Synthesis S. Thapa et al. Feature

Copper-Catalyzed Negishi Coupling of Diarylzinc Reagents with Aryl Iodides

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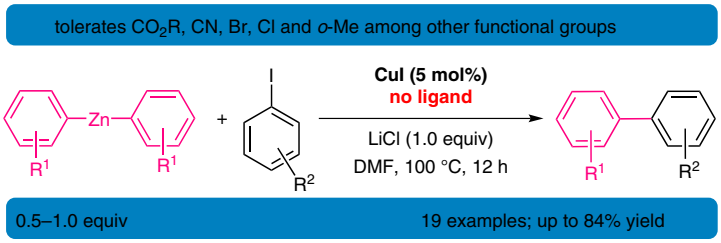

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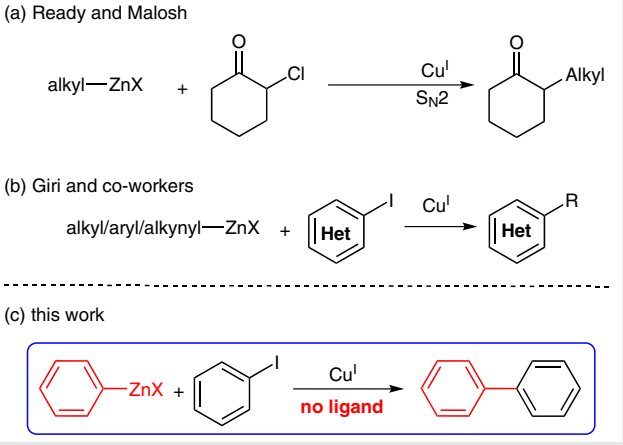
Abstract We report an efficient copper(I) iodide catalyzed cross-coupling of diarylzinc reagents with aryl iodides. The reaction proceeds under ligand-free conditions at low catalyst loading (5 mol%) and tolerates a variety of functional groups.

Key words copper, cross-coupling, diarylzinc, ligand-free, Negishi coupling

The Negishi coupling represents one of the most powerful synthetic methods for the construction of carbon–carbon (C–C) bonds in organic molecules.[1] The synthetic versatility of this transformation stems from the use of organozinc reagents that are tolerant of a wide variety of functional groups encountered in organic synthesis.[1d] In addition, organozinc reagents are also readily prepared from the reaction of organo halides with metallic zinc.[2] As such, tremendous progress has been made over the course of the last three decades in the context of the scope of this reaction as well as its application to the synthesis of natural products,[3] pharmaceuticals[4] and materials.[5] While palladium and nickel have remained the 'gold-standard' catalysts for various cross-couplings including the Negishi coupling, copper, which is earth-abundant and has low toxicity, has recently gained popularity as an alternative catalyst.[6] In this respect, copper has already been shown to enable the cross-couplings of the organometallic reagents of magnesium,[7] tin,[8] boron,[9] silicon,[10] zirconium,[11] and indium[12] with alkyl and aryl halides. Surprisingly, despite clear evidence of the ability of organozinc reagents to transmetalate to copper halides, as demonstrated both in the stoichiometric syntheses of organocopper(I) complexes[13] and catalytic reactions such as conjugate,[14] allylic,[2a] and 1,2-additions,[15] very little is known on the application of copper as a catalyst for the Negishi coupling.[16] In 2004, Ready and Malosh demonstrated that copper could catalyze the reaction of alkylzinc reagents with α-chloro ketones by an S_N2 process (Scheme 1, a).[17] Recently, we also reported that copper(I) iodide could catalyze the cross-couplings of alkyl-, aryl-, and alkynylzinc reagents with heteroaryl iodides under ligand-free conditions (Scheme 1, b).[18] However, we found that when arylzinc bromides were coupled with non-heterocyclic aryl iodides, the reactions afforded the biaryl products in low yields only. In this article, we report the optimization of reaction conditions that enabled the cross-coupling of arylzinc reagents with aryl iodides to afford biaryl products (Scheme 1, c). We demonstrate that the current copper-catalyzed Negishi coupling tolerates a wide variety of functional groups and affords the cross-coupled products in good to excellent yields under ligand-free conditions.



