)magnesium bromide	1.1	6.0	48
6	(2-Ethylbutyl)magnesium bromide	1.5	5.0	73
7	(2-Ethylbutyl)magnesium bromide	1.5	10.0	89
8	(2-Ethylhexyl)magnesium bromide	1.1	2.5	51
9	(2-Ethylhexyl)magnesium bromide	1.5	2.5	68
10	(2-Ethylhexyl)magnesium bromide	1.5	20.0	65

[a] Isolated yields after filtration over alumina.

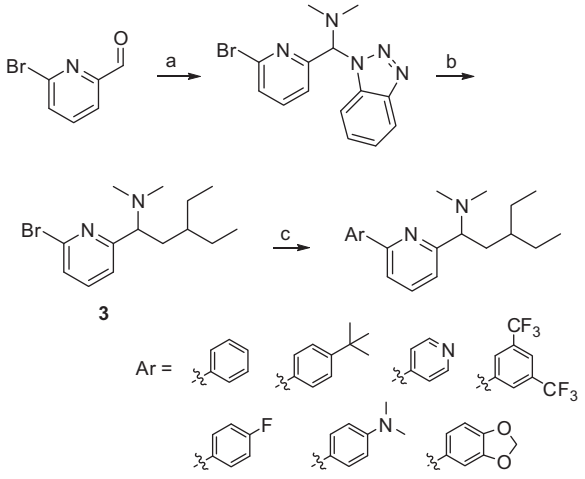


Figure 2. Revised pyridyl amine synthetic protocol. Reagents and conditions: (a) benzotriazole, Me_2NH, $MgSO_4$, CH_2Cl_2, filtration; (b) 2-ethylbutylmagnesium bromide, diethyl ether, filtration, 90%; (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, H_2O, MeOH, tol, reflux, silica gel chromatography, 60–95%.

diversification at the 6-position, the revised protocol gives pyridyl amines in approximately 20% higher overall yield than the original sequence of steps. The significance of the improved synthesis was demonstrated with a large-scale (50 g) preparation of pyridyl amine ligand in 74% overall yield.

In conclusion, a practical, scalable synthesis of pyridyl amine ligands has been developed. This protocol expedited identification of a suitable catalyst for potential commercialization. Key to the success and ease of large-scale syntheses is the replacement of a standard aqueous workup of a Grignard addition with a filtration to remove a benzotriazole salt.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.069.

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