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An efficient Negishi cross-coupling reaction catalyzed by nickel(II) and diethyl phosphite

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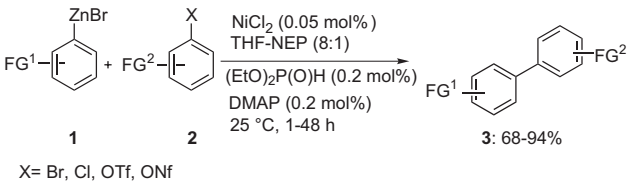
Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—A combination of diethyl phosphite–DMAP and Ni(II) salts forms a very effective catalytic system for the cross-coupling reactions of arylzinc halides with aryl, heteroaryl, and alkenyl bromides, chlorides, triflates, and nonaflates. The choice of solvent is quite important and the mixture of THF–*N*-ethylpyrrolidinone (NEP) (8:1) was found to be optimal. The reaction usually requires only 0.05 mol % of $NiCl_2$ or $Ni(acac)_2$ as catalyst and proceeds at room temperature within 1–48 h.

1. Introduction

The formation of C–C bonds by cross-coupling reactions between aryl organometallics and aryl or alkenyl electrophiles is very important in modern organic chemistry.[1] Organozinc derivatives are attractive partners in this reaction due to their availability and tolerance toward the presence of functional groups.[2] They can be easily prepared from aryl bromides or iodides by a halogen–magnesium exchange,[3] followed by the transmetalation with zinc halides, by a direct zinc insertion[4] or from the corresponding organolithium compounds. Recently, we reported an aryl–aryl cross-coupling reaction of arylzinc halides in the presence of a new catalytic system: nickel chloride–diethyl phosphite–DMAP (Scheme 1).[5] Herein, we wish to report our full results on this highly synthetically attractive process. We found also that alkenyl halides or triflates undergo this reaction as well, although a higher amount of the catalyst is required in these cases.



Scheme 1. Ni-catalyzed cross-coupling reaction of arylzinc bromides with aryl halides and sulfonates.[5]

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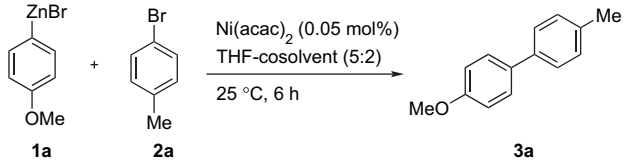
2. Results and discussion

While studying the cross-coupling reactions of arylzinc compounds, we noticed that the reaction between 4-methoxyphenylzinc bromide, prepared by the transmetalation of 4-methoxyphenylmagnesium bromide with $ZnBr_2$ and some reactive electrophiles like ethyl 4-bromobenzoate in a THF–NMP mixture gave traces of product at room temperature even in the absence of any added catalyst. This could be ascribed to the presence of Pd or Ni traces in commercial $ZnBr_2$. Indeed, no product was formed, when extra pure $ZnBr_2$ (Aldrich, 99.999% purity) was used for the reaction. Further experiments excluded the influence of Pd traces, whereas Ni salts were found to promote the coupling even at the level of 10^{-4} mol % under these conditions, and 0.01 mol % was sufficient to achieve full conversion for some substrates.[6] Other transition metals like Fe or Mn were not active as catalysts under such conditions. Two issues had to be addressed during the reaction optimization: the low reactivity of electron-rich aryl halides and the extensive homocoupling of the organozinc reagent.

For the optimization of the solvent mixture, we chose the test reaction between 4-methoxyphenylzinc bromide (**1a**) and 4-bromotoluene (**2a**) (Scheme 2, 0.05 mol % $Ni(acac)_2$, 1.3 equiv 4-$MeOC_6H_4ZnBr$, THF–cosolvent 5:2, rt, 6 h). The conversion of 4-bromotoluene was determined by GC-analysis with *n*-octadecane as an internal standard. The effect of different cosolvents on the reaction conversion is summarized in Table 1.



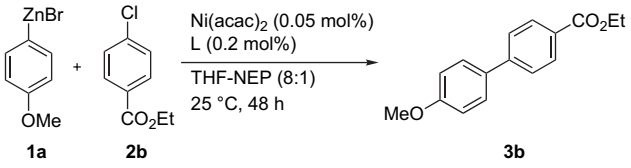
Scheme 2. Ni(acac)$_2$-catalyzed cross-coupling reaction of 4-methoxyphenylzinc bromide (**1a**) and 4-bromotoluene (**2a**).

Table 1. The influence of cosolvents in the Ni-catalyzed Negishi cross-coupling reaction between 4-methoxyphenylzinc bromide (**1a**) and 4-bromotoluene (**2a**)

Solvent	Conversion[a] [%]	Solvent	Conversion[a] [%]
THF	<5	DMF	<5
NMP	44	DMSO	<5
DMAC	<5	Et_3N	11
DMPU	<5	2-Methoxy-ethylpyrrolidinone	68
TMU	<5	*N*-Ethyl-pyrrolidinone (NEP)	88

[a] Substrate conversion was determined by GC-analysis with *n*-octadecane as an internal standard. NMP=*N*-methylpyrrolidinone, DMAC=*N*,*N*-dimethylacetamide, DMPU=*N*,*N*′-dimethylpropyleneurea, TMU=tetramethylurea.

None of the tested solvents afforded the coupling product except *N*-alkylpyrrolidinones,[7] among which *N*-ethylpyrrolidinone (NEP) was the most efficient. The optimal ratio of THF–NEP after further optimization turned out to be 8:1. With higher concentration of NEP in the reaction mixture the final conversion decreased. In most cases, a complete conversion was observed within 1 h and a significant amount of 4,4′-dimethoxybiphenyl as a by-product was formed. To inhibit this side reaction, we have investigated the influence of different ligands on this cross-coupling reaction, using 4-methoxyphenylzinc bromide (**1a**) and ethyl 4-chlorobenzoate (**2b**) as substrates (Scheme 3, 0.05 mol % Ni(acac)$_2$, 0.2 mol % ligand, 1.3 equiv 4-MeOC$_6$H$_4$ZnBr, THF–NEP (8:1), 25 °C, 48 h). The yield of the coupling product (**3b**) was determined by GC-analysis, using *n*-octadecane as an internal standard and by comparing with an authentic sample.

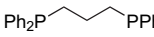
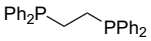
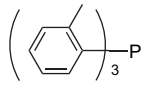
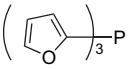
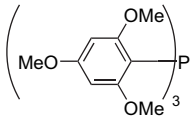
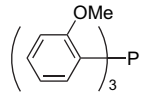
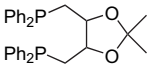
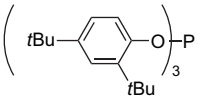
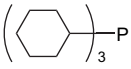
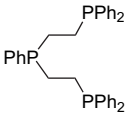
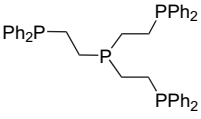
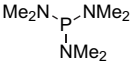
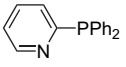
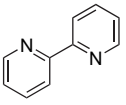
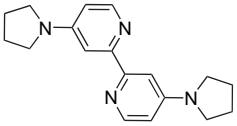
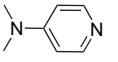
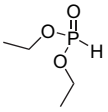


Scheme 3. Ni-catalyzed cross-coupling reaction of 4-methoxyphenylzinc bromide (**1a**) with ethyl 4-chlorobenzoate (**2b**) in presence of a ligand (L).

Without a ligand, this reaction is very sluggish and gives only traces of the desired product **3b**. The results of the ligand screening are shown in Table 2.

