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Unified Protocol for Cobalt-Catalyzed Oxidative Assembly of Two Aryl Metal Reagents Using Oxygen as an Oxidant

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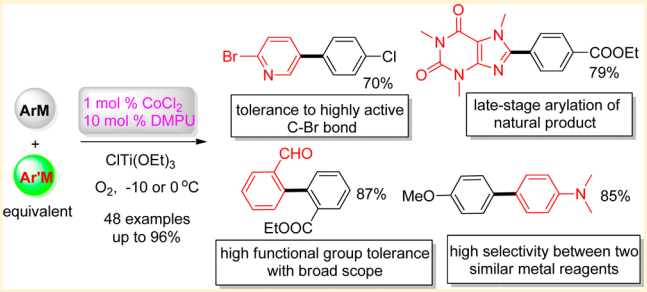
Supporting Information

ABSTRACT: The first cobalt-catalyzed oxidative cross-coupling reaction of two aryl metal reagents is described. An equivalent amount of two aryl Grignard or lithium reagents, after mediation by an equivalent amount of simple $ClTi(OEt)_3$, was facilely assembled under the catalysis of 1 mol % of $CoCl_2$/10 mol % of DMPU using oxygen. The cross-couplings between various aryl metal reagents, especially between two structurally similar aryl Grignard reagents, proceeded smoothly and selectively and, thus, provided a highly general and efficient method for the construction of biaryl compounds.



1. INTRODUCTION

Oxidative couplings of metal reagents have become a very attractive method to construct C−C bonds.[1] The prominent advantages of these couplings lie not only in the rapid advances in organometalllic chemistry that provide a wide range of various metal reagents for this transformation[2] but also the fact that direct metalation of arenes enables this type of couplings using simple or functionalized arenes.[3] In transition-metal-catalyzed reactions, catalysts are usually expensive not only because of the use of expensive transition metals as catalyst centers but also owing to the requirement of complex ligands to sustain the activity of catalyst. In this regard, an oxidative coupling may eliminate the use of special ligands because it proceeds through double transmetalation without the use of an aryl halide or pseudohalide as well as the process of oxidative addition that usually requires a special ligand for unreactive halides.[4] As illustrated in Scheme 1, under the catalysis of an inexpensive and simple catalyst system as well as with molecular oxygen as an oxidant, an ideal oxidative coupling will provide the desired products with peroxide inorganic salts as only side products under mild conditions. Despite these advantages, the undesired homocoupling side reactions of two metal reagents remain a serious problem to be controlled in the oxidative cross-coupling reactions. As such, only a few examples of the oxidative cross-coupling have been described to date, most of which are achieved between different hybridized carbon atoms such as C(sp)−C(sp2),[5] C(sp)−C(sp3),[6] and C(sp2)−C(sp3)[7] and usually with one of the metal reagents in large excess. The examples of oxidative aryl−aryl cross couplings are very rare.[5b,8] Obviously, the similar reactivity of the organometallic reagents makes the aryl−aryl oxidative cross couplings remarkably challenging due to the homocoupling side reactions. On the other hand, due to the high cost of palladium and the high toxicity of nickel catalysts, cobalt salts or complexes are viable alternatives. Recently intense research has been conducted on cobalt-catalyzed coupling reactions;[9,10] however, to the best of our knowledge, there has been no report on cobalt-catalyzed oxidative cross-couplings between two aryl metal reagents to date.

Recently, we have reported a highly selective iron-catalyzed aryl−aryl oxidative cross-coupling reaction of titanate-mediated aryl metal reagents.[11] We have also observed a remarkable synergistic effect of Co and Ti in the Co-catalyzed biaryl cross-couplings.[12] Prompted by these findings, we decided to develop a facile Co-catalyzed oxidative biaryl cross-coupling reaction of aryl metal reagents, on which we present our full investigations herein. Meanwhile, a series of iron-catalyzed cross-couplings of this type was also examined for comparison. This Co-catalyzed reaction represents one of most desirable oxidative cross-couplings between two aryl metal reagents and meets almost all of the requirements of the ideal oxidative cross-couplings (Scheme 1). Importantly, low loading of catalyst cobalt salt (1 mol % of $CoCl_2$) as well as simple ligand (DMPU) showed a high catalytic effect.

2. RESULTS AND DISCUSSION

At the outset of our studies, we investigated the oxidative cross-coupling of titanate-mediated PhMgBr (**1a**) and 1-methyl-imidazolyl-2-lithium (**3a**) with the selected examples shown in Table 1. Compared with iron catalysis,[11] the Co-catalyzed reaction under similar conditions gave a low yield of cross-coupling product (entries 1 and 2). The screening of ligands indicated that the simple phosphine ligands such as PBu_3 and PCy_3 and bidentate nitrogen ligands such as 2,2-bipyridine (BPY) and 1,10-phenanthroline (PTL) were not as effective as

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Scheme 1. Comparison of an Ideal Oxidative Cross-Coupling with the Cobalt-Catalyzed Oxidative Assembly of Two Titanate-Mediated Aryl Metal Reagents

