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Access to 2-Aminopyridines – Compounds of Great Biological and Chemical Significance

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Abstract: 2-Aminopyridines are key structural cores of bioactive natural products, medicinally important compounds, and organic materials and thus, extremely valuable synthetic targets. The few reported 6-substituted 2-aminopyridines and the lack of flexible, efficient and general applicable methods for their synthesis demonstrates the urgent need of new methods for their preparation. Reactions between 2,6-dibromopyridine and primary or secondary, cyclic or acyclic, and aliphatic or aromatic amines were shown to selectively yield the respective 6-bromopyridine-2-amines in very high yields which were successfully used as substrates for subsequent C–C cross-coupling reactions. The recently introduced dichloro-bis[1-(dicyclohexylphosphanyl)piperidine]palladium (**1**) was used as catalyst for the cross-coupling of 6-bromopyridine-2-amines with arylboronic acids, diaryl- and dialkylzinc reagents or olefins and hence, is also an excellent C–C cross-coupling catalyst for this type of substrate. Moreover, all the reaction protocols presented were in each of the catalyses uniformly applied. The scope of both the amination and the cross-coupling reactions are well defined and allow one to simply adapt the reaction protocols directly to other amines and/or coupling partners and, thus, provide for the first time a very flexible and generally applicable reaction protocol to get access to 2-aminopyridines.

Keywords: aminophosphines; aminopyridines; C–C bond formation; palladium; pincer complexes; Suzuki–Miyaura reaction

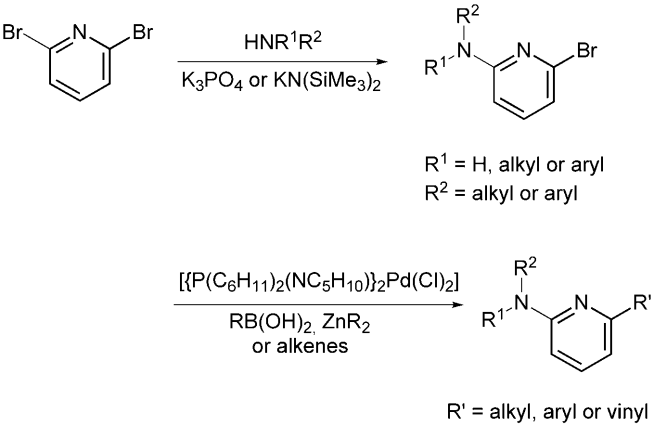
Introduction

Nitrogen-containing heterocyclic compounds are key structural cores of various bioactive natural products, medicinally important compounds, and organic materials and thus, of great biological and chemical significance.[1–3] In particular, pyridines and fused pyridines, such as quinoline, isoquinoline alkaloids,[4] as well as nicotine and its analogues are frequent moieties in natural products.[5] The high incidence of pharmacological and biological activity of heteroaromatic amines, such as 2-aminopyridines, on which we have focused,[6] make them extremely valuable synthetic targets. 2-Amino-6-(aminoethyl)pyridines, for example, are potent inhibitors of nitric oxide synthase (NOS), which could find their application in the treatment of NOS-related diseases, e.g., inflammation, septic shock, rheumatoid arthritis, osteoarthritis, Parkinson's disease, cardiovascular diseases, allergy, cancer, obesity and pain. Furthermore, they also have been shown to inhibit apolipoprotein B (Apo B) secretion and thus, are potentially useful in the conditions associated with elevated circulating levels of Apo B, such as hyperlipidemia, hypertriglyceridemia, atherosclerosis, restenosis, pancreatitis, non-insulin dependent diabetes mellitus and coronary heart diseases,[7] which stimulated tremendeous efforts to prepare compounds of this structural type. Thus, various methods have been applied for their preparation.[5,8] The most common (classical organic) methods for the synthesis of *N*-substituted 2-aminopyridines include *N*-alkylation of 2-aminopyridines,[8a] reactions of aliphatic amines with 2-halopyridines, pyridinium salts or with imidol silyl ethers derived from the corresponding pyridin-2-ones,[8g–i] aminolysis of 2-alkoxypyridines,[8i,j] reactions of α,β-unsaturated ketones with cyano derivatives and amines,[8l], or reactions of 2-alkoxypyridines with amines in the presence of Et_2AlCl.[8m] Other, more recent strategies include transition metal-catalyzed reactions,[8n] such as the Buchwald–Hartwig amination of 2-halopyridines,[8p] which complement the classical synthetic approaches.

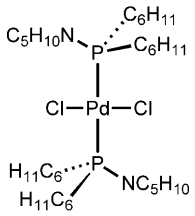
However, despite all the great advantages of metal-catalyzed methods, they often suffer from inefficient bond formations when nitrogen-containing heterocycles are involved. Moreover, catalytic aminations of 2,6-dibromopyridines, which selectively yield 6-bromopyridine-2-amines have not been reported so far. They always lead to mixtures of 2,6-dibromopyridine, 6-bromopyridin-2-amines, and pyridine-2,6-diamines, from which the mono-aminated product is often very difficult to isolate. Thus, even though synthetic strategies exist to prepare 2-aminopyridines, the development of more flexible, efficient, and generally applicable routes (from simple and readily available precursors) that allow the selective and high-yielding synthesis of 6-bromopyridine-2-amines for the fast and easy access to small focused libraries of 2-aminopyridines is of utmost importance for this biologically and chemically significant class of compound. The few reported 6-substituted 2-aminopyridines impressively demonstrate the lack of appropriate methods for their preparation.