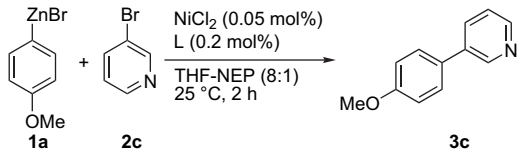
Surprisingly, diethyl phosphite (entry 18) appeared to be the best ligand for the reaction, affording 71% yield of the desired compound along with only a small amount of the homocoupled side product. Among other ligands, dppp (entry 1) and tris-(dimethylamino)phosphine (entry 13) showed good performance. Triphenylphosphine (entry 3)

Table 2. Effect of various ligands in the cross-coupling reaction between 4-methoxyphenylzinc bromide (**1a**) and ethyl 4-chlorobenzoate (**2b**)

Entry	Ligand	Yield [%][a]
1		61
2		51
3		53
4		<5
5		16
6		8
7		27
8		9
9		14
10		47
11		10
12		<5
13		62
14		<5
15		50
16		44
17		18
18		71

[a] Yields are determined by GC-analysis with *n*-octadecane as an internal standard and by comparison with an authentic sample.

was less active and, interestingly, practically did not influence the product yield even in quantities up to 1 mol % (ratio 20:1 for Ni). Noteworthy, the order of reagent mixing significantly influences the reaction rate. The optimal way is the addition of Grignard reagent to the solution of $ZnBr_2$, premixed with NEP. If the Grignard reagent solution is first mixed with $ZnBr_2$, a precipitate forms soon, and the following coupling reaction is much slower. This fact can be explained by the fast formation of oligomers in the arylzinc halide solution, which might possess a lower reactivity. The precomplexation with NEP seems to suppress this process. Some aza-ligands were also found to be active in this process. Thus, 2,2′-bipyridine (entry 15) afforded 50% yield of the product, although along with a large amount of the homocoupling compound. Taking into account that DMAP was also slightly active (entry 17), we prepared 4,4′-bis-(pyrrolidino)-2,2′-bipyridyl[8] (entry 16), an electron-rich *N*,*N*-ligand. However, no improvement was observed for this compound in comparison with 2,2′-bipyridyl (44% yield vs 50% for the latter). Some other aza-ligands were also tested in the reaction between 4-methoxyphenylzinc bromide (**1a**) and 3-bromopyridine (**2c**) (Scheme 4).



Scheme 4. Ni-catalyzed cross-coupling reaction of 4-methoxyphenylzinc bromide (**1a**) with 3-bromopyridine (**2c**).

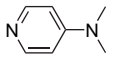
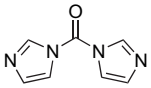
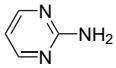
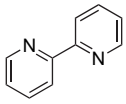
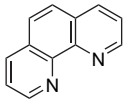
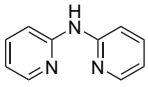
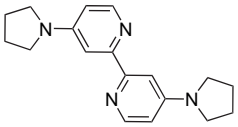
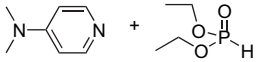
The substrates and the conditions (0.05 mol % $NiCl_2$, 0.2 mol % ligand, 1.3 equiv 4-$MeOC_6H_4ZnBr$, THF–NEP (8:1), rt, 2 h) were changed in order to have a less reactive system for the further catalyst optimization. Since $NiCl_2$ is poorly soluble in THF, it was added as a solution in NEP. The results of aza-ligands screening are given in Table 3.

From all the investigated *N*,*N*-ligands, 2,2′-bipyridine (entry 8) gave the best result with 43% yield of product **3c**. For all aza-ligands tested, the catalytic activity was not superior to diethyl phosphite.

Then we used the same reaction to screen some ligand mixtures. Diethyl phosphite–triphenylphosphine and especially diethyl phosphite–DMAP (1:1) were found superior as additives (entry 12) and yielded 81% of product **3c**. The optimal ratio of Ni–diethyl phosphite turned out to be 1:4. Other phosphites like $(i\text{PrO})_3P$, $(MeO)_2P(O)H$, $(i\text{PrO})_2P(O)H$, $(BuO)_3P$ or $(PhO)_3P$ were found to be by far less active. The results of the aryl–aryl cross-coupling reaction with this optimized catalytic system (0.05 mol % $NiCl_2$, 0.2 mol % $(EtO)_2P(O)H$, and 0.2 mol % DMAP, THF–NEP (8:1), see Scheme 1), are shown in Table 4.

As shown in Table 4, a very broad range of substrates can be involved into this cross-coupling reaction. Electron-rich, electron-poor, and heterocyclic zinc compounds can be coupled with a broad variety of aryl and heteroaryl bromides, chlorides, triflates, and nonaflates. Electron-rich arylzinc halides react with aryl bromides to give the desired products

Table 3. Effect of various *N*-ligands on the cross-coupling reaction between 4-methoxyphenylzinc bromide (**1a**) and 3-bromopyridine (**3c**)

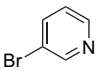
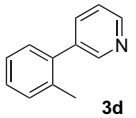
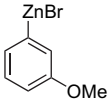
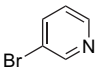
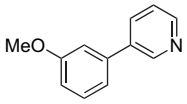
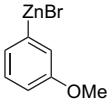
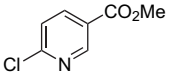
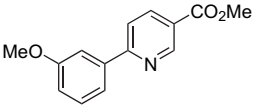
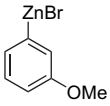
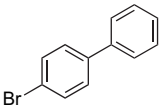
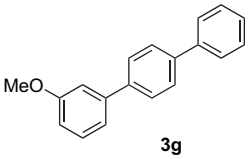
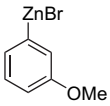
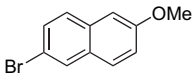
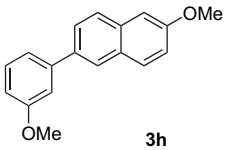
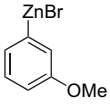
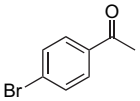
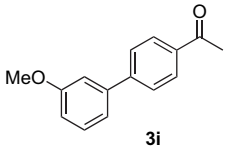
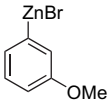
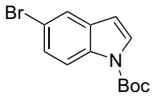
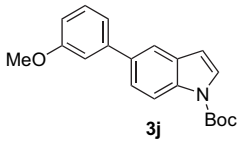
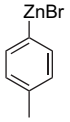
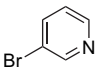
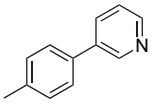
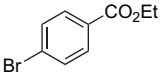
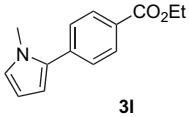
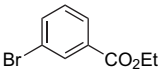
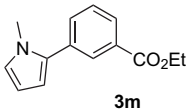
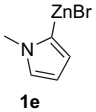
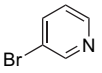
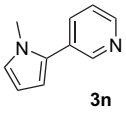
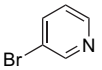
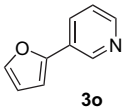
Entry	Ligand	Yield [%][a]
1		35
2		34
3		37
4		36
5		36
6		36
7		38
8		43
9		37
10		32
11		20
12		81

[a] Yields are determined by GC-analysis with *n*-decane as an internal standard and by comparison with an authentic sample.

within few hours at room temperature in good to excellent yields 56–94% (entries 2, 4, 6, 8, 16–20, 22, 29, and 30). With heteroaryl bromides as electrophiles, prolonged reaction time (in most cases about 24 h at room temperature, entries 3, 7, 13, and 15) or elevated temperatures (entries 1 and 14) is required. Aryl and heteroaryl chlorides also react, but compared to bromides the reaction times are longer and the yields decreased (entries 21, 22, 23, and 24). Also the electron-poor zinc bromides, which are often bad substrates for a cross-coupling, could be reacted with various aryl and heteroaryl bromides, affording good yields of the products (entries 25–27).