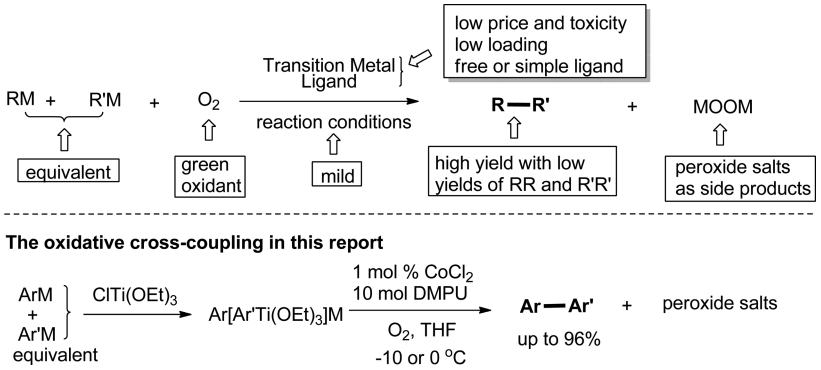
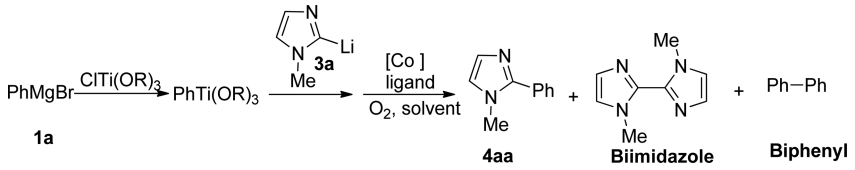


Table 1. Optimization Studies[a]



entry	catalyst[b] (mol %)	ligand (mol %)	titanate (1.0 equiv)	time (h)	yield of **4aa** (%)	yield of biimidazole (%)	yield of biphenyl (%)
1	$FeCl_3$ (8)	TMEDA (20)	$ClTi(OEt)_3$	6	78	trace	11
2	$CoCl_2$ (10)	TMEDA (20)	$ClTi(OEt)_3$	3	40	10	38
3	$CoCl_2$ (10)	Bu_3P (20)	$ClTi(OEt)_3$	4	25	6	55
4	$CoCl_2$ (10)	Cy_3P (20)	$ClTi(OEt)_3$	4	35	8	46
5	$CoCl_2$ (10)	BPY[c] (20)	$ClTi(OEt)_3$	4	20	12	53
6	$CoCl_2$ (10)	PTL[d] (20)	$ClTi(OEt)_3$	4	18	13	51
7	$CoCl_2$ (10)	DMPU[e] (20)	$ClTi(OEt)_3$	4	60	15	23
8	$CoCl_2$ (10)	DMPU (10)	$ClTi(OEt)_3$	4	61	10	28
9	$CoCl_2$ (10)	DMPU (10)	$ClTi(OPr^i)_3$	4	45	22	30
10	$CoCl_2$ (10)	Bu_3P (20)	TBEPC[f]	4	62	8	25
11	$Co(acac)_2$ (10)	Cy_3P (20)	$ClTi(OEt)_3$	4	15	12	65
12	$Co(acac)_2$ (10)	BPY[c] (20)	$ClTi(OEt)_3$	4	12	8	70
13	$CoCl_2$ (5)	DMPU (10)	$ClTi(OEt)_3$	4	72	7	10
14[g,h]	$CoCl_2$ (3)	DMPU (10)	$ClTi(OEt)_3$	5	78	3	9
15	$CoCl_2$ (3)	DMPU (5)	$ClTi(OEt)_3$	5	72	5	12
16	$CoCl_2$ (1)	DMPU (10)	$ClTi(OEt)_3$	6	82	trace	8
17			$ClTi(OEt)_3$	6	6	2	23

[a]The reaction was conducted on a 5 mmol scale at 0 °C unless indicated otherwise. [b]Compound **3a** was prepared by lithiation of 1-methylimidazole using TPMLi at 0 °C. [c]2,2′-Bipyridine. [d]1,10-Phenanthroline. [e]1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone. [f]$ClTi(OPr^i)(OCH_2CH_2OCH_2CH_2O)$.[11] [g]The coupling reactions could not occur when conducted in toluene and hexane under these conditions. [h]Lowering the temperature to −5 or −10 °C did not improve the yield of **4aa**.

expected (entries 3−6). To our delight, the use of an inexpensive ligand, DMPU,[13] could promote the oxidative cross-coupling reactions more efficiently (entries 7 and 8). We also examined the influence of different titanates (entries 9 and 10). While the use of $ClTi(OPr^i)_3$ resulted in a lower yield, $ClTi(OEt)_3$ and TBEPC[11] gave almost the same results, which was in contrast with the corresponding iron-catalyzed reactions.[11] It was also found that the type of cobalt salt affected the reaction, and $Co(acac)_2$ only resulted in very low yields of cross-coupling product (entries 11 and 12).

After careful observation, we found that the oxidative couplings occurred much more rapidly under catalysis of 10 mol % of $CoCl_2$/10 mol % of DMPU than those catalyzed by $FeCl_3$/TMEDA (entry 1 and the examples in the ref 11). We deduced that lowering the loading of the cobalt catalyst to slow the coupling reaction might help to improve the selectivity of the cross-coupling. As expected, the cross-coupling occurred in 82% yield when $CoCl_2$ was loaded in 1 mol % (entries 13−16). The cross-coupling hardly occurred in the absence of $CoCl_2$ (entry 17). In addition, the reaction conducted in toluene or hexane did not proceed, and further lowering the reaction temperature (to −5 or −10 °C) did not improve the yield of the cross-coupling. Thus, a highly selective Co-catalyzed oxidative cross-coupling with a low loading of cobalt salt (1 mol % of $CoCl_2$) and simple ligand (10 mol % of DMPU) was established using oxygen as an oxidant in single THF solvent at 0 °C.