We report herein simple, short and extremely versatile reaction protocols for the high-yielding synthesis of 6-substituted 2-aminopyridines. The reaction sequence starts with the selective amination of 2,6-dibromopyridine to give the respective 6-bromopyridine-2-amines, which serve as substrates for subsequent cross-coupling reactions (Scheme 1).

The amination reactions were performed with various primary and secondary, cyclic and acyclic, aliphatic and aromatic amines and demonstrate the general applicability of our reaction protocols. All the 6-bromopyridine-2-amines prepared were subsequently used in C–C cross-coupling reactions, namely the Suzuki, Negishi, and Heck reactions, which were successfully catalyzed by the recently introduced palladium-based 1-(dicyclohexylphosphanyl)piperidine complex $[(P(C_6H_{11})_2(NC_5H_{10}))_2Pd(Cl)_2]$ (**1**), which was quantitatively prepared within only a few minutes at



Scheme 1. General synthetic route to substituted 2-aminopyridines.



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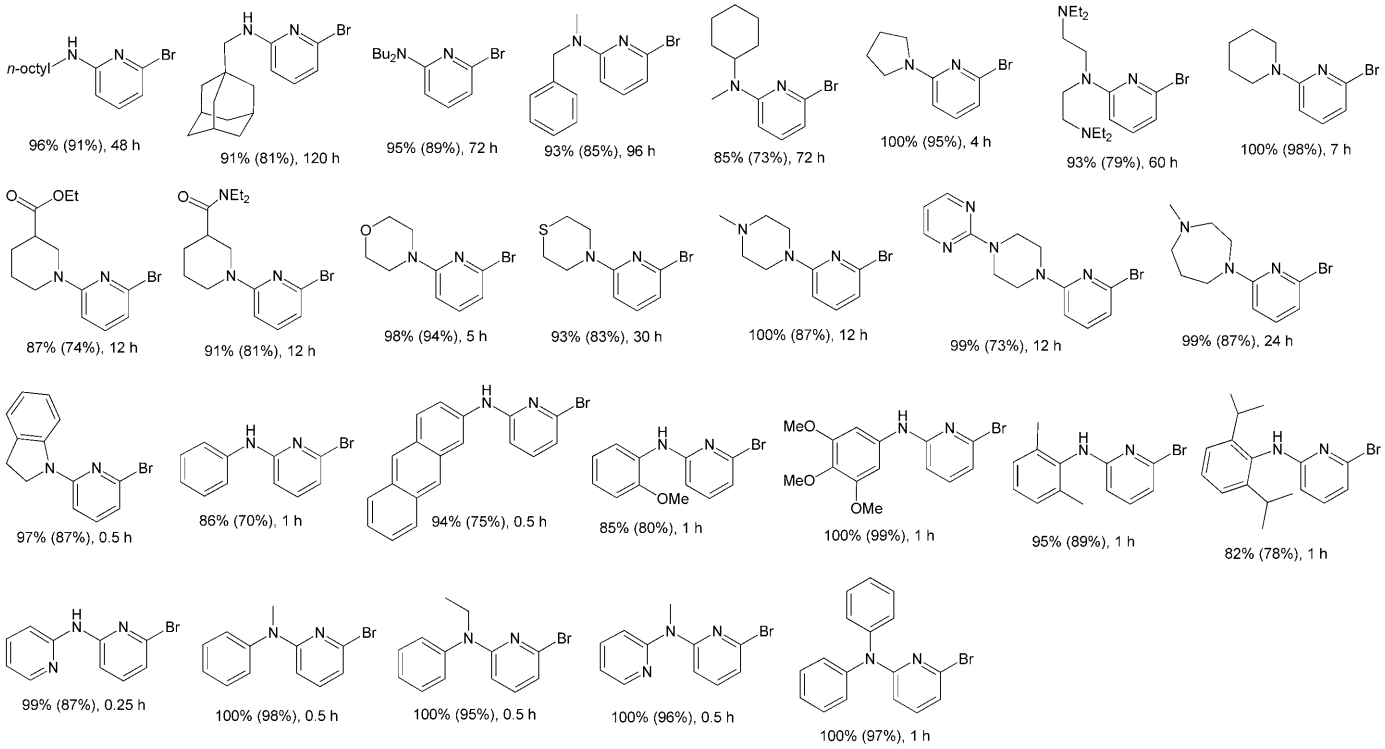
room temperature from reactions of commercially available $[Pd(cod)(Cl)_2]$ (cod = cyclooctadiene) with 2 equiv. of ligand in toluene under N_2.[9] All the cross-coupling reactions were catalyzed by **1** under uniform conditions with a large variety of different but representative 6-bromopyridine-2-amines and coupling partners to demonstrate the flexibility, efficiency and general applicability of our reaction protocols. Furthermore, this report also impressively demonstrates the excellent catalytic activity of dichloro-bis[1-(dicyclohexylphosphanyl)piperidine]palladium (**1**) in C–C cross-coupling reactions performed with 6-bromopyridine-2-amines as substrates. Notably, whereas essentially the same catalytic activity was found for dichloro-bis[1,1′,1″-(phosphinetriyl)tripiperidine]palladium, a dramatically reduced level of activity was obtained in the Suzuki and Heck cross-coupling reactions for $\{[P(C_6H_{11})_3]_2Pd(Cl)_2\}$ – its phosphine-based analogue, where palladium nanoparticles are the catalytically active form. On the other hand, a similar level of activity was expected to be obtained in the Negishi cross-coupling reaction, where a molecular mechanism was found to be operative. This was indeed the case and demonstrates the superior properties of aminophosphine-derived systems when compared with their phosphine-based analogues, since they promote (in contrast to latter) the formation of palladium nanoparticles as well as can operate via a homogeneous mechanisms.[9]