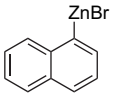
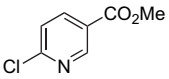
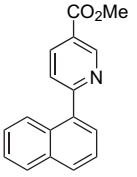
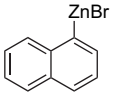
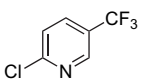
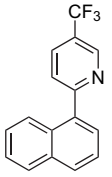
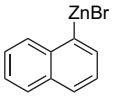
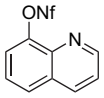
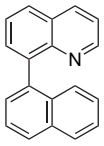
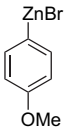
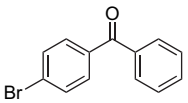
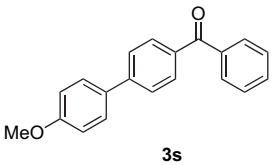
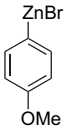
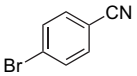
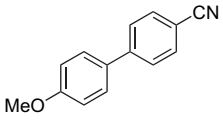
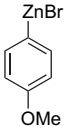
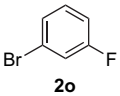
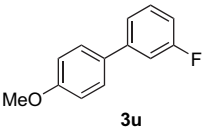
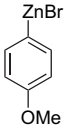
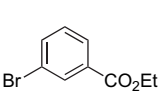
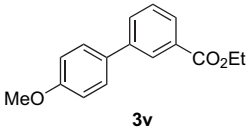
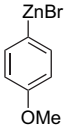
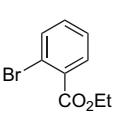
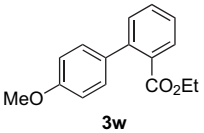
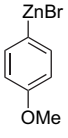
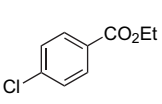
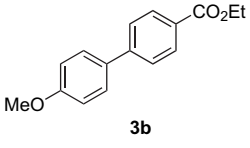
Various heterocyclic zinc compounds like 3-pyridyl-, *N*-methyl-2-pyrrolyl-, and 2-furylzinc bromide could be used. They required elevated temperatures, but lead to the products in satisfactory yields (entries 9–12 and 24). We also attempted to involve some aryl tosylates, mesylates,

Table 4. Ni-catalyzed Negishi cross-coupling between arylzinc compounds and aryl halides in the presence of $(EtO)_2P(O)H$ and DMAP

Entry	Ar^1–ZnX	Ar^2–X	Product	Temperature [°C], reaction time [h]	Yield [%][a]
1	 **1b**	 **2c**	 **3d**	50, 6	47
2	 **1c**	 **2c**	 **3e**	25, 1	66
3	 **1c**	 **2d**	 **3f**	25, 24	74
4	 **1c**	 **2e**	 **3g**	25, 4	77
5	 **1c**	 **2f**	 **3h**	25, 8	86
6	 **1c**	 **2g**	 **3i**	25, 2.5	77
7	 **1c**	 **2h**	 **3j**	25, 24	75
8	 **1d**	 **2c**	 **3k**	25, 1	56
9	 **1e**	 **2i**	 **3l**	70, 22	61
10	 **1e**	 **2j**	 **3m**	70, 22	55
11	 **1e**	 **2c**	 **3n**	70, 22	62
12	 **1f**	 **2c**	 **3o**	110, 22	59

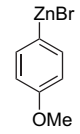
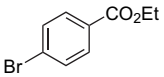
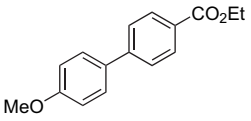
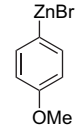
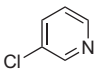
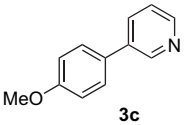
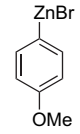
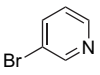
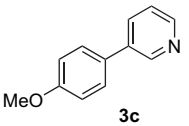
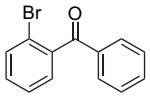
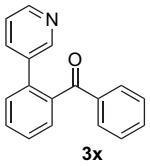
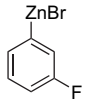
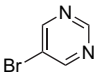
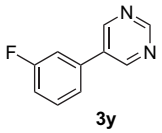
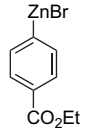
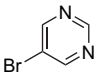
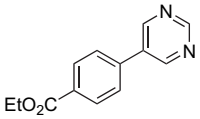
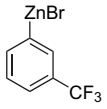
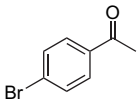
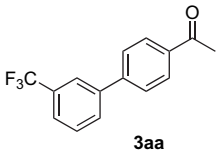
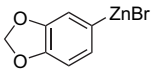
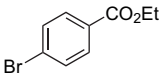
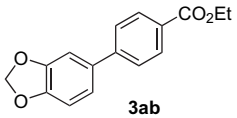
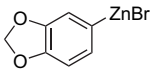
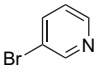
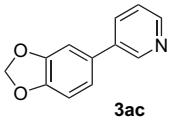
(continued)

Table 4. (*continued*)

Entry	Ar^1–ZnX	Ar^2–X	Product	Temperature [°C], reaction time [h]	Yield [%][a]
13	 **1g**	 **2d**	 **3p**	25, 23	73
14	 **1g**	 **2k**	 **3q**	95, 2	82
15	 **1g**	 **2l**	 **3r**	25, 24	88
16	 **1a**	 **2m**	 **3s**	25, 3	73
17	 **1a**	 **2n**	 **3t**	50, 48	54
18	 **1a**	 **2o**	 **3u**	25, 2	86
19	 **1a**	 **2j**	 **3v**	25, 1	91
20	 **1a**	 **2p**	 **3w**	25, 4	52
21	 **1a**	 **2b**	 **3b**	25, 48	81

(continued)

Table 4. (*continued*)

Entry	Ar^1–ZnX	Ar^2–X	Product	Temperature [°C], reaction time [h]	Yield [%][a]
22	 **1a**	 **2i**	 **3b**	25,1	87
23	 **1a**	 **2q**	 **3c**	25, 12	68
24	 **1a**	 **2c**	 **3c**	25, 2	81
25	 **1h**	 **2r**	 **3x**	50, 3	76
26	 **1i**	 **2s**	 **3y**	25, 1	82
27	 **1j**	 **2s**	 **3z**	50, 24	60
28	 **1k**	 **2g**	 **3aa**	25, 18	68
29	 **1l**	 **2i**	 **3ab**	25, 5	94
30	 **1l**	 **2c**	 **3ac**	25, 5	83

[a] Isolated yield of analytically pure product.

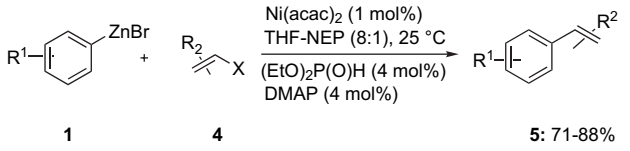
and phosphates into this reaction, but could not achieve acceptable yields of products under our conditions.

The required organozinc reagents were obtained mostly from the corresponding bromides or iodides via halogen–magnesium exchange with *i*-PrMgCl–LiCl,[3a] or by direct insertion of Mg, followed by the transmetalation with 1 equiv of $ZnBr_2$. In the cases of furan and *N*-methylpyrrole, the organometallic species was prepared by direct metalation with *n*-BuLi.[14]

The reaction was found to be rather sensitive to steric hindrance both in the organozinc reagent and aryl electrophile. In the case of *o*-tolylzinc bromide the yield drops significantly (entry 1) and we could not obtain a significant amount of the coupling product from mesitylzinc bromide and

any aryl bromide under our conditions. Functional groups like esters or ketones as well as heteroatoms were perfectly tolerated. Nitriles are less active as substrates probably due to the coordination of the nitrile group with the catalyst species.

Beside aryl–aryl cross-coupling, we have found that arylzinc halides can also react with alkenyl halides and triflates in the presence of our catalytic system, although with a higher amount of catalyst (1 mol % $Ni(acac)_2$, 4 mol % $(EtO)_2P(O)H$, 4 mol % DMAP, 1.3 equiv ArZnBr, THF–NEP (8:1), Scheme 5).