With optimized reaction conditions in hand, we then explored the generality of this cobalt-catalyzed oxidative cross-coupling. Since *N*-heteroaryl-containing biaryls are widely presented in bioactive and related compounds, the reactions between aryl and *N*-heteroaryl metal reagents were first

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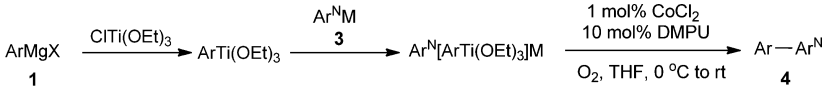
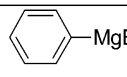
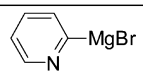
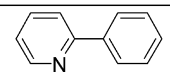
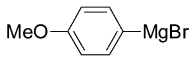
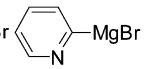
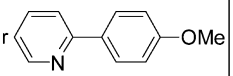
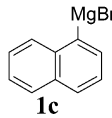
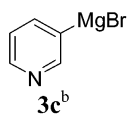
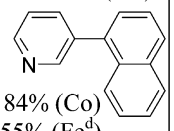
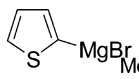
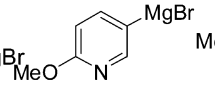
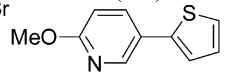
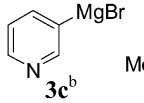
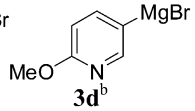
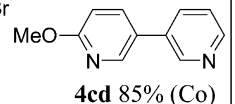
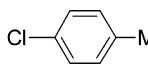
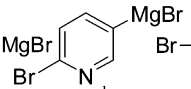
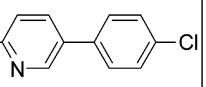
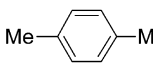
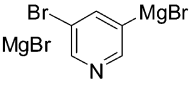
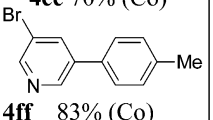
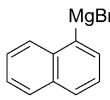
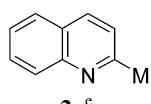
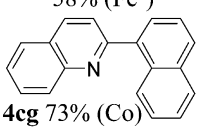
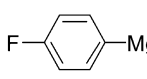
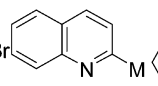
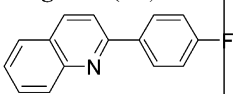
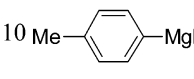
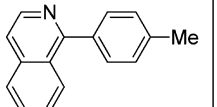
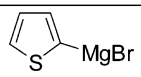
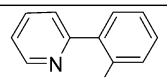
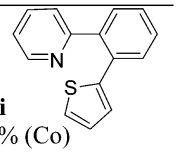
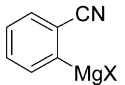
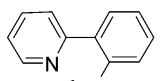
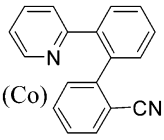
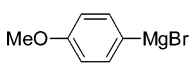
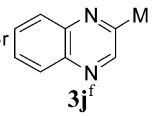
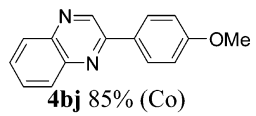
Table 2. Cobalt-Catalyzed Cross-Couplings between Titanate-Mediated *N*-Heteroaryl and Aryl Metal Reagents with Molecular Oxygen[a]



Entry	ArMgX	Ar^NM	Product
1	 **1a**	 **3b**[b]	 **4ab** 90% (Co) 95% (Fe^c)
2	 **1b**	 **3b**	 **4bb** 96% (Co) 96% (Fe^c)
3	 **1c**	 **3c**[b]	 **4cc** 84% (Co) 55% (Fe^d)
4	 **1d**	 **3d**[b]	 **4dd** 75% (Co) 15% (Fe^c) 60% (Fe^d)
5	 **3c**[b]	 **3d**[b]	 **4cd** 85% (Co)
6	 **1e**	 **3e**[b]	 **4ee** 70% (Co)
7	 **1f**	 **3f**[b]	 **4ff** 83% (Co) 45% (Fe^c) 58% (Fe^d)
8	 **1c**	 **3g**[e]	 **4cg** 73% (Co)
9	 **1g**	 **3g**[e]	 **4gg** 77% (Co)
10	 **1f**	 **3h**[f]	 **4fh** 80% (Co)
11	 **1d**	 **3i**[f]	 **4di** 77% (Co)
12	 **1h**	 **3i**[f]	 **4hi** 81% (Co)
13	 **1b**	 **3j**[f]	 **4bj** 85% (Co)
14	**1h**	**3j**[f]	**4hj** 76% (Co)
15	**1g**	**3k**[f]	**4gk** 80% (Co)
16	**1d**	**3a**[f]	**4da** 86% (Co)
17	**1i**	**3a**[f]	**4ia** 78% (Co) 35% (Fe^c) 58% (Fe^d)
18	**1g**	**3l**[g]	**4gl** 80% (Co)
19	**1a**	**3m**[g]	**4am** 82% (Co)
20	**1j**	**3n**[f]	**4jn** 79% (Co)