Results and Discussion

Synthesis of 6-Bromopyridine-2-amines

Reactions of aliphatic amines with 2,6-dibromopyridine in dioxane at 100 °C in the presence of an excess (~4 equiv.) of K_3PO_4, selectively yield the respective 6-bromopyridine-2-amines.[10] Representative reactions have been carried out with a wide variety of primary and secondary amines, such as *n*-octylamine and 1-adamantanemethylamine as well as dibutylamine, *N*-methylbenzylamine, 2,3-dihydro-1*H*-indole, ethyl piperidine-3-carboxylate, *N*,*N*-diethylpiperidine-3-carboxamide, 2-piperazin-1-ylpyrimidine, 1-methyl-1,4-diazepane, *N*-methylcyclohexylamine, and *N*′-[2-(diethylamino)ethyl]-*N*,*N*-diethylethane-1,2-diamine,

Table 1. 6-Bromopyridine-2-amines prepared.[a] >



[a] *Reaction conditions:* 10.0 mmol 2,6-dibromopyridine, 11.0 mmol amine, 40.0 mmol K_3PO_4 or 11.0 mmol $KN(SiMe_3)_2$, 30 mL dioxane, reactions performed at 100 °C or at 25 °C. The conversions are determined by GC/MS, based on 2,6-dibromopyridine; isolated yields are given in brackets.

which in all cases cleanly give the desired coupling products in excellent yields – typically within 12 h when cyclic amines, such as pyrrolidine, piperidine, morpholine, ethyl piperidine-3-carboxylate, *N,N*-diethylpiperidine-3-carboxamide, 1-methylpiperazine, or 2-piperazin-1-ylpyrimidine were used as coupling partners. Clean product formation but prolonged reaction times (up to 5 days for 1-adamantanemethylamine) were required when acyclic amines, such as *n*-octylamine, *N*-methylcyclohexylamine, *N*-methylbenzylamine, dibutylamine or *N*′-[2-(diethylamino)ethyl]-*N,N*-diethylethane-1,2-diamine were used as coupling partners.

