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$[Pd(Cl)_2\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$—A Highly Effective and Extremely Versatile Palladium-Based Negishi Catalyst that Efficiently and Reliably Operates at Low Catalyst Loadings

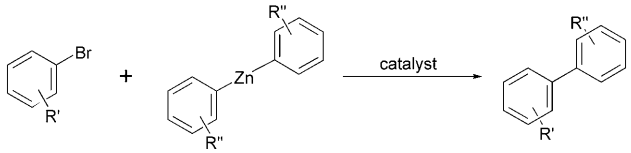
Jeanne L. Bolliger and Christian M. Frech*[a]

Abstract: $[Pd(Cl)_2\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (**1**) has been prepared in quantitative yield by reacting commercially available $[Pd(cod)(Cl)_2]$ (cod = cyclooctadiene) with readily prepared 1-(dicyclohexylphosphanyl)piperidine in toluene under N_2 within a few minutes at room temperature. Complex **1** has proved to be an excellent Negishi catalyst, capable of quantitatively coupling a wide variety of electronically activated, non-activated, deactivated, sterically hindered, heterocyclic, and functionalized aryl bromides with various (also heterocyclic) arylzinc reagents, typically within a few minutes at 100 °C in the presence of just 0.01 mol % of catalyst. Aryl bromides containing nitro, nitrile, ether, ester, hydroxy, carbonyl, and carboxyl groups, as well as acetals, lactones, amides, anilines, alkenes, carboxylic acids, acetic acids, and pyridines and pyrimidines, have been successfully used as coupling partners. Furthermore, electronic and steric variations are tolerated in both reaction partners. Experimental observations strongly indicate that a molecular mechanism is operative.

Keywords: arylzinc reagents · biaryls · C–C coupling · cross-coupling · Negishi cross-coupling · palladium

Introduction

The Negishi reaction (cross-coupling of an aryl halide with an organozinc reagent) is an extremely versatile and mild synthetic method for the formation of carbon–carbon bonds, which (in contrast to the Kumada reaction) tolerates a wide variety of functional groups (Scheme 1).[1,2] Recent improvements in the preparation of organozinc reagents (preparations of aryl- as well as alkylzinc reagents from highly functionalized precursors have been described) have significantly broadened the scope and applicability of the Negishi reaction in organic synthesis.[3] Nowadays, the Negishi reaction belongs to an indispensable set of palladium-catalyzed cross-coupling reactions and finds application in all areas of organic chemistry. Together with the Suzuki reaction, it is among the most important methods for the catalytic formation of symmetric and nonsymmetric biaryls,[4–6] which are found, for example, in polymers,[7] biologically active compounds,[8] ligands,[9] and various materials.[10]



Scheme 1. Negishi cross-coupling reaction between aryl bromides and bis(aryl)zinc reagents.

Even though recent developments have led to a considerable increase in the activity of Negishi catalysts, some of which are very effective and allow the coupling of sterically hindered substrates and even aryl chlorides at low catalyst loadings and occasionally at room temperature,[11] a typical protocol for this reaction still requires prolonged reaction times and relatively high catalyst loadings (typically 0.5–5 mol %), highlighting the need for more efficient systems.[12] Moreover, their (multistep) syntheses are often time-consuming, difficult, and/or require the use of expensive starting materials. Furthermore, many of these catalysts suffer from poor thermal stability, low functional group tolerance, and/or sensitivity towards air, and hence require inconvenient inert-atmosphere techniques for their successful use. In addition, modified reaction conditions are often reported for

[a] J. L. Bolliger, C. M. Frech
Department of Inorganic Chemistry, University of Zürich
Winterthurerstrasse 190, 8057 Zürich (Switzerland)
Fax: (+41) 44-635-6802
E-mail: chfrech@aci.uzh.ch

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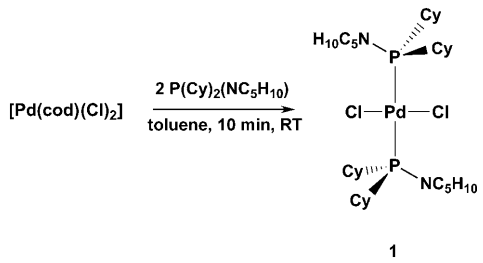
different substrates, which may strongly limit their application in industrial processes.

We report herein the catalytic performance of the simple, inexpensive, and readily prepared palladium complex $[Pd(Cl)_2\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (**1**) in the Negishi cross-coupling reaction with aryl bromides (aryl chlorides have not been tested) and demonstrate that **1** is an extremely efficient, reliable, and versatile Negishi catalyst with excellent functional group tolerance, which allows electronic and steric variations in both reaction partners. Furthermore, the reaction protocol presented is highly convenient, simple, and, most importantly, universally applicable. Moreover, the biaryls are cleanly and quantitatively formed, typically within a few minutes at 100 °C in the presence of just 0.01 mol % of catalyst. The dichloro{bis[1-(dicyclohexylphosphanyl)piperidine]} complex $[Pd(Cl)_2\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (**1**), an extremely effective Suzuki catalyst, was chosen because it promotes the formation of palladium nanoparticles (palladium nanoparticles have been shown to be the catalytically active form of **1** in the Suzuki reaction)[13] and also because it can operate through homogeneous mechanisms. Indeed, mechanistic investigations performed here have indicated that **1** operates through a molecular mechanism in the Negishi reaction.

Results and Discussion

The palladium complex $[Pd(Cl)_2\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (**1**) was prepared in quantitative yield within a few minutes at room temperature by reaction of commercially available $[Pd(cod)(Cl)_2]$ (cod = cyclooctadiene) with two equivalents of readily prepared 1-(dicyclohexylphosphanyl)piperidine in toluene under N_2 (Scheme 2).[13]