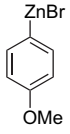
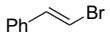
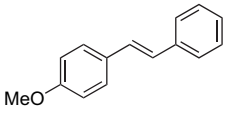
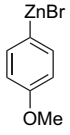
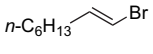
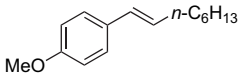
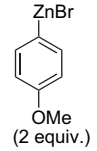
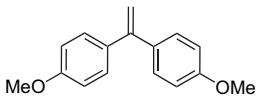
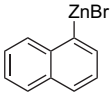
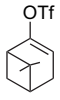
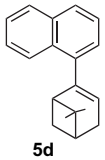
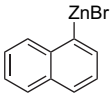
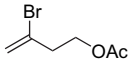
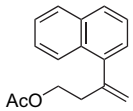
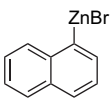
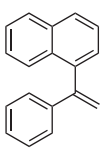


Scheme 5. Ni-catalyzed cross-coupling reaction of arylzinc halides with alkenyl electrophiles.

The reactions were complete at room temperature within a period between 15 min and some hours and gave the desired products **5a**–**5f** in 71–88% yield. The results of the aryl–alkenyl cross-coupling reaction in the presence of a Ni catalyst are summarized in Table 5.

In summary, we have developed a very efficient catalytic system, based on $NiCl_2$, $(EtO)_2P(O)H$, and DMAP for the cross-coupling reaction between arylzinc halides and aryl and alkenyl bromides, triflates, nonaflates, and activated chlorides. A broad range of highly functionalized substrates reacts at room temperature, giving the cross-coupling products in good to excellent yields. An extremely small amount of a transition metal catalyst (0.05 mol % Ni) in comparison with other methods is usually required. In a larger scale, it will hardly pose a problem of waste treatment, or contamination of the products with toxic metals, usually for Ni- and Pd-based cross-coupling processes. The ligands are inexpensive, soluble in water, and therefore easy to remove, and environmentally benign. These are the advantages of this method, which show good perspectives for its future use in industrial processes.

Table 5. Nickel-catalyzed cross-coupling reaction of arylzinc bromides with alkenyl electrophiles

Entry	Arylzinc bromide	Vinyl halide	Product	Temperature [°C], reaction time [h]	Yield [%][a]
1	 **1a**	 **4a**	 **5a**	25, 0.25	85
2	 **1a**	 **4b**	 **5b**	25, 0.5	79
3	 **1a**	 **4c**	 **5c**	25, 6	88
4	 **1g**	 **4d**	 **5d**	25, 12	71
5	 **1g**	 **4e**	 **5e**	25, 12	81
6	 **1g**	 **4f**	 **5f**	25, 6	78

[a] Isolated yield of analytically pure product.

3. Experimental

3.1. General

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in case of air- or moisture-sensitive compounds reactions were carried out in flame-dried glassware under argon. Syringes were used to transfer the reagents and the solvents were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC–MS) or thin-layer chromatography. Solutions of organomagnesium compounds were prepared, unless otherwise stated, by the reaction of Mg with aryl bromides in THF, titrated with a standard solution of I_2 in 0.5 M LiCl in THF and diluted with THF to the mentioned concentration. $ZnBr_2$ and $ZnCl_2$ were dried at 140 °C under high vacuum for 30 min and then dissolved in dry THF. Tetrahydrofuran was freshly distilled from Na–benzophenone ketyl. *N*-Ethylpyrrolidinone and other aprotic solvents were dried with CaH_2, distilled in vacuo, and stored under Ar. All new compounds were determined to be with >95% purity by GC and ^{1}H NMR spectroscopy.

3.2. Typical procedure A

The solution of the nickel catalyst A was prepared as follows. In a 25 mL Schlenk tube under argon in dry degassed *N*-ethylpyrrolidinone (NEP, 10.0 mL) were dissolved in anhydrous $NiCl_2$ (8.2 mg, 0.063 mmol), $(EtO)_2P(O)H$ (34.5 mg, 0.25 mmol), and DMAP (30.5 mg, 0.25 mmol).

In a dry argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, the corresponding arylmagnesium reagent in THF (1.30 mmol) was added slowly with cooling to the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF, 1.00 mmol) and NEP (0.17 mL). To this mixture, the electrophile (aryl halide or sulfonate, 1.00 mmol) was added, followed by the catalyst solution A (0.08 mL). The final THF–NEP volume ratio should be about 8:1. The mixture was stirred at the specified temperature until the GC of an aliquot showed the reaction completion, quenched with satd NH_4Cl solution, extracted with ether, and then the product was purified by column chromatography.

3.3. Typical procedure B

The solution of the nickel catalyst B was prepared as follows. In a 25 mL Schlenk tube under argon in dry degassed *N*-ethylpyrrolidinone (10.0 mL) were dissolved in $Ni(acac)_2$ (103 mg, 0.40 mmol), $(EtO)_2P(O)H$ (221 mg, 1.60 mmol), and DMAP (195 mg, 1.60 mmol).

In a dry argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, the corresponding arylmagnesium reagent in THF (1.30 mmol) was added slowly with cooling to the mixture of $ZnBr_2$ solution (0.67 mL, 1.5 M in THF, 1.00 mmol), catalyst solution B (0.25 mL), and electrophile (aryl halide or sulfonate, 1.00 mmol). The final THF–NEP volume ratio should be approximately 8:1. The mixture was stirred at the specified temperature until the GC of an aliquot showed the reaction completion, quenched with satd NH_4Cl solution, extracted with ether, and then the product was purified by column chromatography.

3.3.1. 3-*o*-Tolyl-pyridine (3d). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 2-tolylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 6 h at 50 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3d** (80 mg, 47%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.52 (dd, J=4.5, 1.5 Hz, 2H), 7.58 (dd, J=2.2, 1.7 Hz, 1H), 7.30–7.12 (m, 5H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 149.0, 147.1, 137.1, 136.4, 135.4, 134.6, 129.5, 128.8, 127.1, 125.1, 122.0, 19.3. *m/z* (EIMS): 169 (100), 168 (89), 154 (5), 141 (16), 115 (18).

3.3.2. 3-(3-Methoxyphenyl)-pyridine (3e). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3e** (122 mg, 66%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (dd, J=2.3, 0.8 Hz, 1H), 8.59 (dd, J=4.8, 1.7 Hz, 1H), 7.87 (ddd, J=8.0, 2.3, 1.7 Hz, 1H), 7.43–7.33 (m, 2H), 7.17 (ddd, J=7.6, 1.7, 1.0 Hz, 1H), 7.11 (dd, J=2.3, 1.8 Hz, 1H), 6.95 (ddd, J=8.3, 2.7, 1.0 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.1, 147.6, 147.4, 138.3, 135.5, 133.4, 129.1, 122.5, 118.6, 112.4, 112.0, 54.3. *m/z* (EIMS): 185 (100), 154 (26), 142 (21), 127 (6), 115 (15).

3.3.3. 6-(3-Methoxyphenyl)-nicotinic acid methyl ester (3f). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL in NEP), and 6-chloronicotinic acid methyl ester **2d** (172 mg, 1.00 mmol). Stirred for 24 h at 25 °C. Standard workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3f** as colorless solid (180 mg, 74%). Mp 89.5–90 °C. IR (KBr): 3059 (w), 3013 (w), 2954 (m), 2925 (m), 1715 (vs), 1596 (vs), 1562 (m), 1480 (s), 1433 (s), 1288 (vs), 1267 (s), 1231 (s), 1117 (s), 1030 (s), 1021 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.24 (d, J=1.9 Hz, 1H), 8.31 (dd, J=8.3, 1.9 Hz, 1H), 7.77 (d, J=8.3 Hz, 1H), 7.63–7.62 (m, 1H), 7.57 (d, J=7.9 Hz, 1H), 7.38 (t, J=8.1 Hz, 1H), 6.99 (dd, J=8.1, 2.4 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 168.0, 162.8, 162.3, 153.1, 141.9, 140.0, 132.0, 126.5, 122.1, 121.8, 118.2, 114.6, 57.6, 54.5. *m/z* (EIMS): 243 (65), 242 (100), 213 (38), 182 (9), 154 (10), 106 (11). HRMS calcd for $C_{14}H_{13}NO_3$: 243.0895, found: 243.0867.