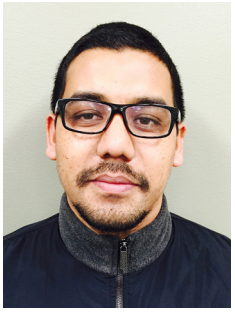
Scheme 1 Copper-catalyzed Negishi cross-couplings

We began our investigation by attempting to couple commercially available phenylzinc bromide (**1**) with 4-iodotoluene (**2**) under our previously reported standard reaction conditions (Table 1, entry 1). However, the cross-coupling product, 4-methylbiphenyl (**3**), was formed in 42% GC yield only. Replacing *N*,*N*-dimethylformamide with other polar, mid-polar, and non-polar solvents did not improve the product yield (entries 2 and 3). We also examined the effects of a wide variety of bases, fluoride sources, and counteranions in the reaction, which also did not improve the product yield (entries 4 and 5). A variety of ligands such as neutral nitrogen- and phosphorus-based monodentate and bidentate ligands, carbene ligands as well as anionic ligands, which afforded the product only in 11–49% yields (entries 6–8). Increasing the amount of lithium chloride and phenylzinc bromide, or running the reaction for a longer time or at a higher temperature either did not improve the reaction or formed the product in only a slightly higher yield (entries 9–13). Surprisingly, when the organozinc reagent was changed from phenylzinc bromide (**1**) to diphenylzinc, the reaction furnished the cross-coupled product **3** in 87% GC yield (entry 14) under the standard reaction conditions using copper(I) iodide (5 mol%) and lithium chloride (1 equiv) in *N*,*N*-dimethylformamide at 100 °C without the need for the addition of ancillary ligands. This reaction required only 0.5 equivalents of diphenylzinc. Lithium chloride plays a crucial role in this cross-coupling because the reaction conducted in its absence afforded **3** in only in 45% GC yield (entry 15). Lithium chloride is generally considered to generate more reactive organozinc species.[19]

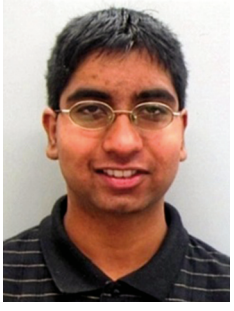
After optimizing the reaction conditions, we examined the substrate scope of the current cross-coupling reaction for aryl–aryl bond formation. The reactions proceed well for the coupling of electron-rich as well as electron-poor aryl iodides with electron-neutral, electron-poor, and electron-rich diarylzinc reagents affording the products in good yield (Table 2). The reactions require only 0.5 equivalents of diphenylzinc (entries 1–4). However, reactions with other diarylzinc reagents required 1.0 equivalents (entries 5–18).

Biographical Sketches

Ramesh Giri was born in Chitwan, Nepal and graduated with distinction from Tribhuvan University (Nepal) with an M.Sc. in organic chemistry in 2000 under the supervision of Prof. S. M. Tuladhar. He then moved to the University of Cambridge (UK) as a Shell Centenary Scholar and received an M.Phil. in bioorganic chemistry in 2003 with Prof. J. B. Spencer. He earned his Ph.D. in chemistry from The Scripps Research Institute in 2009 with Prof. Jin-Quan Yu, where he studied palladium-catalyzed C–H functionalization. As a postdoctoral fellow in the research laboratory of Prof. John F. Hartwig at UC Berkeley/UIUC, he studied the mechanisms of Ullmann amination and biaryl ether forming processes. In 2012, he joined the faculty of the Department of Chemistry & Chemical Biology at the University of New Mexico as an Assistant Professor. His research group is interested in developing organic transformations based on first row late transition metals and investigating their reaction mechanisms.

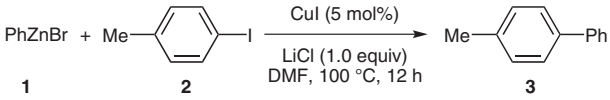


Surendra Thapa was born and raised in Kathmandu, Nepal. After graduating with a B.A. in chemistry from South Dakota State University in Brookings (SD, USA), he began his graduate studies in 2012 at New Mexico Highlands University in Las Vegas, NM, where he worked with Dr. Tatiana Timofeeva, Dr. Kaiguo Chang, and Dr. Carol Linder. He joined the Giri group in the summer of 2013 as a graduate student where he is currently conducting research on copper-catalyzed cross-couplings and mechanistic investigations.



Adarsh Vangala was born in Albuquerque, New Mexico (USA) in 1995. He attended high school at Albuquerque Academy, and after graduating he started attending the University of New Mexico in the fall of 2012. Adarsh joined the Giri group during the summer of 2013 where he has been conducting research in the areas of transition-metal catalysis.