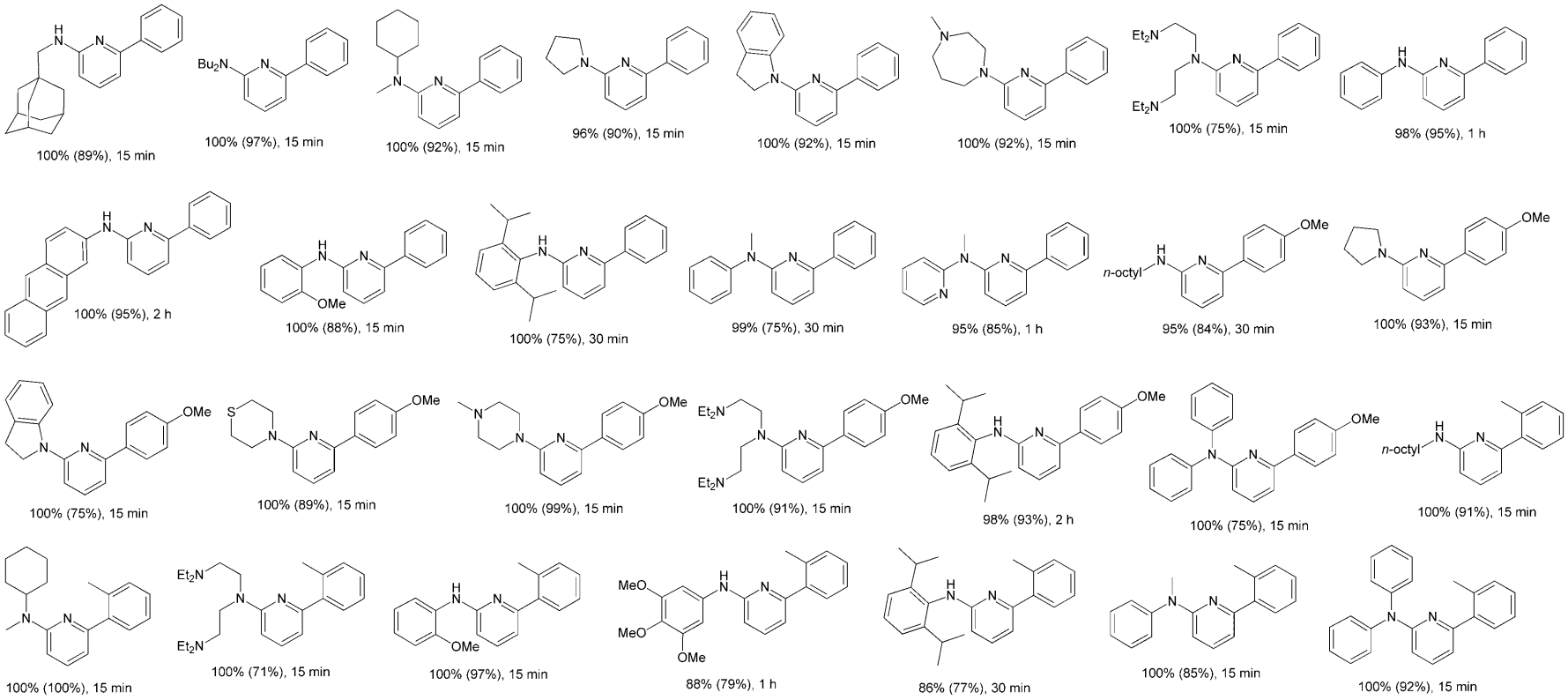
Potassium bis(trimethylsilyl)amide on the other hand, is the base of choice when reactions were performed with aniline derivatives. The respective 6-bromopyridine-2-amines were selectively formed in very high yields, generally in less than 1 hour at 25 °C. Model reactions have been performed with aniline, 3,4,5-trimethoxyaniline, anthracen-2-amine, and sterically hindered 2-methoxyaniline, 2,6-dimethylaniline, and 2,6-bis(1-methylethyl)aniline as well as 2,3-dihydro-1*H*-indole, *N*-methylaniline, *N*-ethylaniline, and *N*-methylpyridine-2-amine. Reaction temperatures of 100 °C were applied when (less nucleophilic) 2-aminopyridine and diphenylamine were used as coupling partners.

Overall, the applicability of both reaction protocols is well-defined, extremely simple, effective and reliably give the 6-bromopyridine-2-amines by reactions of 2,6-dibromopyridines with primary and secondary, cyclic and acyclic, aliphatic and aromatic amines in high yields (>80%) and provide for the first time a highly flexible and versatile synthetic access to 6-bromopyridine-2-amines, which serve as substrates in cross-coupling reactions. All 6-bromopyridine-2-amines shown in Table 1 were prepared accordingly and are used in exemplary C–C bond forming reactions to demonstrate facile synthetic access to 6-substituted 2-aminopyridines.

Suzuki Cross-Coupling

The Suzuki–Miyaura reaction is one of the most important methods for the formation of symmetrical and non-symmetrical biaryls and thus, was expected to offer an efficient and convenient synthetic route to access to 6-arylpyridine-2-amines.[11] Exemplary reactions have been performed with phenylboronic acid, (4-methoxyphenyl)boronic acid and sterically hindered (2-methylphenyl)boronic acid. For example, when 6-bromopyridine-2-amines were coupled with a slight excess (~1.1 equiv.) of arylboronic acid in tolu-

Table 2. Suzuki cross-coupling reactions performed with 6-bromopyridine-2-amines and arylboronic acids catalyzed by **1**.[a]



[a] *Reaction conditions:* 2.0 mmol 6-bromopyridine-2-amine, 2.2 mmol arylboronic acid, 6 mL toluene, **1** (0.2 mol%) added in solution (0.4 mL of a 1×10^{-2}M toluene solution), reaction performed (in air) at 80 °C. Conversions are determined by GC/MS and based on aryl halide; isolated yields are given in brackets.