3.3.4. 3-Methoxy-[1,1;4′,1″]terphenyl (3g). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 4-bromobiphenyl **2e** (233 mg, 1.00 mmol). Stirred for 4 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3g** (201 mg, 77%) as colorless solid. Mp 104.5–105 °C. IR (KBr): 3033 (w), 1602

(m), 1578 (s), 1478 (vs), 1217 (s), 761 (vs) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.65 (m, 6H), 7.49—7.45 (m, 2H), 7.41–7.36 (m, 2H), 7.27–7.24 (m, 1H), 7.20–7.19 (m, 1H), 6.94–6.91 (m, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.4, 172.6, 156.0, 136.2, 134.2, 133.9, 132.2, 131.5, 130.6, 130.2, 129.1, 128.9, 117.3, 110.6. *m/z* (EIMS): 260 (100), 230 (7), 217 (17), 189 (5), 130 (10). HRMS calcd for $C_{19}H_{16}O$: 260.1201, found: 260.1191.

3.3.5. 2-Methoxy-6-(3-methoxyphenyl)-naphthalene (3h). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 2-bromo-6-methoxynaphthalene **2f** (237 mg, 1.00 mmol). Stirred for 8 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3h** (228 mg, 86%) as colorless solid. Mp 85–87.5 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.87 (d, J=1.2 Hz, 1H), 7.69 (dd, J=8.5, 2.0 Hz, 2H), 7.61 (dd, J=8.5, 1.8 Hz, 1H), 7.29 (t, J=7.9 Hz, 1H), 7.22–7.13 (m, 2H), 7.10–7.05 (m, 2H), 6.81 (ddd, J=8.0, 2.5, 0.9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.0, 157.8, 142.7, 136.2, 133.9, 129.8, 129.7, 129.1, 127.2, 126.0, 125.6, 119.7, 119.1, 112.9, 112.4, 110.6, 55.3. *m/z* (EIMS): 264 (100), 249 (9), 221 (43), 189 (79), 178 (18).

3.3.6. 1-(3′-Methoxybiphenyl-4-yl)-ethanone (3i). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 1-(4-bromophenyl)-ethanone **2g** (199 mg, 1.00 mmol). Stirred for 2.5 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3i** (175 mg, 77%) as yellow solid. Mp 35.2–36.2 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.00 (ddd, J=8.5, 2.9, 1.9 Hz, 2H), 7.65 (ddd, J=8.6, 2.0, 1.9 Hz, 2H), 7.38–7.31 (m, 1H), 7.20–7.17 (m, 1H), 7.13–7.12 (m, 1H), 6.94–6.90 (m, 1H), 3.85 (s, 3H), 2.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.1, 160.4, 146.0, 141.8, 136.4, 130.4, 129.3, 127.7, 120.1, 113.9, 113.5, 55.8, 27.0. *m/z* (EIMS): 226 (56), 211 (100), 168 (14), 152 (11), 139 (21).

3.3.7. 5-(3-Methoxy-phenyl)-indole-1-carboxylic acid *tert*-butyl ester (3j). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL) and 5-bromoindole-1-carboxylic acid *tert*-butyl ester **2h** (296 mg, 1.00 mmol). Stirred for 24 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3j** (242 mg, 75%) as yellow solid. Mp 109.5–110 °C. IR (KBr): 3006 (w), 2968 (w), 1721 (vs), 1607 (m), 1471 (s), 1369 (vs), 1164 (s), 781 (m), 713 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, J=8.6 Hz, 1H), 7.69 (d, J=1.4 Hz, 1H), 7.55 (d, J=3.6 Hz, 1H), 7.48 (dd, J=8.6, 1.8 Hz, 1H), 7.31–7.25 (m, 1H), 7.18–7.10 (m, 2H), 6.81 (ddd, J=8.2, 2.5, 0.8 Hz, 1H), 6.54 (d, J=3.7 Hz, 1H), 3.80 (s, 3H), 1.62 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.9, 149.7, 143.2, 135.9, 134.7, 131.0, 129.7, 126.5, 123.7, 119.9, 119.4, 115.3, 113.1, 112.3, 107.5, 83.8, 55.3, 28.2. *m/z* (EIMS): 223 (100), 180 (30), 152 (16), 111 (8), 77 (7). HRMS calcd for $C_{20}H_{21}NO_3$: 323.1521, found: 323.1512.

3.3.8. 3-*p*-Tolyl-pyridine (3k). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-tolylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3k** (95 mg, 56%) as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.85 (s, 1H), 8.57 (d, J=4.2 Hz, 1H), 7.93–7.89 (m, 1H), 7.49 (d, J=8.1 Hz, 2H), 7.41–7.37 (m, 1H), 7.30 (d, J=8.1 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.5, 147.4, 138.3, 136.9, 134.8, 134.6, 129.9, 127.0, 123.8, 21.3. *m/z* (EIMS): 169 (100), 154 (6), 141 (7), 115 (14), 91 (6).

3.3.9. 4-(1-Methyl-1*H*-pyrrol-2-yl)-benzoic acid ethyl ester (3l). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-methyl-1*H*-pyrryllithium[14] (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and ethyl 4-bromobenzoate **2i** (229 mg, 1.00 mmol). Stirred for 22 h at 70 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3l** (141 mg, 61%) as yellow solid. Mp 65.1–65.9 °C. IR (KBr): 3104 (w), 2986 (w), 1710 (vs), 1608 (vs), 1478 (m), 1365(m), 1310 (s), 1291 (vs), 1181 (s), 1109 (s), 740 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.09–8.03 (m, 2H), 7.49–7.43 (m, 2H), 6.77–6.74 (m, 1H), 6.34–6.30 (m, 1H), 6.23–6.20 (m, 1H), 4.39 (q, J=7.1 Hz, 2H), 3.71 (s, 3H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 137.6, 133.6, 129.7, 128.3, 127.9, 125.0, 110.0, 108.2, 60.0, 35.4, 14.4. *m/z* (EIMS): 229 (100), 201 (64), 184 (45), 156 (16), 128 (11). HRMS calcd for $C_{14}H_{15}NO$: 229.1103, found: 229.1080.

3.3.10. 3-(1-Methyl-1*H*-pyrrol-2-yl)-benzoic acid ethyl ester (3m). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-methyl-1*H*-pyrryllithium (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and ethyl 3-bromobenzoate **2j** (229 mg, 1.00 mmol). Stirred for 22 h at 70 °C. The usual workup and purification by flash chromatography (pentane–ether 4:1) yielded **3m** (125 mg, 55%) as colorless oil. IR (neat): 3102 (w), 2988 (m), 1717 (vs), 1607 (m), 1468 (m), 1367 (m), 1310 (s), 1270 (vs), 1236 (vs) 1109 (s), 756 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.10 (td, J=1.8, 0.5 Hz, 1H), 7.99–7.96 (m, 1H), 7.59 (ddd, J=7.7, 1.8, 1.3 Hz, 1H), 7.46 (td, J=7.7, 0.5 Hz, 1H), 6.75–6.73 (m, 1H), 6.29–6.28 (m, 1H), 6.23–6.21 (m, 1H), 4.40 (q, J=7.1 Hz, 2H), 3.68 (s, 3H), 1.40 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 133.6, 133.5, 132.8, 130.7, 129.5, 128.4, 127.7, 124.1, 109.2, 107.9, 61.0, 35.1, 14.3. *m/z* (EIMS): 229 (100), 201 (68), 184 (17), 156 (16), 128 (10). HRMS calcd for $C_{14}H_{15}NO$: 229.1103, found: 229.1095.