[a]The reaction was conducted on a 3 mmol scale unless indicated otherwise. For the Co-catalyzed reaction: 1 mol % of $CoCl_2$/10 mol % of DMPU, $ClTi(OEt)_3$, 0 °C. For the Fe-catalyzed reaction: 8 mol % of $FeCl_3$/20 mol % of TMEDA, $ClTi(OEt)_3$, or TBEPC, rt. [b]The Grignard reagents were prepared through bromine−magnesium exchange using *i*-PrMgCl. [c]In these Fe-catalyzed reactions, $ClTi(OEt)_3$ was used. [d]In these Fe-catalyzed reactions, TBEPC was used. [e]The reagent was prepared through deprotonative metalation using BF_3·Et_2O/TMPMgCl·LiCl. [f]The reagent was prepared through deprotonative metalation using TMPMgCl·LiCl or TMPLi. [g]The reagent was prepared through deprotonative metalation using EtMgBr.

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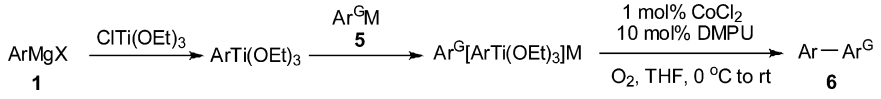
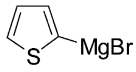
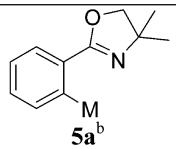
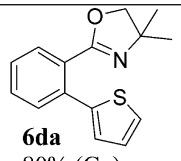
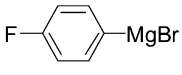
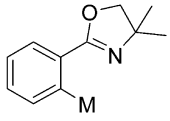
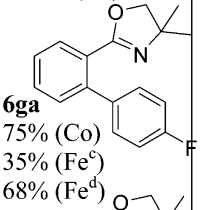
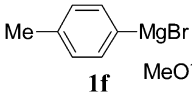
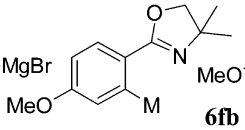
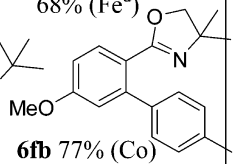
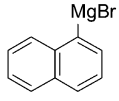
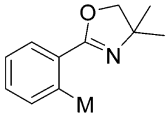
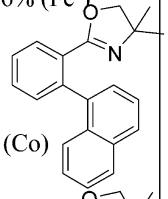
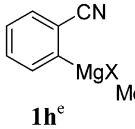
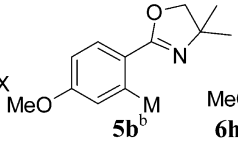
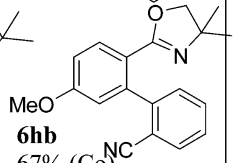
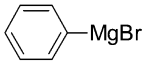
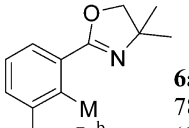
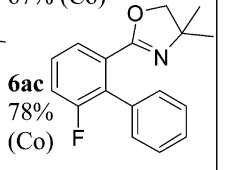
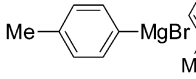
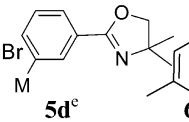
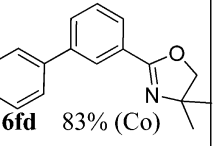
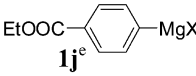
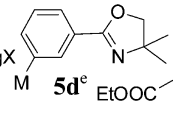
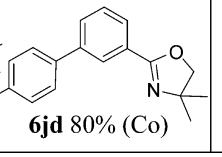
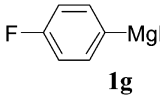
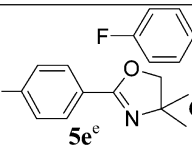
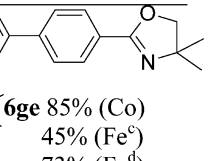
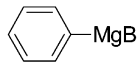
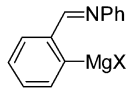
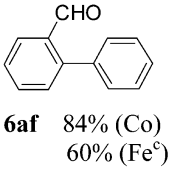
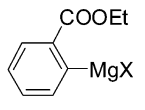
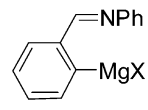
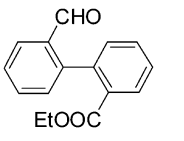
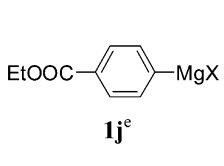
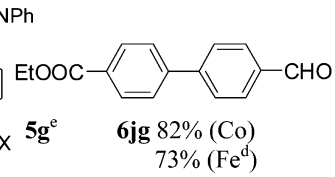
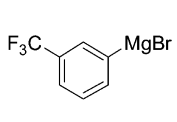
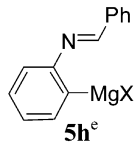
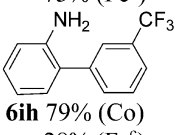
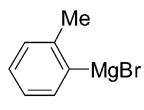
J. Org. Chem. 2015, 80, 9856−9867