ene in the presence of 0.2 mol% of $[(P(C_6H_{11})_2(NC_5H_{10}))_2Pd(Cl)_2]$ (**1**), the respective coupling products were quantitatively formed in almost all the reactions examined within only 15 min at 80 °C in air. Model reactions have been performed with primary and secondary aliphatic aminopyridines, such as 6-bromo-*N*-cyclohexyl-*N*-methylpyridin-2-amine, 6-bromo-*N*,*N*-dibutylpyridin-2-amine and *N*-(6-bromopyridin-2-yl)-*N*-[2-(diethylamino)ethyl]-*N*′,*N*′-diethylethane-1,2-diamine as well as aromatic 6-bromopyridine-2-amines, like 6-bromo-*N*-(3,4,5-trimethoxyphenyl)pyridin-2-amine, 6-bromo-*N*,*N*-diphenylpyridin-2-amine and 6-bromo-*N*-methyl-*N*-pyridin-2-ylpyridin-2-amine. Impressively, the same conversion rates and yields were obtained when electronically deactivated (4-methoxyphenyl)boronic acid and sterically hindered (2-methylphenyl)boronic acid were applied. For example, 1-(6-bromopyridin-2-yl)-2,3-dihydro-1*H*-indole, 4-(6-bromopyridin-2-yl)thiomorpholine, and *N*-[2,6-bis(1-methylethyl)phenyl]-6-bromopyridin-2-amine as well as 6-bromo-*N*-octylpyridin-2-amine, *N*-(6-bromopyridin-2-yl)-*N*-[2-(diethylamino)ethyl]-*N*′,*N*′-diethylethane-1,2-diamine and 6-bromo-*N*-(2-methoxyphenyl)pyridin-2-amine were cleanly (side-reactions have not been detectable) converted into the respective coupling products. The coupling products could be isolated in all the reactions examined, in excellent yields. The same level of activity was noticed when sterically hindered 6-bromopyridine-2-amines, such as *N*-(3-bromophenyl)-2,6-bis(1-methylethyl)aniline were used as substrates and impressively demonstrates that **1** is (in contrast to the phosphine-based analogue) an excellent Suzuki catalyst, which reliably couples a large variety of 6-bromopyridine-2-amines at low catalyst loadings with different arylboronic acids under uniform reaction conditions to provide flexible and facile synthetic access to 2-aminopyridines in excellent overall yields from commercially available 2,6-dibromopyridines via 6-bromopyridine-2-amines in two steps (Table 2).