Table 1 Optimization of the Reaction Conditions[a]



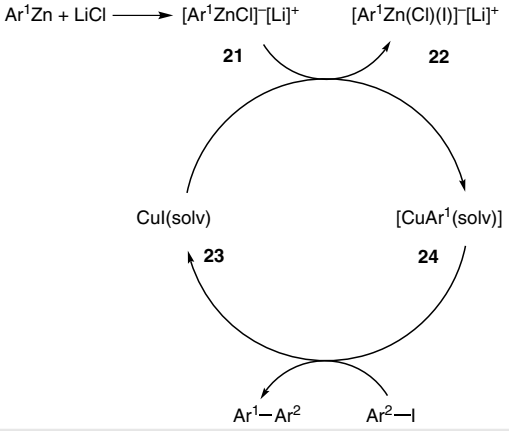
1 2 3

Entry	Modified conditions[b]	Yield (%)[c]
1	none	42
2	change the solvent to: DMSO, DMA, HMPA, or DMPU	trace
3	change the solvent to: toluene, benzene, NMP, or dioxane	10–25
4	change LiCl to: CsF, Cs_2CO_3, K_3PO_4, NaOMe, or NaOAc	10–40
5	addition of: $[Bu_4N]PF_6$, $[Bu_4N]BF_4$, KPF_6, Na_2SiF_6, or $(NH_4)_2TiF_6$	8–30
6	addition of: Ph_3P, dppda, tmopd, tmeda, phen	35–49
7	addition of: dppbe	8
8	addition of: 8-HQ, tmhd, SIMes·HCl	11–25
9	change LiCl (1.0 equiv) to: LiCl (2.0 equiv)	42
10	change time to: 18 h	45
11	change time to: 24 h	50
12	change temperature to: 120 °C	51
13	used PhZnBr (2.0 equiv)	47
14	change PhZnBr to: Ph_2Zn (0.5 equiv)	87 (82)[d]
15	change PhZnBr to: Ph_2Zn (0.5 equiv) without the use of LiCl	45

[a] Using DMF (0.5 mL). Ph_2Zn was generated from the reaction of PhLi with $ZnCl_2$ (99.999% purity). CuI (99.999%) was used.
[b] dppda: 2-(diphenylphosphino)-*N*,*N*-dimethylaniline; tmopd = *N*,*N*,*N*′,*N*′-tetramethyl-*o*-phenylenediamine; phen = 1,10-phenanthroline; dppbe = 1,2-bis(diphenylphosphino)benzene; 8-HQ = 8-hydroxyquinoline; tmhd = 2,2,6,6-tetramethylheptane-3,5-dione.
[c] Calibrated GC yields using 2-nitrobiphenyl as a standard.
[d] Reaction performed on a 1.0-mmol scale in DMF (5 mL); isolated yield. Addition of LiBr (1 equiv) instead of LiCl under the standard reaction conditions decreased the yield of **3** to 76% suggesting that Br^- could inhibit the reaction.

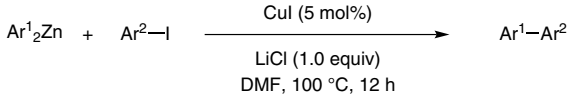
The reaction tolerates a variety of functional groups such as ester, trifluoromethyl, and nitrile on the aryl iodide (entries 2–6, 10–12, and 14–17) and alkoxy and alkyl on the arylzinc reagent (entries 5–17). The reaction also tolerates halides such as chloride and bromide, and *ortho*-substituents on both aryl iodides (entries 7, 8, 13, and 18) and arylzinc reagents (entries 6–14 and 18). The tolerance of these functional groups demonstrates the versatility of the current coupling reaction and its potential synthetic utility.