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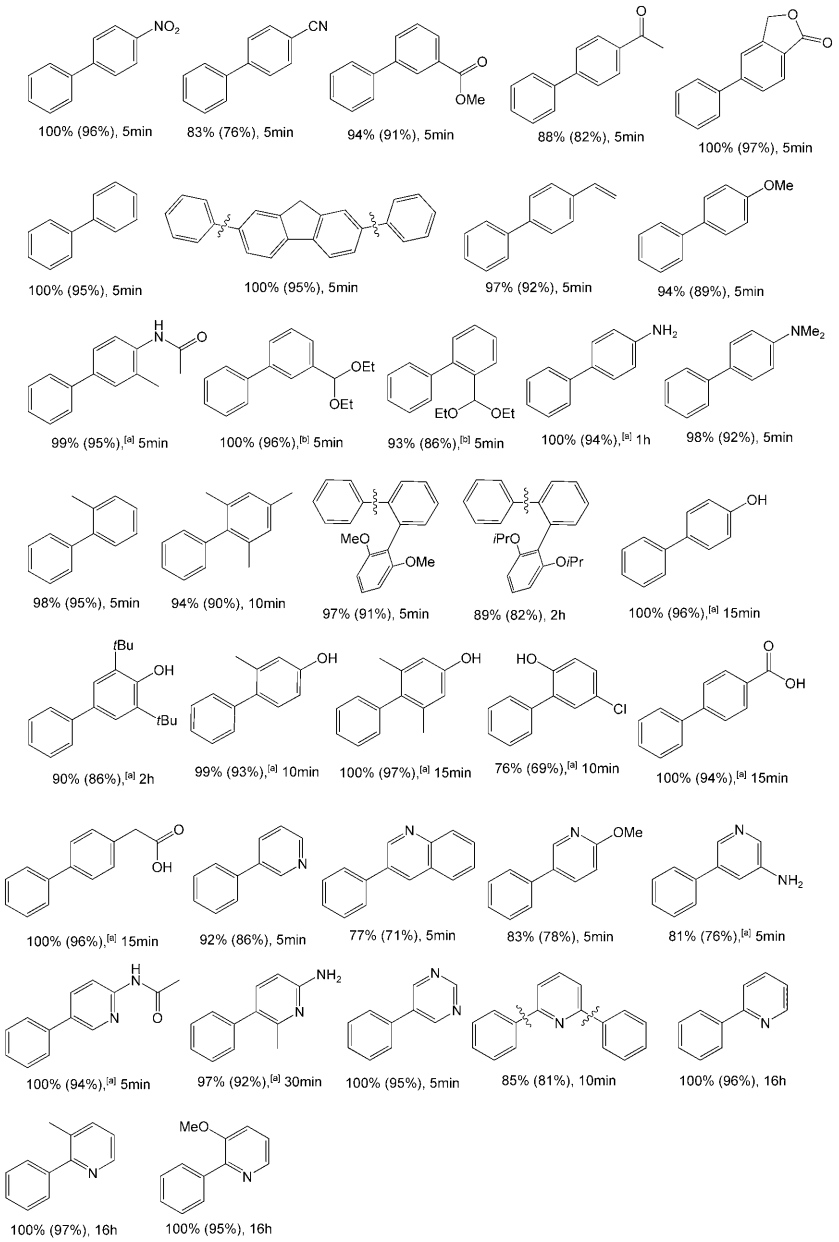
Scheme 2. Synthesis of **1**; Cy = cyclohexyl.

Complex **1** is an extremely active, reliable, and versatile Negishi catalyst with excellent functional group tolerance, which successfully couples a wide variety of substrates. These may contain nitro, nitrile, acetal, ketone, ether, ester, lactone, amide, aniline, alkene, phenol, carboxylic acid, acetic acid, pyridine, or pyrimidine moieties. The aryl bromides may be electronically activated, non-activated, deactivated, and/or sterically hindered or heterocyclic, and are coupled with various (also heterocyclic) arylzinc reagents in excellent yields, generally within a few minutes at 100 °C in the presence of just 0.01 mol % of catalyst.[14] Moreover, electronic and steric variations are tolerated in both reaction partners. Exemplary reactions were performed with diphenylzinc, bis(4-methoxyphenyl)zinc, bis[4-(dimethylamino)-phenyl]zinc, sterically hindered dinaphthalen-1-ylzinc, bis(2-methoxyphenyl)zinc, bis(2,5-dimethoxyphenyl)zinc, bis(2-methylphenyl)zinc, and bis(2,4,6-trimethylphenyl)zinc, as well as with 4-ethoxycarbonylphenylzinc iodide, bis[2-(diethoxymethyl)phenyl]zinc, bis[3-(diethoxymethyl)phenyl]zinc, and dithiophen-2-ylzinc, both aryl groups of which were incorporated into the generated biaryls. Performing the Negishi reactions in *N*-methylpyrrolidone (NMP) afforded the highest conversion rates and yields.

For example, coupling reactions between diphenylzinc and electronically activated aryl bromides, such as 1-bromo-4-nitrobenzene, 4-bromobenzonitrile, methyl 3-bromobenzoate, and 5-bromo-2-benzofuran-1(3*H*)-one, or with non-activated phenyl bromide, 1-bromo-4-ethenylbenzene, and 2,7-dibromofluorene, afforded the coupling products in >90 % yield within only 5 min (Scheme 3). The same level of activity was observed when electronically deactivated 1-bromo-4-methoxybenzene, 4′-bromo-2′-methylacetanilide, 4-bromoaniline, and 4-bromo-*N*,*N*-dimethylaniline or sterically hindered substrates, such as 1-bromo-2-methylbenzene, 2-bromo-1,3,5-trimethoxybenzene, and 2′-bromo-2,6-dimethoxybiphenyl, were used as coupling partners, with which >93 % conversion was obtained in almost all of the reactions examined after 5 min. Even 2′-bromo-2,6-bis(1-methylethoxy)biphenyl, a highly sterically hindered substrate, was smoothly coupled with diphenylzinc: 89 % conversion into 2,6-bis(1-methylethoxy)-1,1′:2′,1″-terphenyl was achieved after 2 h. Excellent performance of the catalyst was also noted for various (also sterically hindered) bromophenols, 4-bromobenzoic acid, as well as (4-bromophenyl)acetic acid, which generally afforded the coupling products in >90 % yield within 15 min. Similar conversion rates and yields were also observed for 3-bromopyridines, such as 3-bromopyridine, 3-bromoquinoline, 5-bromo-2-methoxypyridine, 5-bromopyridin-3-amine, *N*-(5-bromopyridin-2-yl)acetamide, 5-bromo-6-methylpyridin-2-amine, as well as 5-bromopyrimidine and 2,6-dibromopyridine. On the other hand, although very high yields were obtained, prolonged reaction times were required when 2-bromopyridines, such as 2-bromo-3-methylpyridine and 2-bromo-3-methoxypyridine, were used as coupling partners.