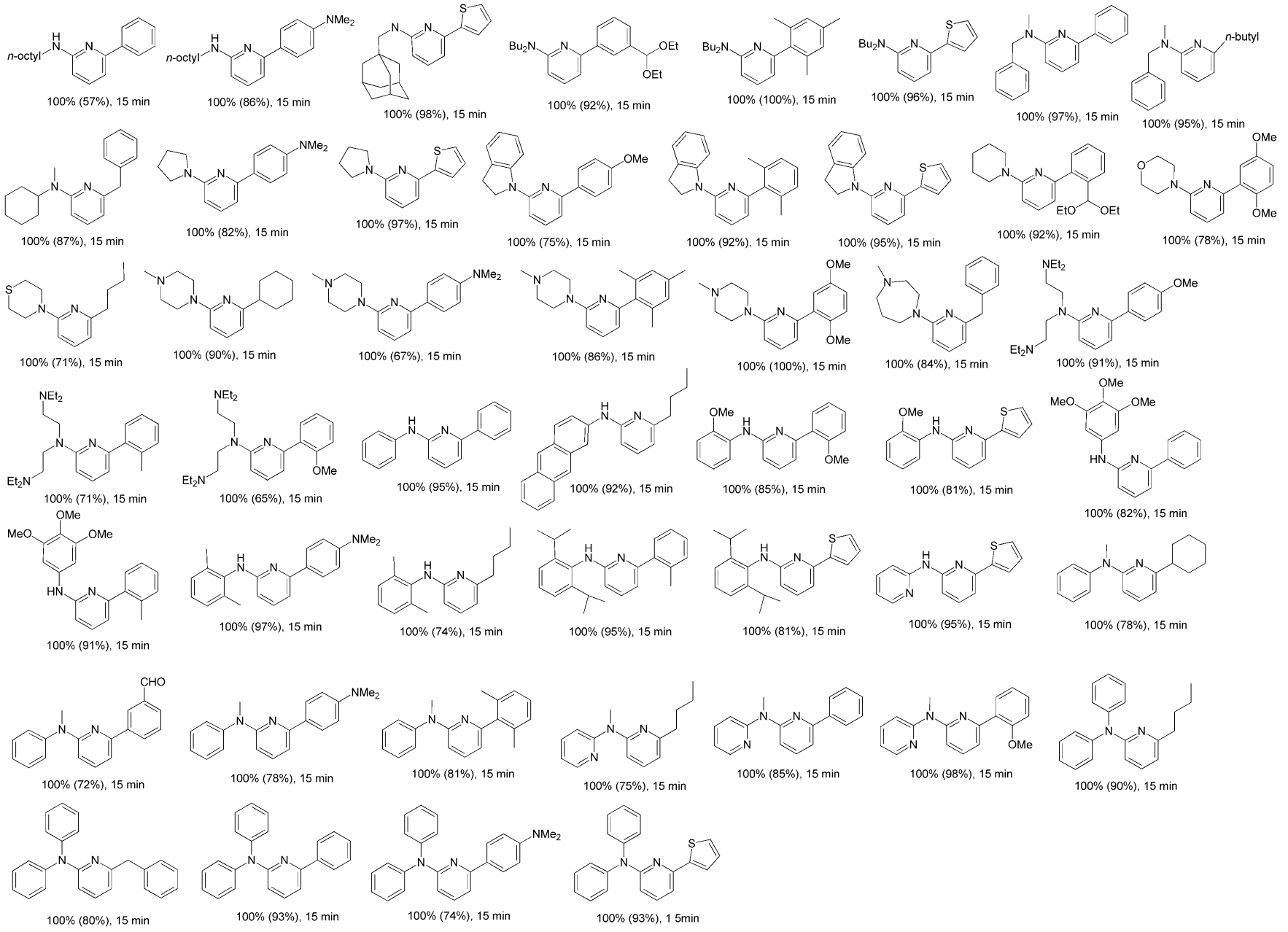
Negishi Cross-Coupling

Another mild, efficient and highly versatile C–C bond forming reaction, which could provide facile synthetic access to 6-substituted 2-aminopyridines is the Negishi reaction – the cross-coupling of aryl halides with organozinc reagents.[11a,b,12] Indeed, 6-bromopyridine-2-amines were reliably coupled with a large variety of representative diaryl- and dialkylzinc reagents in THF/NMP mixtures in the presence of only 0.01 mol% of **1** at 100 °C in air. Reactions have been successfully performed with various 6-bromopyridine-2-amines, containing secondary and tertiary, cyclic and acyclic aliphatic and aromatic amine units. Examples include *N*-octyl-6-bromopyridin-2-amine, *N*-benzyl-6-bromo-*N*-methylpyridin-2-amine, and *N*,*N*-dibutyl-6-bromopyridin-2-amine, 2-bromo-6-piperidin-1-ylpyridine, 1-(6-bromopyridin-2-yl)-2,3-dihydro-1*H*-indole, 6-bromo-*N*-(2-methoxyphenyl)pyridin-2-amine and 6-bromo-*N*,*N*-diphenylpyridin-2-amine. In addition, functionalized 6-bromopyridine-2-amines, such as *N*-(6-bromopyridin-2-yl)-*N*-[2-(diethylamino)-ethyl]-*N*′,*N*′-diethylethane-1,2-diamine and 6-bromo-*N*-methyl-*N*-pyridin-2-ylpyridin-2-amine have been used as coupling partner. These and many other substrates have been successfully coupled (without modification of the reaction protocol) with representative organozic reagents, such as diphenylzinc, electronically deactivated bis(4-methoxyphenyl)zinc or bis[4-(dimethylamino)phenyl]zinc, sterically hindered diarylzinc reagents, such as bis(2-methylphenyl)zinc, bis(2,6-dimethylphenyl)zinc, bis(2,4,6-trimethylphenyl)zinc or bis(2-methoxyphenyl)zinc, bis(2,5-dimethoxyphenyl)zinc as well as dithiophen-2-ylzinc, and also aliphatic organozinc reagents, namely dibutylzinc, dicyclohexylzinc, and dibenzylzinc. Impressively, any 6-bromopyridine-2-amine applied, was almost quantitatively converted into the desired 6-substituted 2-aminopyridine within only a few minutes. Isolated yields of the desired coupling products were in almost all the reactions performed higher than 80%, which impressively demonstrates the excellent catalytic activity of **1** in the Negishi reaction and its practicabillity in the cross-coupling of 6-bromopyridine-2-amines with diaryl or dialkylzinc reagents and thus, the preparation of 6-substituted 2-aminopyridines. Indeed, the presented reaction protocol provides an extremely flexible and versatile synthetic access to 2-aminopyridines and additionally allows its direct adaption for the synthesis of other 2-aminopyridines, which were reliably coupled in the presence of only 0.01 mol% of catalyst under uniform reaction conditions. All the 2-aminopyridines prepared that involve the cross-coupling of a 6-bromopyridine-2-amine with diaryl- or dialkylzinc reagents are listed in Table 3.

Heck Cross-Coupling

The Heck reaction is the most important C–C bond forming process for the arylation of olefins and thus, the method of choice for the preparation of 6-[(1*E*)-alkenyl]pyridine-2-amines.[11a,b,13] Indeed, 6-bromopyridine-2-amines, such as aliphatic ethyl 1-(6-bromopyridin-2-yl)-4-methylpiperazine, ethyl 1-(6-bromopyridin-2-yl)piperidine-3-carboxylate, *N*-benzyl-6-bromo-*N*-methylpyridin-2-amine, as well as aromatic 6-bromo-*N*,*N*-diphenylpyridin-2-amine were successfully coupled with various, representative olefins, such as ethenylbenzene and derivatives, 4-vinylpyridine, *N*,*N*-dimethylacrylamide, as well as butyl prop-2-enoate (Table 4). For example, the cross-coupling of 2-[4-(6-

Table 3. Negishi cross-coupling reactions performed with 6-bromopyridine-2-amines and arylboronic acids catalyzed by **1**.[a]



[a] *Reaction conditions:* 2.0 mmol 6-bromopyridine-2-amine, 0.6 equiv. (rel. to bromide) of diarylzinc reagent (1.2 equiv. for 6-bromo-2-aminopyridines containing N-H groups), 2.5 mL NMP, **1** (0.01 mol%) added in solution (0.2 mL of a 1×10^{-3} M toluene solution), reaction performed (in air) at 100 °C. Conversions are determined by GC/MS and based on aryl halide; isolated yields are given in brackets.