3.3.11. 3-(1-Methyl-1*H*-pyrrol-2-yl)-pyridine (β-nicotyrine, 3n). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were

added dropwise 1-methyl-1*H*-pyrryllithium[14] (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 22 h at 70 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3n** (98 mg, 62%) as yellow oil.[9] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66 (d, J=1.8 Hz, 1H), 8.50 (dd, J=4.8, 1.6 Hz, 1H), 7.70 (ddd, J=7.9, 1.8, 1.6 Hz, 1H), 7.31 (ddd, J=7.9, 4.8, 0.8 Hz, 1H), 6.74 (dd, J=2.5, 1.9 Hz, 1H), 6.27 (dd, J=3.6, 1.9 Hz, 1H), 6.20 (dd, J=3.6, 2.8 Hz, 1H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.3, 147.8, 136.1, 131.1, 129.8, 125.2, 123.7, 110.3, 108.7, 35.5. *m/z* (EIMS): 158 (100), 143 (7), 130 (19), 116 (6), 89 (5).

3.3.12. 3-Furan-2-yl-pyridine (3o). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-furyllithium[14] (2.40 mL, 0.50 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 22 h at 110 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3o** (78 mg, 59%) as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.93 (d, J=1.5 Hz, 1H), 8.49 (dd, J=4.9, 1.5 Hz, 1H), 7.95 (ddd, J=8.0, 2.2, 1.8 Hz, 1H), 7.52 (dd, J=1.8, 0.7 Hz, 1H), 7.32 (ddd, J=8.0, 4.9, 0.9 Hz, 1H), 6.75 (dd, J=3.4, 0.7 Hz, 1H), 6.52–6.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9, 147.9, 145.1, 143.1, 131.0, 126.9, 123.6, 111.8, 106.5. *m/z* (EIMS): 145 (100), 116 (36), 89 (23), 63 (14), 51 (3).

3.3.13. 6-Naphthalen-1-yl-nicotinic acid methyl ester (3p). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 6-chloronicotinic acid methyl ester **2d** (172 mg, 1.00 mmol). Stirred for 23 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 2:1) yielded **3p** (191 mg, 73%) as colorless solid. Mp 90.5–92.5 °C. IR (KBr): 3044 (w), 2953 (w), 1729 (vs), 1596 (vs), 1440 (s), 1376 (s), 1314 (vs), 1198 (m), 1131 (vs) 1024 (m), 782 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.40 (dd, J=2.2, 0.8 Hz, 1H), 8.44 (dd, J=8.2, 2.2 Hz, 1H), 8.10–8.07 (m, 1H), 7.97–7.91 (m, 2H), 7.72–7.47 (m, 5H), 4.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.8, 163.0, 150.6, 137.6, 137.3, 133.9, 130.8, 129.7, 128.5, 127.9, 126.8, 126.1, 125.2, 125.1, 124.7, 124.3, 52.4. *m/z* (EIMS): 262 (100), 248 (5), 202 (13), 176 (7), 127 (4). HRMS calcd for $C_{17}H_{13}NO_2$: 263.0946, found: 263.0936.

3.3.14. 2-Naphthalen-1-yl-5-trifluoromethyl-pyridine (3q). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 2-chloro-5-trifluoromethylpyridine **2k** (182 mg, 1.00 mmol). Stirred for 2 h at 95 °C. The usual workup and purification by flash chromatography (pentane–ether 4:1) yielded **3q** (225 mg, 82%) as colorless solid. Mp 67–68 °C. IR (KBr): 3055 (w), 1605 (s), 1566 (m), 1331 (vs), 1161 (s), 1128 (vs), 1016 (s), 804 (s), 784 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.08–9.07 (m, 1H), 8.10–8.04 (m, 2H), 7.99–7.92 (m, 2H), 7.53 (d, J=8.2 Hz, 1H), 7.65–7.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.8, 146.4, 146.3, 137.0, 133.9, 133.7, 133.6, 130.8, 129.8, 128.5, 127.9, 126.9, 126.2, 125.3, 125.1, 124.7. *m/z* (EIMS): 273 (41), 272 (100), 252 (6), 203 (6), 176 (4), 136 (5). HRMS calcd for $C_{16}H_{10}NF_3$: 273.0765, found: 273.0726.

3.3.15. 8-(1-Naphthyl)-quinoline (3r). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 8-quinolyl nonaflate[5] **2l** (427 mg, 1.00 mmol). Stirred for 24 h at 25 °C. The standard workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3r** as a white solid (224 mg, 88%). Mp 163–164 °C. IR (KBr): 3042 (w), 1593 (w), 1492 (s), 829 (s), 797 (vs), 782 (vs), 773 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76–8.74 (m, 1H), 8.16–8.13 (m, 1H), 7.89–7.82 (m, 3H), 7.69–7.66 (m, 1H), 7.60–7.46 (m, 3H), 7.41–7.18 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.9, 147.7, 140.6, 138.5, 136.6, 134.1, 133.3, 132.0, 128.9, 128.7, 128.5, 128.4, 128.3, 127.1, 126.6, 126.1, 126.0, 125.8, 121.5. *m/z* (EIMS): 127 (9), 226 (9), 252 (14), 254 (100), 255 (47). HRMS calcd for $C_{19}H_{13}N$: 255.1048, found: 255.1020.

3.3.16. (4′-Methoxy-[1,1′-biphenyl]-4-yl)-(phenyl)-methanone (3s). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 4-bromobenzophenone **2m** (261 mg, 1.00 mmol). Stirred for 3 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 19:1) yielded **3s** as a white solid (210 mg, 73%). Mp 167–168 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.87 (d, J=8.1 Hz, 2H), 7.83 (d, J=8.3 Hz, 2H), 7.66 (d, J=8.3 Hz, 2H), 7.60–7.57 (m, 3H), 7.49 (t, J=7.6 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 Hz): δ 196.3, 159.9, 144.8, 137.9, 135.6, 132.4, 132.2, 130.8, 129.9, 128.4, 128.3, 126.4, 114.4, 55.4. *m/z* (EIMS): 288 (100), 211 (76), 183 (6), 168 (8), 139 (8), 105 (11), 77 (10), 51 (1).

3.3.17. 4′-Methoxy[1,1′-biphenyl]-4-carbonitrile (3t). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL), were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 4-bromobenzonitrile **2n** (182 mg, 1.00 mmol). Stirred for 48 h at 50 °C. The standard workup and purification by flash chromatography (pentane–ether 9:1) yielded **3t** as white solid (113 mg, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69–7.61 (m, 4H), 7.53 (d, J=8.9 Hz, 2H), 7.00 (d, J=8.9 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.17, 145.15, 132.50, 131.43, 128.29, 127.04, 119.02, 114.51, 110.05, 55.34. *m/z* (EIMS): 209 (100, M^+), 194 (25), 166 (31), 140 (13), 113 (2), 63 (2).

3.3.18. 3-Fluoro-4′-methoxy-1,1'-biphenyl (3u). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added

dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromofluorobenzene **2o** (175 mg, 1.00 mmol). Stirred for 2 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 19:1) yielded **3u** as white solid (174 mg, 86%). Mp 67.0–67.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (d, J=8.9 Hz, 2H), 7.28–7.11 (m, 3H), 6.90–6.84 (m, 3H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.2 (q, ^1J (C, F)=245 Hz), 159.5, 143.1 (q, ^3J (C, F)=7.6 Hz), 132.4 (q, ^4J (C, F)=2.1 Hz), 130.1 (q, ^3J (C, F)=8.2 Hz), 128.1, 122.2 (q, ^4J (C, F)=2.6 Hz), 114.5, 113.5 (q, ^2J (C, F)=21.7 Hz), 113.3 (q, ^2J (C, F)=21.1 Hz), 55.3. *m/z* (EIMS): 209 (100), 187 (50), 159 (54), 133 (24), 107 (10), 77 (13).