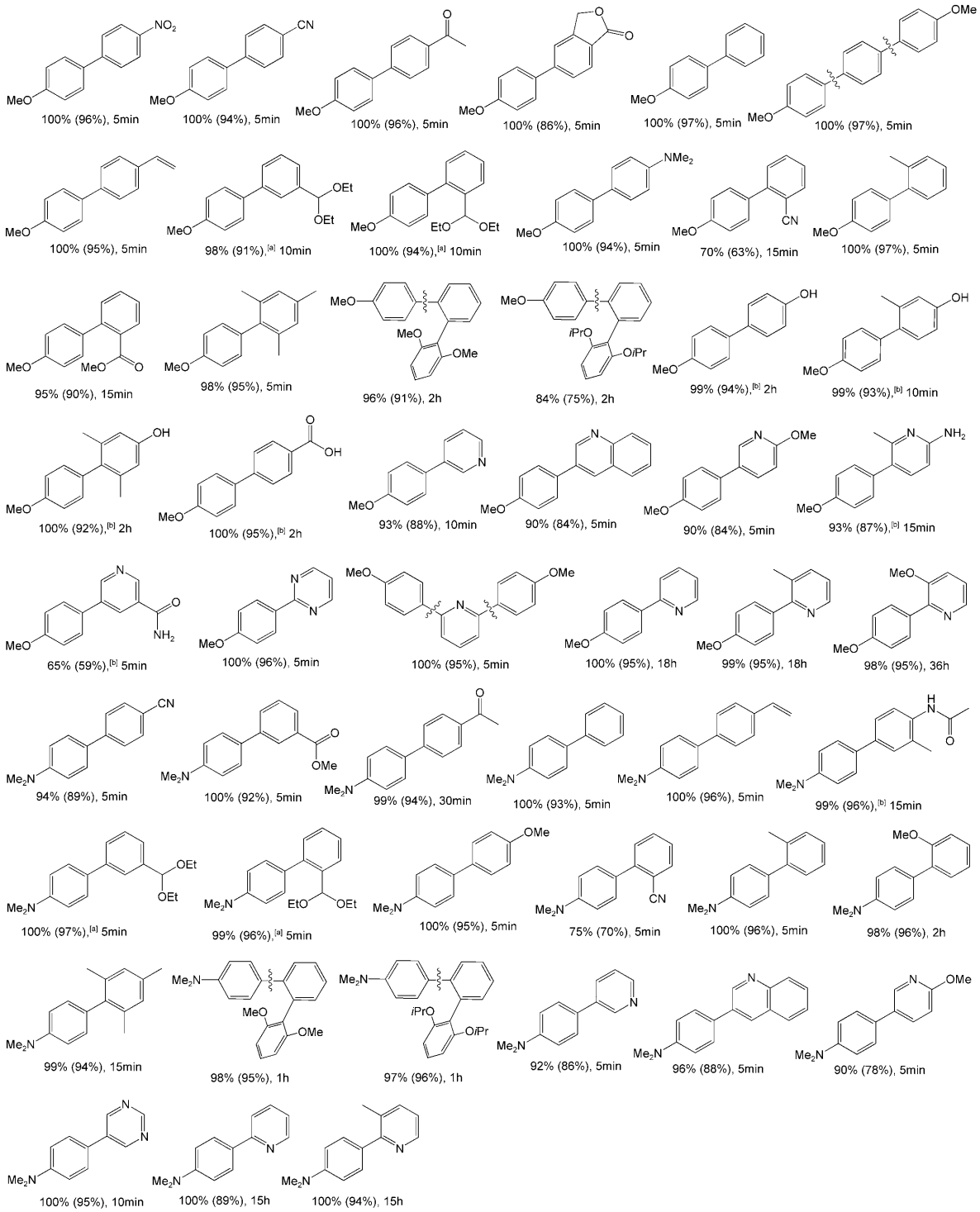
Excellent performance was also observed when using diarylzinc reagents with increased electron density on the aryl unit. For example, complete C–C bond formation within only 15 min was generally achieved in coupling reactions between bis(4-methoxyphenyl)zinc and various electronically activated, non-activated, or deactivated aryl bromides, such as 4-bromobenzonitrile, 1,4-dibromobenzene, 1-bromo-4-ethenylbenzene, 1-bromo-2-(diethoxymethyl)benzene, and 4-bromo-*N*,*N*-dimethylaniline (Scheme 4). Essentially the same yields were obtained, but slightly lower conversion rates were sometimes noted, when sterically hindered 1-bromo-2-methylbenzene and 2-bromo-1,3,5-trimethylben-



Scheme 3. Negishi cross-coupling reactions of aryl bromides with diphenylzinc catalyzed by **1**. Reaction conditions: 2.0 mmol aryl bromide, 1.1 mmol diphenylzinc (relative to bromide), 4 mL NMP, catalyst (0.01 mol%) added in solution (THF), reaction performed at 100°C. The conversions were determined by GC-MS, based on aryl bromide; yields of the isolated products are given in brackets. [a] 2.1 mmol of diphenylzinc was used. [b] Isolated as the aldehyde.