Based on literature reports and our recent mechanistic work on copper-catalyzed cross-couplings,[9a,10b,12] we propose a catalytic cycle for the current reaction (Scheme 2). It is evident from the optimization of the reaction conditions that the use of lithium chloride is critical in this coupling of diarylzinc reagents with aryl iodides (Table 1, entries 14 and 15). As such, we envision that diarylzincate complexes such as **21**, generated from the binding of lithium chloride to the diarylzinc reagent, are the actual species in solution that undergo transmetalation with copper(I) iodide to generate [CuAr] complexes as the reaction intermediates. Organozinc complexes are known to form organozincate species in the presence of lithium halides in solution.[19b,20] In addition, diarylzinc reagents have been demonstrated to undergo transmetalation with copper salts to form arylcopper(I) complexes.[13] We have previously shown that the [CuPh] complex reacts with aryl iodides to afford biaryl products.[10b,21] Therefore, we believe that a similar mechanistic scenario can also be envisioned in the current copper-catalyzed cross-coupling of diarylzinc reagents with aryl iodides that involves [CuAr] as the reaction intermediate.



Scheme 2 Proposed catalytic cycle

Table 2 Coupling of Diarylzinc Reagents with Aryl Iodides[a]



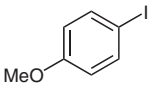
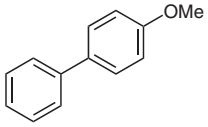
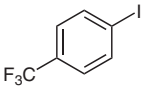
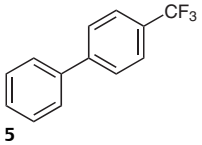
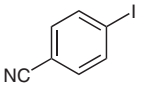
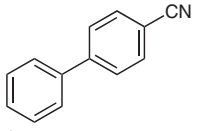
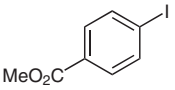
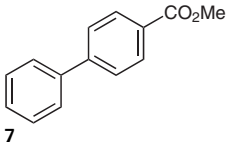
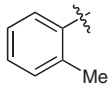
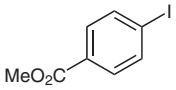
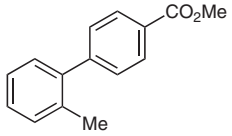
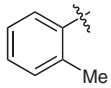
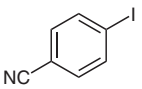
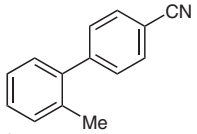
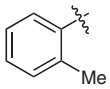
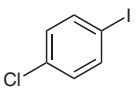
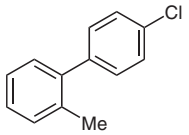
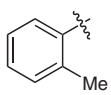
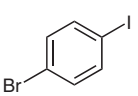
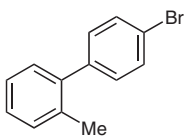
Entry	Ar^1	Ar^2I	Ar^1–Ar^2	Yield[b] (%)
1			 **4**	72[c]
2			 **5**	79[c]
3			 **6**	83[c]
4			 **7**	78[c]
5			 **8**	74
6			 **9**	84
7			 **10**	72
8			 **11**	76

Table 2 (continued)

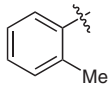
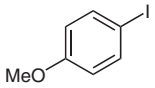
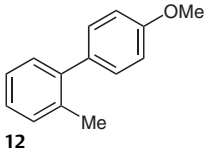
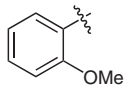
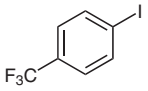
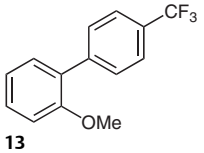
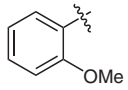
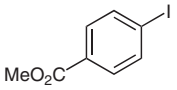
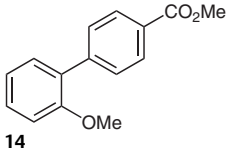
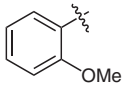
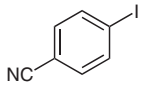
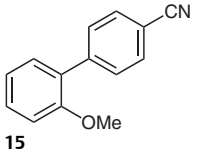
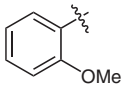
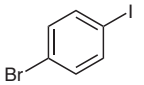
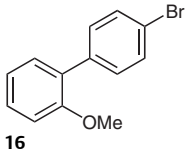
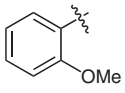
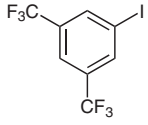
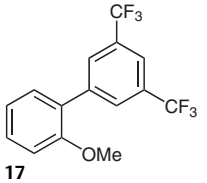
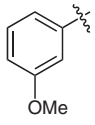
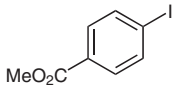
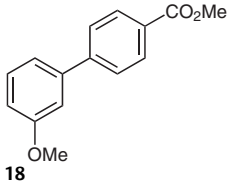
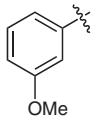
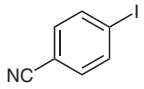
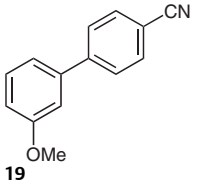
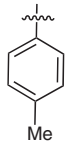
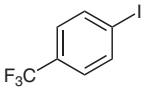
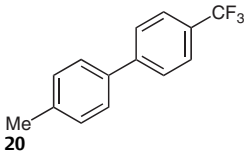
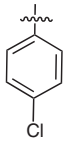
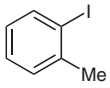
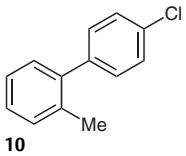
Entry	Ar^1	Ar^2I	Ar^1–Ar^2	Yield[b] (%)
9			 **12**	55
10			 **13**	82
11			 **14**	57
12			 **15**	67
13			 **16**	51
14			 **17**	59
15			 **18**	73
16			 **19**	71