3.3.19. Ethyl 4′-methoxy[1,1′-biphenyl]-3-carboxylate (3v). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 3-bromobenzoate **2j** (229 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The standard workup and purification by flash chromatography (pentane–ether 9:1) yielded **3v** as a colorless oil (234 mg, 91%). IR (KBr): 2981 (w), 1717 (vs), 1610 (m), 1518 (s), 1439 (m), 1367 (w), 1300 (s), 1249 (vs), 1182 (m), 1109 (s), 1049 (m), 1030 (m), 834 (m), 758 (s), 574 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (s, 1H), 8.00–7.97 (m, 1H), 7.73–7.70 (m, 1H), 7.56 (d, J=8.8 Hz, 2H), 7.46 (t, J=7.7 Hz, 1H), 6.99 (d, J=8.7 Hz, 2H), 4.41 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 159.4, 140.9, 132.5, 130.9, 130.8, 128.6, 128.1, 127.6, 127.1, 114.2, 60.9, 55.2, 14.2. *m/z* (EIMS): 256 (100), 241 (9), 228 (11), 211 (20), 183 (10), 168 (6), 139 (12), 105 (3).

3.3.20. Ethyl 4′-methoxybiphenyl-2-carboxylate (3w). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 2-bromobenzoate **2p** (229 mg, 1.00 mmol). The mixture was stirred for 4 h at 25 °C. The standard workup and purification by flash chromatography (pentane–ether 9:1) yielded **3w** as colorless oil (134 mg, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.68 (m, 1H), 7.42–7.37 (m, 1H), 7.30–7.25 (m, 2H), 7.16 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.03 (q, J=7.1 Hz, 2H), 3.74 (s, 3H), 0.97 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.97, 158.97, 141.92, 133.82, 131.34, 130.98, 130.60, 129.59, 129.49, 126.75, 113.47, 60.85, 55.26, 13.79. *m/z* (EIMS): 256 (100), 241 (9), 228 (12), 211 (93), 183 (8), 168 (21), 139 (18), 105 (5), 77 (4), 43 (5).

3.3.21. Ethyl 4′-methoxy-biphenyl-4-carboxylate (3b). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 4-bromobenzoate **2i** (229 mg, 1.00 mmol) or ethyl 4-chlorobenzoate **2b** (184 mg, 1.00 mmol). The mixture was stirred for 1 h at 25 °C (48 h for ethyl 4-chlorobenzoate). The usual workup and purification by flash chromatography (pentane–ether 9:1) yielded **3b** as white solid (224 mg, 87% for ethyl 4-bromobenzoate, 209 mg, 81% for ethyl 4-chlorobenzoate). Mp 100.5–101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, J=8.7 Hz, 2H), 7.62–7.55 (m, 4H), 6.99 (d, J=8.7 Hz, 2H), 4.39 (q, J=7.1 Hz, 2H), 3.84 (s, 3H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 159.8, 145.0, 132.4, 130.0, 128.6, 128.3, 126.4, 114.3, 60.8, 55.3, 14.3.

3.3.22. 3-(4-Methoxyphenyl)-pyridine (3c). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 3-bromopyridine **2c** (159 mg, 1.00 mmol) or 3-chloropyridine **2q** (114 mg, 1.00 mmol). Stirred for 2 h at 25 °C (12 h for 3-chloropyridine). The usual workup and purification by flash chromatography (pentane–ether 1:1) yielded **3c** as a white solid (150 mg, 81% for 3-bromopyridine and 126 mg, 68% for 3-chloropyridine). The same reaction with 3-bromopyridine, performed in 20 mmol scale, gave 82% yield. Mp 62–63 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.81–8.80 (m, 1H), 8.53 (dd, J=4.8, 1.6 Hz, 1H), 7.84–7.80 (m, 1H), 7.52 (d, J=8.8 Hz, 2H), 7.34–7.30 (m, 1H), 7.01 (d, J=8.8 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 159.7, 148.0, 147.9, 136.3, 133.8, 130.3, 128.2, 123.5, 114.6, 55.4. *m/z* (EIMS): 185 (100, M$^+$), 170 (44), 142 (46), 115 (17), 89 (11), 63 (8).

3.3.23. 2-(3-Pyridino)-benzophenone (3x). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-pyridylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 2-bromobenzophenone **2r** (270 mg, 1.00 mmol). Stirred for 3 h at 50 °C. The standard workup and purification by flash chromatography (pentane–CH_2Cl_2 1:1) yielded **3x** as a white solid (197 mg, 76%). Mp 106–106.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.56–8.52 (m, 1H), 8.44–8.40 (m, 1H), 7.72–7.10 (m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.3, 149.8, 148.8, 139.5, 137.9, 137.6, 136.6, 136.3, 133.6, 131.1, 130.6, 130.3, 129.5, 128.7, 128.2, 123.3. *m/z* (EIMS): 77 (27), 105 (25), 127 (20), 182 (36), 230 (100), 231 (26), 259 (19).

3.3.24. 5-(3-Fluorophenyl)-pyrimidine (3y). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-fluoro-phenylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 5-bromopyrimidine **2s** (159 mg, 1.00 mmol). Stirred for 1 h at 25 °C. The standard workup and purification by flash chromatography (pentane–ether) yielded **3y** as a white solid (143 mg, 82%). Mp 63–63.5 °C. IR (KBr): 2239 (w), 1591 (s), 1416 (s), 909 (vs), 734 (vs) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.13 (s, 1H), 8.85 (s, 2H), 7.44–7.23 (m, 1H), 7.29–7.26 (m, 1H), 7.22–7.17 (m, 1H), 7.10–7.03 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.7 (d, J=248 Hz), 158.3, 155.2, 136.8 (d, J=7.9 Hz), 133.5, 131.5 (d, J=8.5 Hz), 123.0, 116.3 (d, J=21.1 Hz), 114.3 (d, J=21.1 Hz). *m/z* (EIMS): (12), 105 (25), 120 (100), 173

(21), 174 (96). HRMS calcd for $C_{10}H_7N_2F$: 174.0593, found: 174.0577.

3.3.25. 4-Pyrimidin-5-yl-benzoic acid ethyl ester (3z). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 4-(ethoxycarbonyl)-phenylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 5-bromopyrimidine **2s** (159 mg, 1.00 mmol). Stirred for 24 h at 50 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–ether 1:1) yielded **3z** (130 mg, 60%) as colorless solid. Mp 64–65.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.25 (s, 1H), 8.99 (s, 2H), 8.19 (m, 2H), 7.66 (m, 2H), 4.42 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.9, 157.2, 157.0, 154.1, 154.0, 137.5, 132.4, 130.0, 129.6, 125.9, 60.3, 13.3. *m/z* (EIMS): 228 (21), 200 (33), 183 (100), 128 (40), 101 (32).

3.3.26. 1-(3′-Trifluoromethyl-biphenyl-4-yl)-ethanone (3aa). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 3-(trifluoromethyl)phenylmagnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and 1-(4-bromo-phenyl)-ethanone **2g** (199 mg, 1.00 mmol). Stirred for 18 h at 25 °C. The usual workup and purification by flash chromatography (CH_2Cl_2–pentane 1:1) yielded **3aa** (180 mg, 68%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (ddd, J=8.6, 2.4, 2.0 Hz, 2H), 7.87–7.78 (m, 2H), 7.73–7.57 (m, 4H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.9, 144.6, 141.1, 136.9, 132.2, 132.0, 131.6, 130.9, 130.2, 129.9, 129.5, 127.4, 125.3, 124.4, 27.1. *m/z* (EIMS): 264 (35), 249 (100), 221 (6), 201 (34), 152 (21).