Table 3. Cobalt-Catalyzed Oxidative Assembly of Titanate-Mediated Oxazoline or Imine-Containing Aryl Metal Reagents and Aryl Grignard Reagents Using Oxygen[a]



Entry	ArMgX	Ar^GM	Product
1	 **1d**	 **5a**[b]	 **6da** 80% (Co)
2	 **1g**	 **5a**[b]	 **6ga** 75% (Co) 35% (Fe^c) 68% (Fe^d)
3	 **1f**	 **5b**[b]	 **6fb** 77% (Co) 26% (Fe^c)
4	 **1c**	 **5a**[b]	 **6ca** 72% (Co)
5	 **1h**[e]	 **5b**[b]	 **6hb** 67% (Co)
6	 **1a**	 **5c**[b]	 **6ac** 78% (Co)
7	 **1f**	 **5d**[e]	 **6fd** 83% (Co)
8	 **1j**[e]	 **5d**[e]	 **6jd** 80% (Co)
9	 **1g**	 **5e**[e]	 **6ge** 85% (Co) 45% (Fe^c) 73% (Fe^d)
10	 **1a**	 **5f**[e]	 **6af** 84% (Co) 60% (Fe^c)
11	 **1k**[e]	 **5f**[e]	 **6kf** 87% (Co)
12	 **1j**[e] **5g**[e]		 **6jg** 82% (Co) 73% (Fe^d)
13	 **1i**	 **5h**[e]	 **6ih** 79% (Co) 28% (Fe^c) 51% (Fe^d)
14	 **1l**	**5h**[e]	**6lh** 78% (Co)
15	**1e**	**5i**[e]	**6ei** 82% (Co)
16	**1m**	**5i**[e]	**6mi** 73% (Co) 34% (Fe^c)

[a]The reaction was conducted on a 3 mmol scale unless indicated otherwise. For the Co-catalyzed reaction: 1 mol % of $CoCl_2$/10 mol % of DMPU, $ClTi(OEt)_3$, 0 °C. For the Fe-catalyzed reaction: 8 mol % of $FeCl_3$/20 mol % of TMEDA, $ClTi(OEt)_3$ or TBEPC, rt. [b]The reagent was prepared through deprotonative metalation using TMPMgCl·LiCl. [c]In these Fe-catalyzed reactions, $ClTi(OEt)_3$ was used. [d]In these Fe-catalyzed reactions, TBEPC was used. [e]The Grignard reagents were prepared through iodine−magnesium exchange using *i*-PrMgCl·LiCl.

investigated with the results outlined in Table 2. It can be seen that this reaction was quite general and exhibited a high tolerance for various sensitive functional groups. Almost all common *N*-heteroarenes including pyridine, (iso)quinolone, imidazole, benzoimidazole, benzothiazole, aryloxazole, quinoxaline, and caffeine were all readily amenable to this Co-catalyzed

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J. Org. Chem. 2015, 80, 9856−9867

cross-coupling. In general, the yields of the present cross-couplings under the catalysis of 1 mol % of $CoCl_2$ and 10 mol % of DMPU with the mediation of simple $ClTi(OEt)_3$ were comparable to or even better than those catalyzed by 10 mol % of $FeCl_3$ and 20 mol % of TMEDA with the mediation of TBEPC.

Although iron- or cobalt-catalyzed coupling reactions of the 2-pyridyl moiety have been well developed,[14] the corresponding cross-couplings using 3-pyridyl species often show disappointing results. Our investigations clearly indicated that the Co- or Fe-catalyzed oxidative cross-couplings using both 2-pyridyl and 3-pyridyl Grignard reagents were achieved facilely (Table 2, entries 1−7). While the iron-catalyzed couplings of 2-pyridyl Grignard reagents proceeded equally well using $ClTi(OEt)_3$ and TBEPC (Table 2, entries 1 and 2), the corresponding couplings of 3-pyridyl Grignard reagents showed a significant difference between the two titanates, where the couplings using TBEPC resulted in higher yields (Table 2, entries 3 and 4). Nevertheless, the cobalt-catalyzed couplings of 3-pyridyl Grignard reagents mediated with simple $ClTi(OEt)_3$ proceeded equally well compared with those of 2-pyridyl moiety (entries 3−7), demonstrating the broad scope and robustness of the cobalt catalysis. It is noteworthy that two highly similar 3-pyridyl Grignard reagents were also selectively assembled to yield **4cd** in 85% yield (Table 2, entry 5). The tolerance of C−Cl, C−Br bonds, especially the highly active C−Br bond at the C2 position of pyridyl ring, offers an attractive and useful feature for this oxidative cross-coupling (Table 2, entries 6 and 7), for the chlorine or bromine handle can be derivatized to afford other products.[15] Since the deprotonative metalation has been well established,[3] the present oxidative cross-couplings could be achieved using simple (hetero)arenes. For example, 2-quinolinyl metal reagents were facilely prepared from quinoline using BF_3·Et_2O/TMPMgCl·LiCl[16] and oxidatively coupled with Grignard reagents in 73% and 77% yields (Table 2, entries 8 and 9). Meanwhile, isoquinoline, 2-phenylpyridine, and quinoxaline were all directly metalated using TMPMgCl·LiCl or TMPLi and coupled with various Grignard reagents including functionalized or heteroaryl ones to give the desired products in 76−85% yields (Table 2, entries 10−14). Similarly, various imidazole, benzoimidazole, benzothiazole, and aryloxazole derivatives that are often found in pharmaceutical compounds were prepared in 78−86% yields (Table 2, entries 15−19). Additionally, a mild arylation of caffeine could also be achieved, demonstrating a convenient late-stage functionality of natural product (Table 2, entry 20).