Table 2 (continued)

Entry	Ar^1	Ar^2I	$Ar^1–Ar^2$	Yield[b] (%)
17			 **20**	75
18			 **10**	77

[a] Performed on a 1.0-mmol scale using $Ar^1{}_2Zn$ (1 equiv) in DMF (5 mL) unless otherwise stated. $Ar^1{}_2Zn$ was prepared in situ from $ZnCl_2$ with Ar^1Li (2 equiv) in THF at r.t.
[b] Isolated yield.
[c] Ph_2Zn (0.5 equiv) was used.

In summary, we have developed an efficient ligand-free copper(I) iodide catalyzed Negishi coupling of diarylzinc reagents with aryl iodides that furnishes cross-coupled biaryl products in good to excellent yields. The reaction tolerates a variety of functional groups, such as chloride, bromide, ester, trifluoromethyl, and nitrile on the aryl iodide and alkoxy, alkyl, and chloro on the arylzinc reagent.

All the reactions and handling of chemicals were done inside a N_2-filled glovebox unless stated otherwise. All the glassware were properly dried in an oven before use. Bulk solvents and reagents were obtained from commercial sources and used directly without further purification. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker instrument (300, 75, and 282 MHz, respectively) and internally referenced to the residual solvent signals (^1H NMR: $CDCl_3$, δ = 7.26; ^{13}C NMR: $CDCl_3$, δ = 77.16; for ^{19}F NMR: C_6F_6, δ = –164.9).

Biphenyls; General Procedure

Diarylzinc reagents were generated in situ as described below. In all reactions, 1 equiv of diarylzinc reagent was used except for reactions with diphenylzinc reagent, where only 0.5 equiv was used.

In a glovebox, $ZnCl_2$ (136.3 mg, 1.0 mmol) and aryllithium (2.0 mmol) were weighed into a 4-dram and a 1-dram vial, respectively. Then a solution of aryllithium in THF (2 mL) was added dropwise to the suspension of $ZnCl_2$ in THF (2 mL) at r.t. The mixture was stirred for 1 h, THF was removed, and the in situ generated diarylzinc reagent was dissolved in DMF (5 mL). CuI (9.5 mg, 0.050 mmol), aryl halide (1.0 mmol), and LiCl (42.3 mg, 1.0 mmol) were weighed into a 15-mL pressure vessel and the diarylzinc reagent was added. The pressure vessel was then tightly capped, taken out of the glovebox, and placed in an oil bath preheated to 100 °C with vigorous stirring. After 12 h, the mixture was cooled to r.t., diluted with EtOAc (15 mL) and washed with H_2O (3 × 5 mL); the aqueous fraction was back-extracted with EtOAc (3 × 5 mL). All of the EtOAc extracts were combined and dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The product was purified by column chromatography (silica gel, 0–10% EtOAc–hexanes).

4-Methylbiphenyl (3)

Purification by column chromatography (silica gel) gave **3** as a white solid; yield: 137.9 mg (82%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.40–7.43 (m, 1 H), 7.50 (t, *J* = 8.1 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 7.65–7.68 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 127.1, 128.8, 129.6, 137.1, 138.5, 141.3.

GC-MS: *m*/*z* = 168.1.