3.3.27. Ethyl 4-(1,3-benzodioxol-5-yl)-benzoate (3ab). Prepared according to Section 3.2. To the solution of $ZnBr_2$ (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1,3-benzodioxol-5-yl-magnesium bromide[3a] (1.57 mL, 0.83 M in THF), then the catalyst A solution (0.08 mL), and ethyl 4-bromobenzoate **2i** (229 mg, 1.00 mmol). Stirred for 5 h at 25 °C. The usual workup and purification by flash chromatography (pentane–ether 1:1) yielded **3ab** as white solid (253 mg, 94%). Mp 92.5–93.5 °C. IR (KBr): 2904 (w), 1707 (vs), 1606 (m), 1522 (w), 1503 (m), 1486 (s), 1410 (s), 1274 (vs), 1256 (s), 1235 (m), 1182 (s), 1107 (s), 1036 (s), 932 (m), 858 (m), 772 (s), 702 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, J=8.7 Hz, 2H), 7.56 (d, J=8.7 Hz, 2H), 7.11–7.07 (m, 2H), 6.89 (d, J=8.6 Hz, 1H), 5.00 (s, 2H), 4.39 (q, J=7.1 Hz, 2H), 1.40 (d, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 148.3, 147.7, 145.1, 134.3, 130.0, 128.8, 126.6, 121.0, 108.6, 107.6, 101.3, 60.9, 14.3. *m/z* (EIMS): 270 (100), 242 (32), 225 (70), 139 (40), 112 (5), 63 (2). HRMS calcd for $C_{16}H_{14}O_4$: 270.0892, found: 270.0888.

3.3.28. 3-(1,3-benzodioxol-5-yl)-pyridine (3ac). Prepared according to Section 3.2. To the $ZnBr_2$ solution (0.67 mL, 1.5 M in THF) and NEP (0.17 mL) were added dropwise 1,3-benzodioxol-5-yl-magnesium bromide (1.57 mL, 0.83 M in THF), then the catalyst solution (0.08 mL in NEP), and 3-bromopyridine **2c** (158 mg, 1.00 mmol). Stirred for 5 h at 25 °C. The standard workup and purification by flash chromatography yielded **3ac** as a white solid (165 mg, 83%). Mp 91.5–92.5 °C. IR (KBr): 2912 (w), 1512 (s), 1479 (vs), 1420 (s), 1294 (w), 1266 (m), 1238 (s), 1111 (w), 1037 (s), 931 (m), 806 (s), 706 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76 (d, J=1.9 Hz, 1H), 8.54–8.51 (m, 1H), 7.78–7.74 (m, 1H), 7.32–7.27 (m, 1H), 7.04–7.00 (m, 2H), 6.90–6.87 (m, 1H), 5.99 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.4, 148.1, 148.0, 147.7, 136.3, 133.9, 131.9, 123.4, 120.8, 108.8, 107.5, 101.3. *m/z* (EIMS): 199 (100), 140 (10), 114 (11), 88 (4), 63 (3). HRMS calcd for $C_{12}H_9NO_2$: 199.0633, found: 199.0602.

3.3.29. 4-Methoxy-stilbene (5a). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and α-bromostyrene **4a** (183 mg, 1.00 mmol) was added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 15 min at 25 °C. The standard workup and purification by flash chromatography yielded **5a** as a white solid (179 mg, 85%). The analytical data corresponded to those obtained from an authentic sample.

3.3.30. 1-(4-Methoxyphenyl)-octene (5b). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 1-bromo-1-octene[15] **4b** (191 mg, 1.00 mmol) was added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 30 min at 25 °C. The standard workup and purification by flash chromatography yielded **5b** as a colorless oil (172 mg, 79%). The analytical data are in accordance with those reported in the literature.[10]

3.3.31. 1,1-Bis-(*p*-methoxyphenyl)-ethylene (5c). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 1,1-dichloroethylene **4c** (49 mg, 0.50 mmol) was added dropwise 4-methoxyphenylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 6 h at 25 °C. The standard workup and purification by flash chromatography yielded **5c** as a white solid (106 mg, 88%). The analytical data are in accordance with those reported in the literature.[11]

3.3.32. 6,6-Dimethyl-2-(1-naphthalenyl)-bicyclo[3.1.1]-hept-2-ene (5d). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl triflate **4d** (prepared from nopinone,[16] 270 mg, 1.00 mmol) was added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 12 h at 25 °C. The standard workup and purification by flash chromatography yielded **5d** as a white solid (176 mg, 71%). The analytical data are in accordance with those reported in the literature.[12]

3.3.33. γ-Methylene-2-naphthalene-propyl acetate (5e). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and 3-bromo-3-buten-1-yl acetate **4e** (193 mg, 1.00 mmol) was added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 12 h at 25 °C. The standard workup and purification by flash

chromatography yielded **5e** as a colorless oil (195 mg, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (dd, J_1=9.5 Hz, J_2=3.6 Hz, 1H), 7.70 (dd, J_1=9.5 Hz, J_2=3.6 Hz, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.34–7.25 (m, 3H), 7.11 (t, J=8.0 Hz, 1H), 5.32 (s, 1H), 5.04 (s, 1H), 3.97 (t, J=6.7 Hz, 2H), 2.70 (t, J=6.7 Hz, 2H), 1.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 144.7, 140.1, 133.7, 131.1, 128.3, 127.5, 125.9–125.1 (m), 117.6, 62.7, 37.4, 20.8. *m/z* (EIMS): 240 (11, M^+), 180 (46), 179 (52), 167 (19), 165 (100), 153 (20), 152 (37). HRMS calcd for $C_{16}H_{16}O_2$: 240.1150, found: 240.1127.

3.3.34. 1-(1-Phenylethenyl)-naphthalene (5f). Prepared according to Section 3.3. To the mixture of $ZnBr_2$ (0.67 mL, 1.5 M in THF), catalyst B solution (0.25 mL), and α-bromostyrene **4f** (183 mg, 1.00 mmol) was added dropwise 1-naphthylmagnesium bromide (1.57 mL, 0.83 M in THF). Stirred for 6 h at 25 °C. The standard workup and purification by flash chromatography yielded **5f** as a white solid (179 mg, 78%). The analytical data are in accordance with those reported in the literature.[13]

3.3.35. 4,4′-Bis-(*N*-pyrrolidino)-2,2′-bipyridyl. 4,4′-Dichloro-2,2′-bipyridyl-*N*,*N*′-dioxide[17] (386 mg, 1.50 mmol) was dissolved in the mixture of pyrrolidine (4 mL) and H_2O (2 mL). The solution was heated in a sealed tube at 140 °C for 20 h. The mixture was cooled down and the volatiles were removed in vacuo. The solid residue was dissolved in $CHCl_3$ (40 mL) and PCl_3 (4 mL, 46 mmol) was added. The mixture was refluxed under Ar for 3.5 h and poured on ice (150 g). The organic phase was extracted with H_2O (50 mL) and the combined water phases were evaporated in vacuo. To the residue, 30% KOH was added. The precipitate was filtered off and redissolved in CH_2Cl_2. After the addition of Et_2O, the precipitate was filtered and dried in vacuo. Yield 160 mg (35%). Mp 255–256 °C (decomp.) IR (KBr): 2966 (w), 2851 (w), 1586 (vs), 1538 (m), 1478 (s), 1378 (m), 1262 (w), 992 (s), 802 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, J=5.8 Hz, 2H), 7.52 (d, J=2.5 Hz, 2H), 6.36 (dd, J_1=5.8 Hz, J_2=2.5 Hz, 2H), 3.40 (t, J=6.6 Hz, 8H), 2.00 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 152.6, 148.9, 106.6, 103.9, 47.1, 25.3. *m/z* (EIMS): 294 (48, M^+), 265 (100), 239 (13), 225 (29), 146 (12). HRMS calcd for $C_{18}H_{22}N_4$: 294.1844, found: 294.1828.

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8. 4,4′-Bis-(*N*-pyrrolidino)-2,2′-bipyridyl was prepared from 4,4′-dichloro-2,2′-bipyridyl-*N*,*N*′-dioxide, see Section 3.
9. This compound is a naturally occurring alkaloid (β-nicotyrine), see, for example: Wei, X.; Crooks, P. *Synth. Commun.* **2003**, *33*, 3305 and Refs. therein.
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