Based on the above findings, we further extended the scope of the Co-catalyzed oxidative cross-couplings to the reactions between two aryl metal reagents, one of which contained an oxazoline or imine group. The results were illustrated in Table 3. Oxazolines are usually used as protecting groups, directing groups for metalation, chiral ligands, or auxiliaries and, therefore, are a class of important structural blocks for cross-couplings. Taking advantage of *ortho* deprotonative metalation of oxazolines using TMPMgCl·LiCl,[17] a series of aryloxazolines were arylated in 67−80% yields based on this Co-catalyzed oxidative cross-coupling (Table 3, entries 1−6). Relatively, the corresponding iron-catalyzed reaction mediated with TBEPC gave a comparable yield while those using $ClTi(OEt)_3$ resulted in low yields (Table 3, entries 2 and 3). The sterically hindered oxazoline products such as **6ca** and **6hb** were conveniently prepared as well. It is worth noting that the oxidative arylation at the position *meta* or *para* to the oxazoline group proceeded equally well (Table 3, entries 7−9) and can function as a complementary protocol to the existing Ru-catalyzed *ortho* arylation of 2-aryloxazolines.[18]

The imine group is also an important functionality in organic chemistry and is often used as a protecting group for primary amines, aldehydes, and ketones.[19] As illustrated in Table 3 (entries 10−16), various Grignard reagents containing an imine group (derivatized from amines or aldehydes) were oxidatively coupled with another aryl Grignard reagent under the present Co-catalyzed conditions to afford the desired products in 73−87% yields. Once again, while the Co-catalyzed reactions using $ClTi(OEt)_3$ proceeded well, the iron-catalyzed couplings using $ClTi(OEt)_3$ gave lower yields relative to those using TBEPC (Table 3, entries 10, 12, 13, and 16). To date, although the Co-catalyzed arylation, alkenylation, and alkylation of ketimines and aldimines have been well established at the positions *ortho* to the carbonyl group,[9c,d,10] the corresponding arylation *ortho* to the amine group has been investigated relatively rarely. With Grignard reagent **5h**, this oxidative coupling reaction produced the 2-arylated anilines in good yields (Table 3, entries 13 and 14). Notably, the arylations beyond the *ortho* position of the imine group also proceeded well (Table 3, entries 12, 15, and 16). Based on our present procedure, two structurally similar Grignard reagents as well as sterically hindered Grignard reagents were all facilely assembled (Table 3, entries 11, 12, and 14).

Selective oxidative cross-coupling of two structurally similar aryl metal reagents is remarkably challenging because a similar reactivity of the organometallic reagents makes the homocoupling side reactions very difficult to control. As illustrated in the aforementioned examples (Table 2, entry 5; Table 3, entries 5, 11, and 12), a few such selective cross-couplings have already been achieved successfully. To further extend the generality of this coupling reaction, additional Co-catalyzed oxidative cross-couplings between two structurally similar aryl metal reagents were examined, and the results were summarized in Table 4. To our delight, two common structurally highly similar aryl Grignard reagents were coupled to give the cross-coupling product in 79% yield (Table 4, entries 1−3), demonstrating the high amenability to various aryl metal reagents as well as the robustness of this Co-catalyzed oxidative cross-coupling. Importantly, this oxidative cross-coupling reaction still showed broad scope with remarkable selectivity over homocouplings, and at the same time sensitive functional groups such as ester, amide, and nitrile were tolerated. While the Co-catalyzed couplings using $ClTi(OEt)_3$ and TBEPC showed a slight difference, the Fe-catalyzed ones showed a significant difference (Table 4, entries 1, 2, and 11). Sterically hindered biaryls could still be assembled smoothly (Table 4, entries 7−11). Besides, not only the couplings between electronically different aryl Grignard reagents occurred with good yields (Table 4, entries 3, 4, 5, 8−10); the couplings between electronically similar aryl Grignard reagents also proceeded equally well (Table 4, entries 1, 2, 6, and 7).