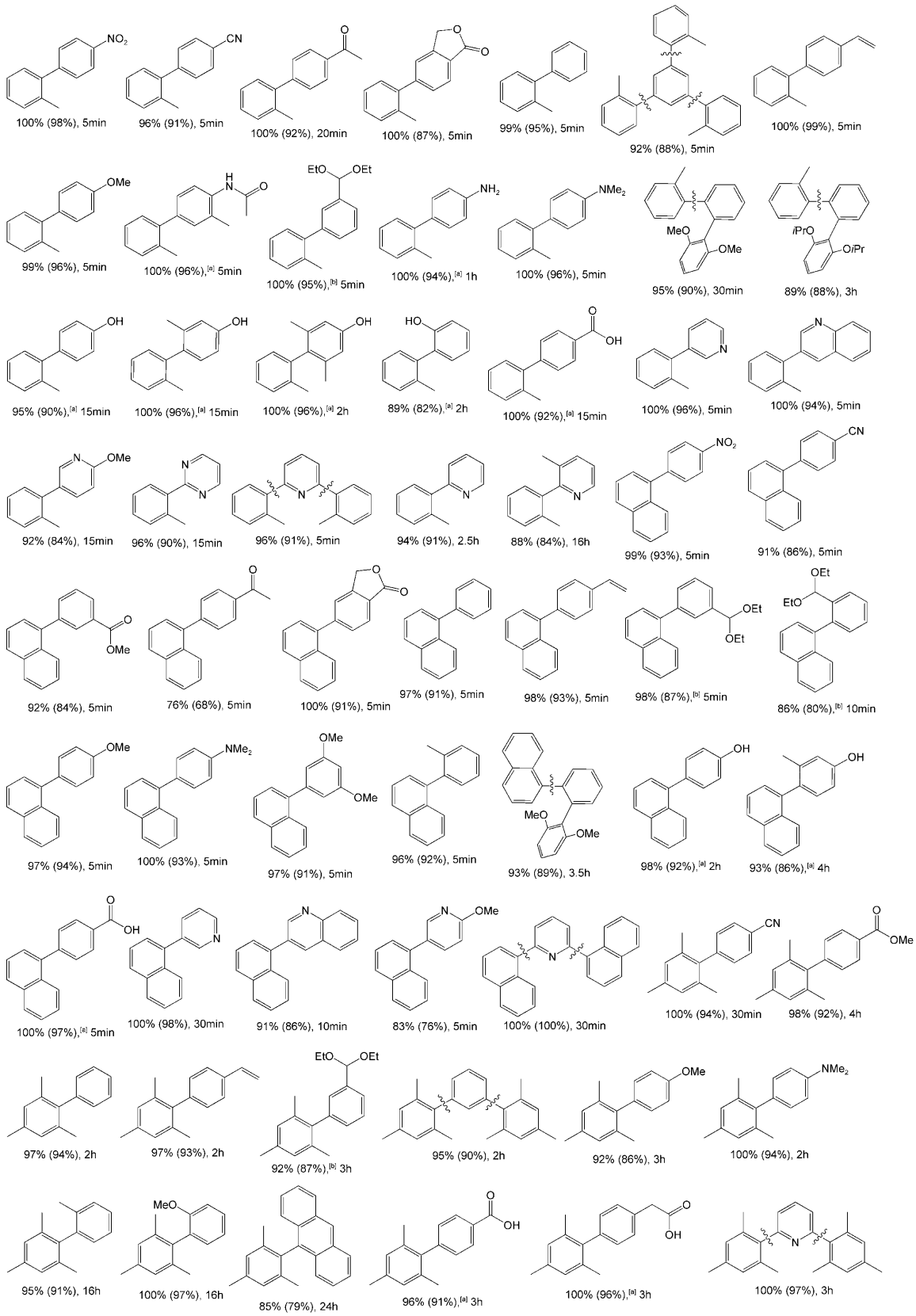
zene were used as coupling partners. Impressively, even 2′-bromo-2,6-dimethoxybiphenyl and 2′-bromo-2,6-bis(1-methylethoxy)biphenyl were smoothly coupled with bis(4-methoxyphenyl)zinc to give 2,4″,6-trimethoxy-1,1′:2′,1″-terphenyl and 4″-methoxy-2,6-bis(1-methylethoxy)-1,1′:2′,1″-terphenyl in yields of 96% and 83%, respectively, in reaction times of just 2 h. Slightly improved conversions were noted when bromophenols were used as coupling partners, which quantitatively yielded the respective coupling products within 2 h. On the other hand, a reaction time of 5 min was sufficient for the complete conversion of 4-bromobenzoic acid into 4′-methoxybiphenyl-4-carboxylic acid. Similar conversion rates and yields were observed when using 3-bromopyridines, 5-bromopyrimidine, and 2,6-dibromopyridine as coupling partners. Exemplary reactions were performed with 3-bromopyridine, 3-bromoquinoline, 5-bromo-2-methoxypyridine, 5-bromo-6-methylpyridine-2-amine, and 5-bromopyridine-3-carboxamide. Quantitative conversions were achieved, although prolonged reaction times were required for 2-bromopyridines. Essentially the same performance was noted with bis[4-(dimethylamino)phenyl]zinc as the coupling partner.

Whereas similar conversion rates and yields were achieved when sterically hindered diarylzinc reagents, such as bis(2-methylphenyl)zinc and dinaphthalen-1-ylzinc, were used as coupling partners, reduced catalytic activity was noted with bis(2,4,6-trimethylphenyl)zinc (Scheme 5). For example, coupling reactions of electronically activated aryl bromides such as 1-bromo-4-nitrobenzene and 4-bromobenzonitrile, non-activated aryl bromides such as 5-bromo-2-benzofuran-1(3*H*)-one, phenyl bromide, 1-bromo-4-ethenylbenzene, 4′-bromo-2′-methylacetanilide, and 1,3,5-tribromobenzene, or deactivated aryl bromides such as 4-bromo-*N*,*N*-dimethylaniline with bis(2-methylphenyl)zinc generally yielded the respective biaryls within a few minutes. 2′-Bromo-2,6-dimethoxybiphenyl and 2′-bromo-2,6-bis(1-methylethoxy)biphenyl were also successfully converted into 2,6-dimethoxy-2″-methyl-1,1′:2′,1″-terphenyl (95%) and 2″-methyl-2,6-bis(1-methylethoxy)-1,1′:2′,1″-terphenyl (89%) within 30 min and 3 h, respectively. Similarly, whereas complete C–C bond formation was achieved within 15 min with 4-bromophenol, 4-bromo-3-methylphenol, and 4-bromobenzoic acid as coupling partners, prolonged reaction times were required to fully convert 4-bromo-3,5-dimethylphenol and 2-bromophenol into the respective biaryls. Similar conversion rates and yields were noted for 3-bromopyridines, 5-bromopyrimidine, and



Scheme 4. Negishi cross-coupling reactions of aryl bromides with bis(4-methoxyphenyl)zinc and bis[4-(dimethylamino)phenyl]zinc catalyzed by **1**. Reaction conditions: 2.0 mmol aryl bromide, 1.1 mmol diarylzinc (relative to bromide), 4 mL NMP, catalyst (0.01 mol%) added in solution (THF), reaction performed at 100 °C. The conversions were determined by GC-MS, based on aryl bromide; yields of the isolated products are given in brackets. [a] Isolated as the aldehyde. [b] 2.1 mmol of diarylzinc was used.

2,6-dibromopyridine. On the other hand, prolonged reaction times were required to fully convert 2-bromopyridine and 2-bromo-3-methylpyridine into 2-(2-methylphenyl)pyridine and 3-methyl-2-(2-methylphenyl)pyridine, respectively. Whereas the same level of activity was observed for dinaphthalen-1-ylzinc, comparable yields but a decreased catalytic activity were observed for bis(2,4,6-trimethylphenyl)zinc as coupling partner. For example, although full conversions of



Scheme 5. Negishi cross-coupling reactions of aryl bromides with bis(2-methylphenyl)zinc, dinaphthalen-1-ylzinc, and bis(2,4,6-trimethylphenyl)zinc catalyzed by **1**. Reaction conditions: 2.0 mmol aryl bromide, 1.1 mmol diarylzinc (relative to bromide), 4 mL NMP, catalyst (0.01 mol%) added in solution (THF), reaction performed at 100°C. The conversions were determined by GC-MS, based on aryl bromide; yields of the isolated products are given in brackets. [a] 2.1 mmol of diarylzinc was used. [b] Isolated as the aldehyde.