Table 4. Heck cross-coupling reactions performed with 6-bromopyridine-2-amines and olefins catalyzed by **1**.[a]

[a] *Reaction conditions:* 2.0 mmol 6-bromopyridine-2-amine, 3.0 mmol olefin, ~3.0 mmol K_2CO_3, 5 mL DMF, **1** (0.05 mol%) added in solution (0.2 mL of a 5×10^{-3} M THF solution), reaction performed under an N_2 atmosphere at 140 °C. The conversions and the product ratios (*trans/cis/gem*) are determined by GC/MS, based on aryl halide; isolated yields are given in brackets. Unless otherwise stated the *trans*-isomer was exclusively formed.

bromopyridin-2-yl)piperazin-1-yl]pyrimidine with ethenylbenzene under a nitrogen atmosphere in DMF and K_2CO_3 as base at 140 °C in the presence of 0.05 mol% of **1** was fully converted into 2-(4-{6-[(*E*)-2-phenylethenyl]pyridin-2-yl}piperazin-1-yl)pyrimidine in 2 h. The isolated yield was 95%. 4 h of reaction time were required for the preparation of *N*-benzyl-*N*-methyl-6-[(*E*)-2-phenylethenyl]pyridin-2-amine, which could have been isolated in 82% yield. Essentially the same catalytic performances were obtained for the cross-coupling of 6-bromopyridines with other ethenylbenzene derivatives, such as 1-ethenyl-4-methylbenzene, 1-ethenyl-4-methoxybenzene, 1-chloro-3-ethenylbenzene, and 4-vinylpyridine. An exemplary reaction includes the conversion of 6-bromo-*N*,*N*-diphenylpyridin-2-amine into 6-[(*E*)-2-(4-methoxyphenyl)ethenyl]-*N*,*N*-diphenylpyridin-2-amine, which was complete after 4 h. A slightly retarded conversion was obtained by using 1-chloro-3-ethenylbenzene as substrate. Comparable conversion rates and yields were noticed when *N*,*N*-dimethylacrylamide and butyl prop-2-enoate were used as coupling partners. In general, the 6-[(1*E*)-alkenyl]pyridine-2-amines are in almost all the reactions examined exclusively (>95%) formed and impressively demonstrates that the aminophosphine-derived palladium complex **1** is (in contrast to their phosphine based analogues) an efficient Heck catalyst, which smoothly couples 6-bromopyridine-2-amines at low catalyst loadings with olefins. Overall, the Heck reaction is an appropriate synthetic method for the vinylation of 6-bromopyridine-2-amines, even though NH-containing 6-bromopyridine-2-amines were found to be incompatible under the reaction conditions applied. All the Heck coupling products prepared are given in Table 4. The reaction conditions applied were in all the reactions examined the same.

Conclusions

In conclusion, simple and general applicable synthetic methods for the selective and high-yielding synthesis of 6-bromo-2-aminopyridines have been developed, and the products were successfully applied in cross-coupling reactions [catalyzed by the recently introduced dichloro-bis(1-(dicyclohexylphosphanyl)piperidine)palladium (**1**)]. The selective synthesis of 6-bromopyridine-2-amines was achieved from reactions between commercially available 2,6-dibromopyridine and amines in the presence of a base – depending on the amine – either at room temperature or at 100 °C. The reaction protocols were successfully applied to primary and secondary aliphatic, cyclic and acyclic, and aromatic amines and thus, are extremely flexible. Moreover, dichloro-bis(1-(dicyclohexylphosphanyl)piperidine)palladium (**1**) {as well as dichloro-bis[1,1′,1″-(phosphinetriyl)tripiperidine]palladium} are excellent C–C bond forming catalysts, which efficiently couple 6-bromo-2-aminopyridines with a large variety of different types of coupling partners, such as arylboronic acids, dialkyl or diarylzinc reagents and olefins. This is in striking contrast to its phosphine-based analogue that only shows a comparable level of activity in the Negishi reaction but dramatically lower activities under Suzuki and Heck reaction conditions. The 6-substituted 2-aminopyridines, however, were in all the reactions performed, cleanly and rapidly formed and could be isolated in excellent yields. Although one-pot protocols would be desirable for their synthesis, attempts to date have not resulted in improvement and further studies are under way. However, all the reaction protocols presented are uniform and the scope of both, the amination and the C–C cross-coupling reactions, are well defined. This allows one to simply adopt the presented synthetic routes directly to other amines and coupling partners and hence, provide a powerfull tool to get facile access to 2-aminopyridines *via* simple (systematic) modifications of the amine and/or the R units, which is of great importance for the preparation of pharmaceuticals and targets in material science, for example. The few reported 6-substituted 2-aminopyridines and the lack of flexible, efficient and general applicable methods for their synthesis impressively demonstrates the urgent need of new methods to obtain synthetic access to 2-aminopyridines – compounds, which are not only of great chemical importance, but also for biological, medicinal and pharmaceutical applications and material science – and thus, the importance of this report.

Experimental Section

General Remarks

All synthetic operations for the catalyst preparation were carried out in oven-dried glassware using a combination of glovebox (M. Braun 150B-G-II) and Schlenk techniques under a dinitrogen atmosphere. Solvents were reagent grade or better and freshly distilled under N_2 atmosphere by standard procedures. Deuterated solvents were purchased from Armar, dried by standard procedures, and degassed by freeze-thaw cycles before use. All chemicals were purchased from Aldrich Chemical Co. or Acros Organics and used as received.