Mechanistically, we assume that a cobalt−titanium bimetallic cooperativity in this oxidative cross-coupling suppresses the formation of the symmetrical diaryl cobalt complex [$Co(Ar)_2$ or $Co(Ar')_2$] and the subsequent undesired homocouplings. The preparation and isolation of the cobalt−titanium bimetallic complexes are being carried out in our laboratories. This oxidative coupling seemed not to proceed through a radical mechanism since it was not inhibited by the addition of a

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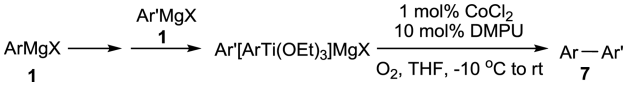
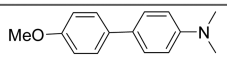
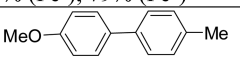
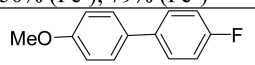
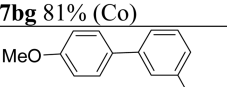
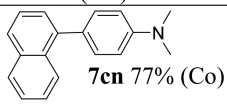
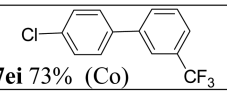
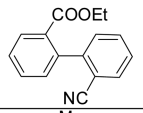
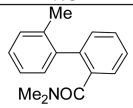
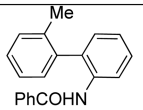
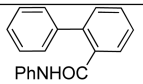
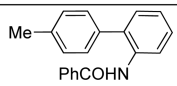
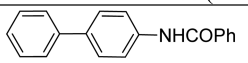
J. Org. Chem. 2015, 80, 9856−9867

Table 4. Cobalt-Catalyzed Oxidative Assembly of Two Structurally Similar Titanate-Mediated Aryl Grignard Reagents Using Oxygen as Oxidant[a]



Entry	ArMgX	Ar′MgX	Product
1	**1b**	**1n**	 **7bn** 79% (Co);85% (Co[d]) 56% (Fe[c]); 79% (Fe[d])
2	**1b**	**1f**	 **7bf** 78% (Co); 86% (Co[d]) 50% (Fe[c]); 79% (Fe[d])
3	**1b**	**1g**	 **7bg** 81% (Co)
4	**1b**	**1i**	 **7bi** 81% (Co) 84% (Fe[d])
5	**1c**	**1n**	 **7cn** 77% (Co)
6	**1e**	**1i**	 **7ei** 73% (Co)
7	**1k**[e]	**1h**[e]	 **7kh** 83% (Co)
8[b]	**1l**	**1o**[e]	 **7lo** 78% (Co)
9[b]	**1l**	**1p**[e]	 **7lp** 76% (Co)
10[b]	**1a**	**1q**[e]	 **7aq** 74% (Co)
11[b]	**1f**	**1p**[e]	 **7fp** 76% (Co) 85% (Co[d])
12[b]	**1a**	**1r**[e]	 **7ar** 85% (Co)

[a]The reaction was conducted on 3 mmol scale unless indicated otherwise. For the Co-catalyzed reaction: 1 mol % of $CoCl_2$/10 mol % of DMPU, $ClTi(OEt)_3$, −10 °C. For the Fe-catalyzed reaction: 8 mol % of $FeCl_3$/20 mol % of TMEDA, $ClTi(OEt)_3$ or TBEPC, 0 °C. [b]In these reactions, the Co-catalyzed reaction was performed at 0 °C while the Fe-catalyzed reaction was performed at rt. [c]In these Fe-catalyzed reactions, $ClTi(OEt)_3$ was used. [d]In these Co- or Fe-catalyzed reactions, TBEPC was used. [e]The Grignard reagents were prepared through iodine−magnesium exchange using *i*-PrMgCl·LiCl.

radical scanvengner (TMPO). Besides, the peroxide group from the expected peroxide salt [Scheme 1; MOOM, M = Li, MgX, $Ti(OEt)_3$] was also detected by potassium iodide−starch solution after the quench of the reactions. Further mechanistic studies are being investigated in our laboratories.

3. CONCLUSION

The first Co-catalyzed oxidative cross-coupling reaction between titanate-mediated two aryl metal reagents using oxygen has been developed. It represents one of most desirable oxidative cross-couplings between two aryl metal reagents because it can highly selectively assemble two various aryl Grignard or lithium reagents in an equivalent amount with peroxide salts as side products. Attractive features include the use of low-loading $CoCl_2$ as well as inexpensive ligand DMPU; simple $ClTi(OEt)_3$ as titanate, oxygen as greenest oxidant, broad generality, high selectivity over homocouplings, remarkable functional group tolerance, mild conditions, and single THF solvent. Besides, the mediation of titanates only requires simple combination of titanates with metal reagents. Meanwhile, titanium is a nontoxic, abundant, and environmentally safe element.[20] Therefore, the present cross-coupling reaction provides an eco-friendly, simple, and efficient method to access various biaryl compounds.

4. EXPERIMENTAL SECTION

General Information. IR spectra were recorded using a FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer (100 or 125 MHz for ^{13}C spectroscopy) using TMS as an internal standard. High-resolution mass spectra (HRMS) were obtained with a microTOF (ESI). Melting points were recorded on a microscopic instrument and are uncorrected.