4-Methoxybiphenyl (4)

Purification by column chromatography (silica gel) gave **4** as a white solid; yield: 132.6 mg (72%).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 7.08 (d, *J* = 9.0 Hz, 2 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 2 H), 7.61–7.68 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 114.3, 126.7, 126.8, 128.2, 128.8, 133.8, 140.8, 159.2.

GC-MS: *m*/*z* = 184.1.

4-(Trifluoromethyl)biphenyl (5)

Purification by column chromatography (silica gel) gave **5** as a white solid; yield: 175.5 mg (79%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.51 (m, 3 H), 7.59–7.62 (m, 2 H), 7.70 (s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 122.7, 125.9 (q, J_{CF} = 3.5 Hz), 127.4, 127.6, 128.3, 129.1, 129.7, 139.9, 144.9.

^{19}F NMR (282 Hz, $CDCl_3$): δ = –60.8.

GC-MS: *m*/*z* = 222.1.

Biphenyl-4-carbonitrile (6)

Purification by column chromatography (silica gel) gave **6** as a white solid; yield: 148.7 mg (83%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.51 (m, 3 H), 7.58–7.60 (m, 2 H), 7.67–7.74 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.0, 119.1, 127.3, 127.8, 128.8, 129.2, 132.7, 139.3, 145.8.

GC-MS: *m*/*z* = 179.1.

Methyl Biphenyl-4-carboxylate (7)

Purification by column chromatography (silica gel) gave **7** as a white solid; yield: 165.5 mg (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 7.44–7.52 (m, 3 H), 7.64–7.69 (m, 4 H), 8.11 (dd, *J* = 6.6, 1.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.1, 127.0, 127.3, 128.1, 128.9, 130.1, 140.0, 145.6, 167.0.

GC-MS: *m*/*z* = 212.1.

Methyl 2′-Methylbiphenyl-4-carboxylate (8)

Purification by column chromatography (silica gel) gave **8** as a white solid; yield: 167.5 mg (74%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 3.96 (s, 3 H), 7.24–7.29 (m, 4 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 8.11 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 52.2, 126.0, 127.9, 128.7, 129.3, 129.5, 129.6, 130.6, 135.2, 140.9, 146.8, 167.1.

GC-MS: *m*/*z* = 226.2.

2′-Methylbiphenyl-4-carbonitrile (9)

Purification by column chromatography (silica gel) gave **9** as a white solid; yield: 162.3 mg (84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 7.19 (d, *J* = 6.6 Hz, 1 H), 7.27–7.32 (m, 3 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 110.8, 119.1, 126.2, 128.4, 129.5, 130.1, 130.8, 132.1, 135.1, 140.1, 146.9.

GC-MS: *m*/*z* = 193.2.

4-Chloro-2′-methylbiphenyl (10)

Reaction of di-2-tolylzinc reagent and 1-chloro-4-iodobenzene followed by purification by column chromatography (silica gel) gave **10** as a colorless oil; yield: 145.9 mg (72%). Reaction of di-4-chlorophenylzinc reagent and 2-iodotoluene followed by purification by column chromatography (silica gel) gave **10**; yield: 156.1 mg (77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 7.24–7.33 (m, 6 H), 7.44 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 126.0, 127.7, 128.4, 129.8, 130.5, 130.6, 132.9, 135.4, 140.5, 140.8.

GC-MS: *m*/*z* = 202.1.

4-Bromo-2′-methylbiphenyl (11)

Purification by column chromatography (silica gel) gave **11** as a colorless oil; yield: 187.8 mg (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 7.21–7.30 (m, 6 H), 7.57 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 121.1, 126.0, 127.7, 129.7, 130.6, 131.0, 131.3, 135.3, 140.7, 140.9.

GC-MS: *m*/*z* = 245.9.

4-Methoxy-2′-methylbiphenyl (12)

Purification by column chromatography (silica gel) gave **12** as a colorless oil; yield: 109.0 mg (55%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 3.86 (s, 3 H) 6.94–6.97 (m, 2 H), 7.22–7.28 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 55.4, 113.6, 125.8, 127.1, 130.0, 130.3, 134.5, 135.6, 141.7, 158.6.

GC-MS: *m*/*z* = 198.1.