General Procedure for the Selective Synthesis of 6-Bromopyridin-2-Amines with Aliphatic Amines

A Young Schlenk was charged (in air) with 10.0 mmol of 2,6-dibromopyridine, 11.0 mmol of amine, 40.0 mmol of K_3PO_4, and 30 mL of dioxane and closed with a Teflon screw cap. Then the reaction mixture was placed in a preheated 100 °C oil bath and stirred vigorously. Samples taken from the reaction mixture were quenched with water. The

products were extracted with ethyl acetate and analyzed by GC/MS. At the end of the reaction the mixtures were allowed to cool to room temperature, were quenched with 1 M NaOH and extracted with 30–50 mL of ethyl acetate. The combined extracts were washed with 1 M NaOH (3× 50 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. Where necessary, the product was purified by flash chromatography on silica gel or on alumina.

General Procedure for the Selective Synthesis of 6-Bromopyridin-2-Amines with Aniline-Derived Amines

Inside a glovebox a vial was successively charged with 11.0 mmol of amine, 11.0 mmol of $KN(SiMe_3)_2$ (secondary aniline derivatives) or 15.0 mmol of $KN(SiMe_3)_2$ (primary aniline derivatives), respectively, 30 mL of dioxane and 10.0 mmol of 2,6-dibromopyridine. Then the reaction mixture was stirred at room temperature unless otherwise stated. Samples taken from the reaction mixture were quenched with 1 M NaOH. The products were extracted with ethyl acetate and analyzed by GC/MS. At the end of the reaction the mixtures were quenched with 1 M NaOH and extracted with 30–50 mL of ethyl acetate. The combined extracts were washed with 1 M NaOH (3×50 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. Where necessary, the product was purified by flash chromatography on silica gel or on alumina.

General Procedure for the Suzuki Cross-Coupling

All catalytic reactions were carried out in reaction vessels open to the air. A round-bottomed flask was charged with the arylboronic acid (2.2 mmol), the 6-bromo-2-aminopyridine (2.0 mmol), powdered K_3PO_4 (3.0 mmol), and toluene (6 mL). The mixture was vigorously stirred and heated to 80 °C. Then the catalyst was added by syringe as a toluene solution (0.2 mol%, 0.4 mL of a 1×10^{-2} M solution). Samples were periodically taken from the reaction mixture, quenched with 1 M NaOH, extracted with diethyl ether, and analyzed by GC/MS. At the end of catalytic reaction, the reaction mixtures were allowed to cool to room temperature, quenched with 1 M NaOH, and extracted with diethyl ether (2×40 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The crude material was purified by flash chromatography on silica gel, as necessary.

General Procedure for the Negishi Cross-Coupling

All catalytic reactions were carried out in reaction vessels open to the air. A round-bottomed flask was charged with the 6-bromo-2-aminopyridine (2.0 mmol) and 0.6 equiv. of the zinc reagent (1.2 equiv. for 6-bromo-2-aminopyridines containing N-H groups) and NMP (2.5 mL). The mixture was vigorously stirred and heated to 100 °C. Then the catalyst was added by syringe as a THF solution (0.01 mol%, 0.2 mL of a 1×10^{-3} M solution). Samples were periodically taken from the reaction mixture, quenched with 1 M NaOH, extracted with diethyl ether, and analyzed by GC/MS. At the end of catalytic reaction, the reaction mixtures were allowed to cool to room temperature, quenched with basic EDTA solution (0.5 M, 4 equiv. NaOH relative to EDTA), and extracted with diethyl ether (2×40 mL). The organic phase was washed with basic EDTA solution. The combined extracts were dried over $MgSO_4$, filtered through silica or aluminium oxide (compounds containing aliphatic tertiary amines), respectively, and evaporated to dryness. The crude material was purified by flash chromatography on silica gel, as necessary.

The diarylzinc reagents were prepared in THF by converting the aryl halides to the Grignard reagents which were then reacted with zinc dichloride to afford the corresponding diarylzinc reacents. Dibutylzinc was prepared in THF by reacting butyllithium with zinc dichloride at −78 °C. Dibenzylzinc and dicyclohexylzinc were prepared by convertion their alkyl halide to the Grignard reagent followed by the addidion of zinc dichloride.NMP was added to the zinc reagents, resulting in a NMP/THF solution (2:1), which was used within 2 days.

General Procedure for Heck Cross-Coupling

A round-bottomed flask was charged under an N_2 atmopshere with the appropriate olefin (3.0 mmol), 6-bromo-2-aminopyridine (2.0 mmol), powdered K_2CO_3 (3.0 mmol), and DMF (5 mL). The mixture was vigorously stirred and heated to 140 °C. Then the catalyst was added by syringe as a toluene solution (0.05 mol%, 0.2 mL of a 5×10^{-3} M solution). Samples were periodically taken from the reaction mixture, quenched with 1 M NaOH, extracted with ethyl acetate, and analyzed by GC/MS. At the end of catalysis, the reaction mixtures were allowed to cool to room temperature, quenched with water, and extracted with ethyl acetate (2×40 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The crude material was purified by flash chromatography on silica gel, as necessary.

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