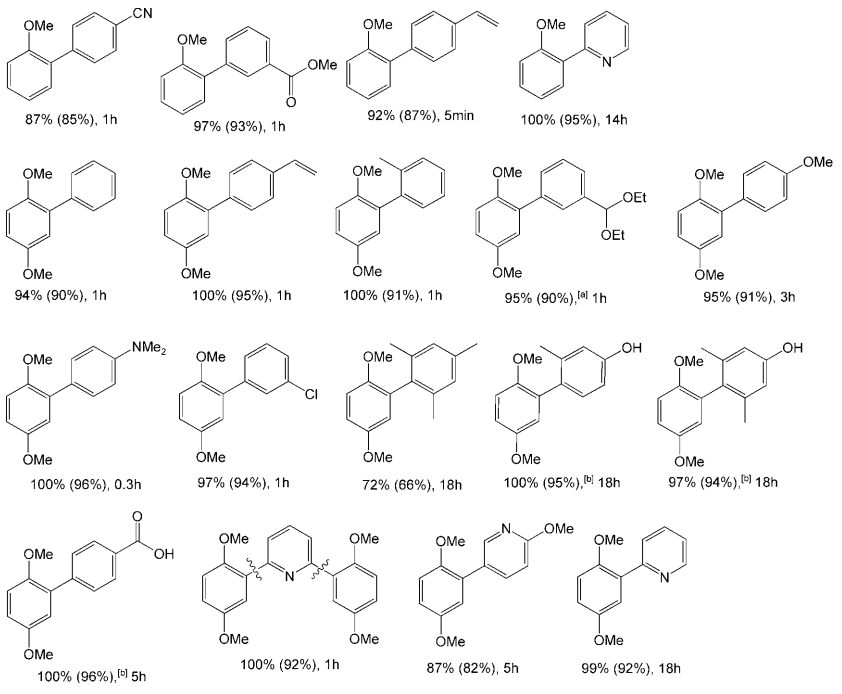
1-bromo-3-(diethoxymethyl)benzene, 4-bromo-*N,N*-dimethylaniline, 1-bromo-2-methylbenzene, and 4-bromobenzoic acid into 1-[3-(diethoxymethyl)phenyl]naphthalene, *N,N*-dimethyl-4-naphthalen-1-ylaniline, 1-(2-methylphenyl)naphthalene, and 4-naphthalen-1-ylbenzoic acid, respectively, were achieved within 5 min, reaction times of 2 h or more were required for the formation of 3′-(diethoxymethyl)-2,4,6-trimethylbiphenyl, *N,N*,2′,4′,6′-pentamethylbiphenyl-4-amine, 2,2′,4,6-tetramethylbiphenyl, and 2′,4′,6′-trimethylbiphenyl-4-carboxylic acid, respectively.

Further reactions were performed with bis(2,4,6-trimethylphenyl)zinc and sterically hindered aryl bromides, such as 1-bromo-2-methoxybenzene, 9-bromoanthracene, and 2-bromo-1,3,5-trimethylbenzene. While full conversions into 2′-methoxy-2,4,6-trimethylbiphenyl and 9-(2,4,6-trimethylphenyl)anthracene were achieved within 24 h, almost no activity was observed with 2-bromo-1,3,5-trimethylbenzene.

A slightly reduced level of activity was generally noted for sterically hindered diarylzinc reagents with increased electron density on the aryl unit, such as bis(2-methoxyphenyl)zinc and bis(2,5-dimethoxyphenyl)zinc (Scheme 6), for which reaction times of 1 h were required to achieve >90% conversion to the respective biaryls. Exemplary reactions were performed with aryl bromides such as 4-bromobenzonitrile, methyl 3-bromobenzoate, phenyl bromide, 1-bromo-4-ethenylbenzene, 1-bromo-2-methylbenzene, 1-bromo-3-(diethoxymethyl)benzene, 1-bromo-4-methoxybenzene, and 4-bromo-*N,N*-dimethylaniline. Excellent yields were obtained for phenols and pyridines, albeit only after extended reaction times.

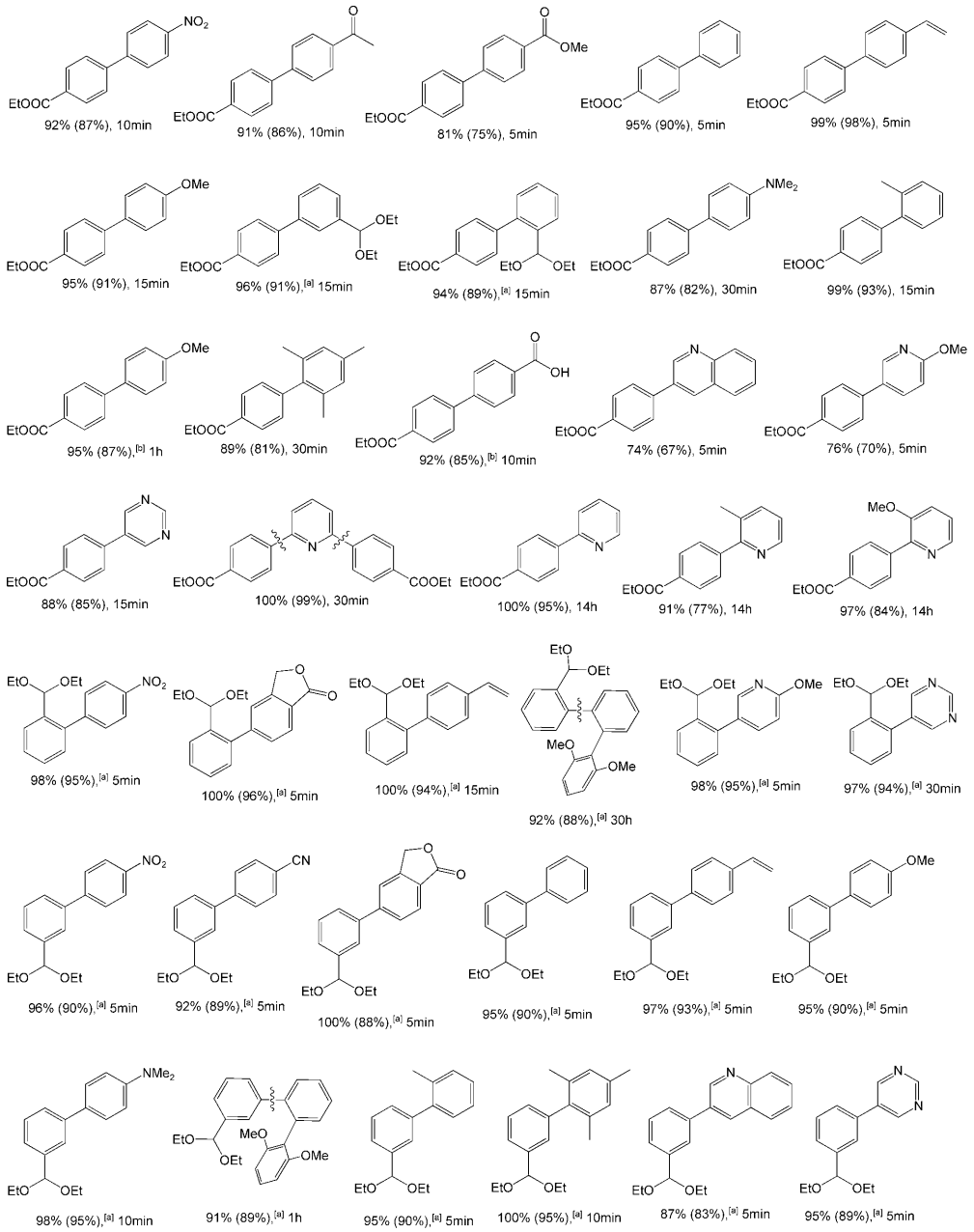
Excellent performance was found in C–C bond-forming reactions with electron-deficient [4-(ethoxycarbonyl)phenyl]-(iodo)zinc as a coupling partner, with which a >90% yield of the respective biaryl was obtained within 30 min in almost all of the reactions examined. Examples include reactions with electronically activated 1-bromo-4-nitrobenzene and methyl 4-bromobenzoate, non-activated phenyl bromide and 1-bromo-4-ethenylbenzene, and deactivated 1-bromo-4-methoxybenzene, 1-bromo-3-(diethoxymethyl)benzene, and 4-bromo-*N,N*-dimethylaniline, as well as with sterically hindered 1-bromo-2-(diethoxymethyl)benzene, 1-bromo-2-methylbenzene, 1-bromo-2-methoxybenzene, 2-bromo-1,3,5-trimethylbenzene, and even 2′-bromo-2,6-dimethoxybiphenyl (Scheme 7). Whereas very high conversion rates and yields were observed with 3-bromopyridines and 2,6-dibromopyridine, prolonged reaction times were required for the complete conversion of 2-bromopyridines into the corresponding biaryls. Essentially the same level of performance was noted in coupling reactions carried out with bis[2-(diethoxymethyl)phenyl]zinc and bis[3-(diethoxymethyl)phenyl]zinc, with which >90% conversion to the respective (diethoxymethyl)biphenyls (which were isolated as biphenyl carbaldehydes) was obtained in almost all of the reactions examined.