2-Methoxy-4′-(trifluoromethyl)biphenyl (13)

Purification by column chromatography (silica gel) gave **13** as a colorless oil; yield: 206.8 mg (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 7.00–7.09 (m, 2 H), 7.33 (dt, *J* = 8.4, 1.8 Hz, 1 H), 7.38–7.41 (m, 1 H), 7.63–7.69 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 111.5, 121.2, 125.0 (d, J_{CF} = 3.6 Hz), 129.3, 129.4, 129.6, 129.9, 130.9, 142.4, 156.6.

^{19}F NMR (282 Hz, $CDCl_3$): δ = –60.8.

GC-MS: *m*/*z* = 252.1.

Methyl 2′-Methoxybiphenyl-4-carboxylate (14)

Purification by column chromatography (silica gel) gave **14** as a white solid; yield: 138.1 mg (57%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.94 (s, 3 H), 6.99–7.08 (m, 2 H), 7.33–7.40 (m, 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 8.09 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 52.6, 111.4, 121.0, 128.6, 129.4, 129.5, 129.6,130.8, 143.5, 156.5, 167.2.

GC-MS: *m*/*z* = 242.1.

2′-Methoxybiphenyl-4-carbonitrile (15)

Purification by column chromatography (silica gel) gave **15** as a white solid; yield: 140.2 mg (67%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 7.00–7.09 (m, 2 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 8.4 Hz, 1 H), 7.66 (q, *J* = 8.4 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 110.4, 111.4, 119.2, 121.1, 128.7, 129.9, 130.2, 130.6, 131.8, 143.4, 156.4.

GC-MS: *m*/*z* = 209.1.

4-Bromo-2′-methoxybiphenyl (16)

Purification by column chromatography (silica gel) gave **16** as a colorless oil; yield: 134.2 mg (51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 6.97–7.06 (m, 2 H), 7.27–7.37 (m, 2 H), 7.41 (d, *J* = 8.7 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 111.3, 120.9, 121.1, 129.0, 129.5, 130.6, 131.1, 131.2, 137.4, 156.3.

GC-MS: *m*/*z* = 262.0.

2-Methoxy-3′,5′-bis(trifluoromethyl)biphenyl (17)

Purification by column chromatography (silica gel) gave **17** as a colorless oil; yield: 188.9 mg (59%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 7.04–7.12 (m, 2 H), 7.35 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.43 (dt, *J* = 8.4, 1.8 Hz, 1 H), 7.85 (s, 1 H), 8.02 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 111.5, 120.7 (t, J_{CF} = 4.1 Hz), 121.3, 123.7 (d, J_{CF} = 270.9 Hz), 127.7, 129.1, 130.6 (d, J_{CF} = 28.6 Hz), 131.4 (d, J_{CF} = 33.0 Hz), 132.0, 140.7, 156.5.

^{19}F NMR (282 Hz, $CDCl_3$): δ = –61.2.

GC-MS: *m*/*z* = 320.1.

Methyl 3′-Methoxybiphenyl-4-carboxylate (18)

Purification by column chromatography (silica gel) gave **18** as a white solid; yield: 176.9 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 3.94 (s, 3 H), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.15 (t, *J* = 2.4 Hz, 1 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 8.10 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 55.4, 113.1, 113.6, 119.8, 127.2, 129.1, 130.0, 130.1, 141.5, 145.5, 160.1, 167.0.

GC-MS: *m*/*z* = 242.1.

3′-Methoxybiphenyl-4-carbonitrile (19)

Purification by column chromatography (silica gel) gave **19** as a colorless oil; yield: 148.5 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 6.97 (dd, *J* = 7.8, 2.1 Hz, 1 H), 7.10 (t, *J* = 2.1 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.66–7.73 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 111.1, 113.2, 114.0, 119.0, 119.8, 127.9, 130.3, 132.7, 140.7, 145.6, 160.2.

GC-MS: *m*/*z* = 209.1.

4-Methyl-4′-(trifluoromethyl)biphenyl (20)

Purification by column chromatography (silica gel) gave **20** as a white solid; yield: 177.2 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 7.29 (d, *J* = 8.4, 2 H), 7.49–7.52 (m, 2 H), 7.69 (s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 122.7, 125.8 (d, J_{CF} = 3.8 Hz), 126.1 (d, J_{CF} = 3.8 Hz), 127.2, 127.3, 127.8, 129.2 (d, J_{CF} = 32.3 Hz), 129.9, 137.0, 138.3, 144.8.

^{19}F NMR (282 Hz, $CDCl_3$): δ = –60.8.

GC-MS: *m*/*z* = 236.1.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560397.

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