High yields were obtained, but only after reaction times of between 2 and 24 h, with dithiophen-2-ylzinc as a coupling partner. The results obtained are summarized in Scheme 8.



Scheme 6. Negishi cross-coupling reactions of aryl bromides with bis(2-methoxyphenyl)zinc and bis(2,5-dimethoxyphenyl)zinc catalyzed by **1**. Reaction conditions: 2.0 mmol aryl halide, 1.1 mmol diarylzinc (relative to bromide), 4 mL NMP, catalyst (0.01 mol%) added in solution (THF), reaction performed at 100°C. The conversions were determined by GC-MS, based on aryl bromide; yields of the isolated products are given in brackets. [a] Isolated as the aldehyde. [b] 2.1 mmol of diarylzinc was used.

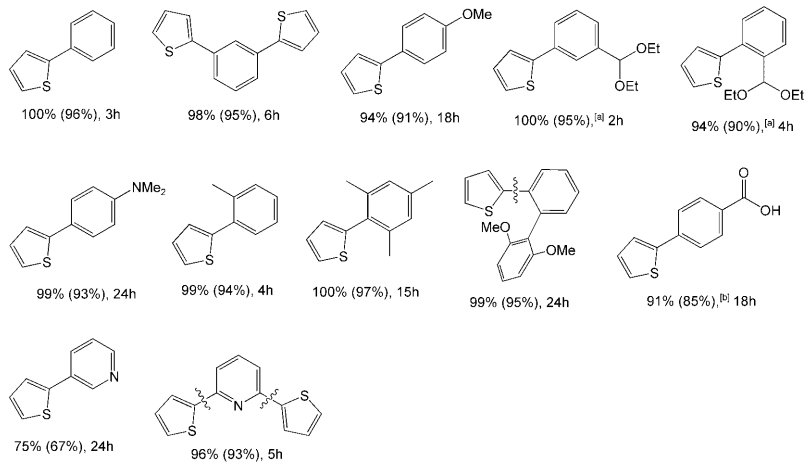
Overall, complex **1** is one of the most convenient, versatile, and active Negishi catalysts reported to date,[15] and enables a wide variety of aryl bromides to be coupled with diarylzinc reagents in very high yields. The couplings are performed using just 0.01 mol% of catalyst, are generally complete within a few minutes, and, most importantly, the same reaction protocol could be used in all of the reactions examined. In contrast to **1**, which reliably operates at very low catalyst loadings, most of the hitherto reported palladium-based Negishi catalysts have had to be deployed at 1–5 mol% to efficiently couple aryl bromides with arylzinc halides or diarylzinc reagents.[16–18] Exceptions include [Pd(C$_3$H$_5$)(Cl)]$_2$/tedicyp(tedicyp=*cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane), which has been reported



Scheme 7. Negishi cross-coupling reactions of aryl bromides with [4-(ethoxycarbonyl)phenyl](iodo)zinc, bis[2-(diethoxymethyl)phenyl]zinc, and bis[3-(diethoxymethyl)phenyl]zinc catalyzed by **1**. Reaction conditions: 2.0 mmol aryl bromide, 1.1 mmol diarylzinc or 2.2 mmol [4-(ethoxycarbonyl)phenyl](iodo)zinc (relative to bromide), 4 mL NMP, catalyst (0.01 mol %) added in solution (THF), reaction performed at 100 °C. The conversions were determined by GC-MS, based on aryl bromide; yields of the isolated products are given in brackets. [a] Isolated as the aldehyde. [b] 4.2 mmol of diarylzinc was used.

to efficiently catalyze Negishi reactions of various aryl bromides with phenylzinc bromide at 70 °C at a level of 0.1–0.001 mol % of palladium.[19] Also, the NHC-containing $[Pd(Cl)_2(NC_5H_4Cl)]$ (NHC = N-heterocyclic carbene) complex (PEPPSI catalyst) effectively promotes the coupling of aryl bromides with various arylzinc iodides at 25–50 °C at a level of 0.5 mol % of palladium.[20] A few examples of the coupling of sterically demanding aryl bromides with sterically hindered arylzinc chlorides at 70–100 °C in the presence of 1 mol % of catalyst have been reported.[2f] The most active palladium catalysts reported to date, which are capable of coupling aryl chlorides with arylzinc halides, have been those of Buchwald and Fu.[2f,11b]

However, apart from the excellent catalytic activity and functional group tolerance of **1** in the Negishi reaction, a further advantage of **1** when compared with (water-insoluble) phosphine-based systems is its reactivity towards water. It has recently been demonstrated that dichloro{bis[1-(dicyclohexylphosphanyl)piperidine]}palladium degrades in the presence of water in air at elevated temperatures to form di-



Scheme 8. Negishi cross-coupling reactions of aryl bromides with dithiophen-2-ylzinc catalyzed by **1**. Reaction conditions: 2.0 mmol aryl bromide, 1.1 mmol dithiophen-2-ylzinc (relative to bromide), 4 mL NMP, catalyst (0.01 mol%) added in solution (THF), reaction performed at 100 °C. The conversions were determined by GC-MS, based on aryl bromide; yields of the isolated products are given in brackets. [a] Isolated as the aldehyde. [b] 2.1 mmol of dithiophen-2-ylzinc was used.

cyclohexyl phosphinate.[13] In a similar way, treatment of **1** with aqueous hydrochloric acid in air (and thus, under work-up conditions) leads to rapid degradation of the catalyst and ligand to form decomposition products, which are easily separated from the coupling products.[21]

Although detailed mechanistic investigations have not been performed, the following experimental observations strongly indicate that **1** catalyzes the Negishi reaction through the generally accepted (classical) reaction mechanism.[22] 1) The catalytic activities of **1**, dichloro{bis[1,1′,1″-(phosphanetriyl)tripiperidine]}palladium, and dichloro-bis-(tricyclohexylphosphine)palladium ([Pd(Cl)$_2$(PCy$_3$)$_2$]) are essentially the same.[24] 2) In none of the reactions examined (with **1**, [Pd(Cl)$_2$(P(NC$_5$H$_{10}$)$_3$)$_2$], or [Pd(Cl)$_2$(PCy$_3$)$_2$]) have sigmoidal-shaped kinetics with an induction period been observed. 3) The catalytic activity of bis[1-(dicyclohexylphosphanyl)piperidine]palladium (**2**) is the same as that of **1**.[26] 4) Treatment of **1** with a slight excess ($\approx$1.2 equiv) of diphenylzinc at 25 °C exclusively yielded complex **2** and the corresponding amount of biphenyl. 5) Treatment of **2** with an excess ($\approx$10 equiv) of phenyl bromide cleanly yielded the phenyl bromide complex [Pd(Br)(C$_6$H$_5$){P(C$_6$H$_{11}$)$_2$-(NC$_5$H$_{10}$)}$_2$] (**3**) even at 25 °C. 6) The phenyl bromide complex **3** showed the same catalytic activity as that of **1** or **2**. 7) Treatment of **3** with approximately 0.55 equiv of bis(4-methoxyphenyl)zinc exclusively yielded complex **2** and the corresponding amount of 4-methoxybiphenyl.[27]

Conclusion

Complex **1** is an extremely efficient, versatile, and reliable Negishi catalyst with excellent functional group tolerance, capable of quantitatively coupling a wide variety of electronically activated, non-activated, deactivated, and/or sterically hindered and functionalized aryl bromides with various diarylzinc reagents in NMP, generally within less than 15 min at 100 °C in the presence of just 0.01 mol% of catalyst. Apart from aldehyde-containing substrates, which lead to the generation of significant amounts of unidentified by-products, nitro, nitrile, acetal, ketone, ether, ester, lactone, amide, aniline, alkene, phenol, carboxylic acid, acetic acid, pyridine, and pyrimidine moieties are all compatible with the reaction conditions. Moreover, electronic and steric variations are tolerated in both reaction partners. The catalyst is readily prepared from very inexpensive staring materials. Moreover, the presented reaction protocol is very simple and, most importantly, is the same for all the reactions examined, which makes our catalyst very attractive for organic laboratories. Even though the formation of palladium nanoparticles cannot be completely excluded (a mercury drop test was positive), the experimental results obtained indicate that **1** operates through a homogeneous (classical) mechanism, which impressively demonstrates that **1** not only promotes the formation of palladium nanoparticles, but can also operate through a homogeneous mechanism.

Experimental Section

General procedures: 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 N_2 atmosphere. Solvents were reagent grade or better, and were freshly distilled under a N_2 atmosphere by standard procedures. Deuterated solvents were purchased from Armar, dried by standard procedures, and degassed by freeze-pump-thaw cycles before use. All chemicals were purchased from Aldrich Chemical Co. or Acros Organics and were used as received.

Analysis: ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectroscopic data were recorded at 500.13, 125.76, and 202.46 MHz, respectively, on a Bruker DRX-500 spectrometer or at 300.1, 121.5, and 75.4 MHz, respectively, on a Varian Gemini spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm), and coupling constants (J) are in Hz. The ^{1}H and ^{13}C NMR chemical shifts are reported relative to tetramethylsilane; the resonance of the residual protons of the solvent was used as an internal standard for ^{1}H (δ = 7.15 for benzene; δ = 3.58, 1.73 for tetrahydrofuran) and all deuterium solvent peaks were used for ^{13}C (δ = 128.0 for benzene; δ = 67.4, 25.2 for tetrahydrofuran). All measurements were carried out at 298 K. Abbreviations used in the description of NMR spectroscopic data are as follows: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. Elemental analyses were performed on a Leco CHNS-932 analyzer at the University of Zurich, Switzerland.

Preparation of [Pd(Cl)$_2${P(NC$_5$H$_{10}$)(C$_6$H$_{11}$)$_2$}$_2$] (1):[13] [Pd(Cl)$_2$(cod)] (100 mg, 0.35 mmol) was suspended in toluene (10 mL). After the addi-

tion of a solution of two equivalents of $P(NC_5H_{10})(C_6H_{11})_2$ in toluene (10 mL), the reaction mixture was stirred for 10 min. Removal of the volatiles under reduced pressure, addition of pentane, followed by filtration afforded the yellow, analytically pure palladium complex **1** in almost quantitative yield. $^{31}P\{^1H\}$ NMR (C_6D_6): $\delta = 80.0$ ppm (s; $P(NC_5H_{10})(C_6H_{11})_2$); ^1H NMR (C_6D_6): $\delta = 3.21$ (br s, 8H), 3.62 (br s, 4H), 3.32–2.28 (m, 4H), 1.95–1.16 ppm (m, 48H); $^{13}C\{^1H\}$ NMR (C_6D_6): $\delta = 51.8$ (t, $J =$ 49.5 Hz), 35.9 (t, $J = 50.3$ Hz), 30.4, 28.6, 27.5–27.2 (overlapping signals), 25.0 ppm.

Preparation of $[Pd\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (2):[26] $[Pd(Cl)_2\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (**1**) (50 mg, 0.07 mmol) was dissolved in THF (10 mL) and the solution was stirred for about 10 h at room temperature in the presence of an excess ($\approx$50 equiv) of metallic sodium. Removal of the volatiles under reduced pressure and extraction of the reduced **1** with pentane, followed by filtration and evaporation of the solvent under reduced pressure, afforded the brownish, analytically pure palladium complex **2** in 96% yield. $^{31}P\{^1H\}$ NMR ([D$_8$]THF): $\delta = 97.9$ ppm (s; $P(NC_5H_{10})(C_6H_{11})_2$); ^1H NMR ([D$_8$]THF): $\delta = 3.26$ (br s, 4H), 1.91–1.19 ppm (m, 60H); $^{13}C\{^1H\}$ NMR ([D$_8$]THF): $\delta = 53.7$, 39.0, 30.7, 28.4, 28.1, 27.8, 26.1 ppm; elemental analysis calcd (%) for $C_{34}H_{64}N_2P_2Pd$: C 61.02, H 9.64, N 4.19; found: C 61.25, H 9.80, N 4.22.

Preparation of $[Pd(Br)(C_6H_5)\{P(C_6H_{11})_2(NC_5H_{10})\}_2]$ (3): $[Pd\{P(NC_5H_{10})(C_6H_{11})_2\}_2]$ (**2**) (30 mg, 0.05 mmol) was dissolved in THF (10 mL) and the solution was stirred for approximately 3 h at room temperature in the presence of an excess ($\approx$10 equiv) of phenyl bromide. Removal of the volatiles under reduced pressure and extraction of **3** with pentane, followed by filtration and evaporation of the solvent under reduced pressure, afforded the off-white, analytically pure palladium complex **3** in 93% yield. $^{31}P\{^1H\}$ NMR ([D$_8$]THF): $\delta = 74.4$ ppm (s; $P(NC_5H_{10})(C_6H_{11})_2$); ^1H NMR ([D$_8$]THF): $\delta = 7.35$ (m, 2H), 6.81 (m, 3H), 3.22 (br s, 8H), 1.72–0.91 ppm (m, 56H); $^{13}C\{^1H\}$ NMR ([D$_8$]THF): $\delta = 156.6$ (t, $J =$ 22.8 Hz), 139.2, 127.5, 122.7, 52.7, 38.8 (t, $J = 46.5$ Hz), 30.27, 29.8, 28.4 (t, $J = 16.8$ Hz), 27.9 (t, $J = 28.8$ Hz), 27.7 (unresolved triplet), 27.6, 25.6 ppm; elemental analysis calcd (%) for $C_{40}H_{69}BrN_2P_2Pd$: C 58.15, H 8.42, N 3.39; found: C 57.99, H 8.37, N 3.36.

General procedure for Negishi cross-coupling reactions: All catalytic reactions were carried out in air. A round-bottomed flask was charged with the aryl bromide (2.0 mmol), a slight excess (1.1 equiv of aryl component relative to bromide) of freshly prepared arylzinc reagent ($\approx$1.0 M; THF/NMP, 1:2), and *N*-methylpyrrolidone (NMP) (2.5 mL). The mixture was vigorously stirred and heated at 100 °C. Then, the requisite amount of catalyst was added by means of a syringe as a solution in THF. Samples were withdrawn from the reaction mixture at timed intervals, quenched with approximately 1 M aqueous HCl, extracted with ethyl acetate, and analyzed by GC-MS (for reactions performed with substrates containing basic groups, samples were quenched with approximately 1 M NaOH and extracted with diethyl ether/THF mixtures). At the end of the catalysis, the reaction mixtures were allowed to cool to room temperature, quenched with 1 M aqueous HCl, and extracted with ethyl acetate (3 × 40 mL). When biaryls containing basic groups, such as pyridine, pyrimidine, and anilines, were used as coupling partners, the reaction mixtures were diluted with diethyl ether and filtered through silica prior to extraction. The combined extracts were dried ($MgSO_4$) and concentrated to dryness. If necessary, the crude material was purified by flash chromatography on silica gel.

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imply that they will exhibit a significantly increased activity when aryl bromides are used as coupling partners.

[13] J. L. Bolliger, C. M. Frech, *Chem. Eur. J.* **2010**, *16*, 4075.

[14] Apart from reactions performed with 3-bromopyridines as coupling partners, in which significant debromination (up to 15%) was obtained, side-product formation (debromination or homocoupling) has only very rarely been observed, and if so, below the 5% level.

[15] It should be mentioned that even though the dichloro-bis(tricyclohexylphosphine)complex $[Pd(Cl)_2(PCy_3)_2]$ exhibits essentially the same catalytic activity in the Negishi cross-coupling reaction as **1**, the latter represents a significant improvement compared with the phosphine-based system, since catalyst **1** (in contrast to $[Pd(Cl)_2(PCy_3)_2]$) promotes the formation of palladium nanoparticles as well as operating through a homogeneous mechanism, depending on the reaction conditions applied. For example, whereas **1** also effectively catalyzes the Suzuki reaction,[13] only a very poor catalytic activity was found for dichloro-bis(tricyclohexylphosphine)palladium.

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[22] The catalytically active species derived from dichloro-bis(phosphine) complexes of palladium in the Negishi reaction are generally accepted to be coordinatively unsaturated $14e^-$ Pd^0 complexes of the type $[Pd(PR_3)_2]$ (arylation of $[Pd(Cl)_2(PR_3)_2]$ and subsequent reductive elimination of the respective homocoupling product generates the catalytically active species), which undergo oxidative addition of aryl halides to yield the tetracoordinated Pd^{II} intermediates of the general formula of $[Pd(Ar)(X)(PR_3)_2]$. Subsequent transmetalation gives the corresponding diaryl-bis(phosphine) complexes. Finally, *cis*/*trans* isomerization (or phosphine dissociation) followed by reductive elimination of the coupling product (and phosphine re-coordination) regenerates the catalyst.[23]

[23] For a mechanistic study of the Negishi cross-coupling involving an aryl chloro-bis(triphenylphosphine) complex of palladium, see: J. A. Casares, P. Espinet, B. Fuentes, G. Salas, *J. Am. Chem. Soc.* **2007**, *129*, 3508.

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[30] For the kinetics, see Graph S1 in the Supporting Information.

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