All reagents and solvents used for arylmagnesium reagents or -lithium reagents and reactions were freshly dehydrated and distilled before use. The corresponding glassware was oven-dried (120 °C) and cooled under a stream of argon gas. Aryl Grignard reagents such as phenyl magnesium or 4-methoxyphenyl magnesium were prepared according to the standard procedure. Pyridyl Grignard reagents were prepared via bromine−magnesium exchange using *i*-PrMgCl, while functionalized aryl Grignard reagents such as 2-cyanophenyl magnesium chloride; 4-(ethoxycarbonyl)phenyl magnesium chloride, 4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl magnesium chloride, and 2-(phenylimino)methylphenyl magnesium chloride were prepared via iodine−magnesium exchange using *i*-PrMgCl·LiCl according to Knochel's method.[21] All of the Grignard reagents were titrated before use.[22] $ClTi(OEt)_3$ and TBEPC were prepared according to the reported method.[11]

Typical Procedure for 4dd (Table 2, Entry 4). Under Ar atmosphere, to a solution of $ClTi(OEt)_3$ (654 mg, 3 mmol) in 10 mL of THF was added dropwise 2-thiophene-yl magnesium bromide (3 mL, 1 M in THF) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The mixture was cooled to 0 °C, and to it was added dropwise a solution of 6-methoxypyridin-3-yl magnesium bromide (3 mL, 1 M in THF, prepared from 5-bromo-2-methoxypyridine through bromine−magnesium exchange using *i*-PrMgCl[23]) and stirred for 40 min at 0 °C. The solution of $CoCl_2$ (3.9 mg, 0.03 mmol) and DMPU (38.4 mg, 0.3 mmol) in THF (5 mL) was added in one portion. The Ar atmosphere was changed to O_2 atmosphere (applied by a balloon filled with dioxygen). The thus-obtained mixture was stirred at 0 °C until completion of the reaction (monitored by TLC). The reaction was quenched with saturated aqueous Na_2CO_3 solution and diluted with CH_2Cl_2. After being filtered, the mixture was extracted with CH_2Cl_2 (50 mL × 4). The organic layer was dried over Na_2SO_4 and concentrated to yield the crude compound, which was purified by column chromatography to yield the desired product **4dd**.

Note 1: For the reactions where the metal reagents were unstable at room temperature (for example, **1h**, **1j**, etc.), combination of the metal reagents with $ClTi(OEt)_3$ was performed at −30 or −40 °C. The

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J. Org. Chem. 2015, 80, 9856−9867

temperature was then allowed to come to room temperature over 2 h, and the mixture was stirred for 2 h at that temperature.

Note 2: For the reactions where the *N*-heteroaryl metal reagents were prepared at −30 or −40 °C (for example, **3j**, **3n**, etc.), the combination of the *N*-heteroaryl metal reagents with the aryltitanium reagents was also conducted at −30 or −40 °C. The following operations were conducted as described in typical procedure.

Note 3: The reactions catalyzed by $FeCl_3$/TMEDA were performed according to the reported procedure.[11]

Typical Procedure for 6af (Table 3, Entry 10). Under Ar atmosphere, to a solution of $ClTi(OEt)_3$ (654 mg, 3 mmol) in 10 mL of THF was added dropwise phenyl magnesium bromide (3 mL, 1 M in THF) at 0 °C. The resulting mixture was stirred for 2 h at room temperature.

Under Ar atmosphere, a solution of *i*-PrMgCl·LiCl (3 mmol, 1.0 M in THF) was added dropwise to a solution of *N*-(2-iodobenzylidene)-aniline (921 mg, 3 mmol) in 10 mL of THF at −40 °C and stirred for 2 h at that temperature, and a solution of the above-prepared titanium reagent was added dropwise at −40 °C. The resulting solution was allowed to come to 0 °C and stirred for 40 min at that temperature. The solution of $CoCl_2$ (3.9 mg, 0.03 mmol) and DMPU (38.4 mg, 0.3 mmol) in THF (5 mL) was added in one portion. The Ar atmosphere was changed to O_2 atmosphere (applied by a balloon filled with dioxygen). The resulting mixture was stirred at 0 °C until completion of the reaction (monitored by TLC). The reaction was quenched with HCl aqueous solution (2 M, 15 mL) and stirred for 4 h at 40 °C. After the temperature was cooled to 25 °C, the mixture was extracted with CH_2Cl_2 (50 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated to yield the crude compound, which was purified by column chromatography to yield a light yellow solid.

Note 1: The post-treatment of the reactions for **6ih**, **6lh**, **6ei**, and **6mi** was performed as follows: the reaction was quenched with HCl aqueous solution (2 M, 25 mL) and stirred for 4 h at 40 °C. The mixture was extracted with ether (50 mL × 3). To the aqueous phase was added saturated aqueous Na_2CO_3 solution to make the solution alkaline (pH > 9). This aqueous phase was then extracted with CH_2Cl_2 (50 mL × 3). The combined CH_2Cl_2 was dried over Na_2SO_4 and concentrated to yield the crude compound, which was purified by column chromatography.

Note 2: The reactions catalyzed by $FeCl_3$/TMEDA were performed according to the reported procedure.[11]

Typical Procedure for 7bn (Table 4, Entry 1). Under Ar atmosphere, a solution of 4-$MeOC_6H_4MgBr$ (3 mmol, 1.0 M in THF) was added dropwise to a solution of $ClTi(OEt)_3$ (654 mg, 3 mmol) in 10 mL of THF at 0 °C and stirred for 2 h at that temperature. To this mixture was added dropwise 4-(dimethylamino)phenyl magnesium bromide (3 mmol, 1.0 M in THF). The resulting mixture was stirred at 0 °C for 1 h and then cooled to −10 °C. A mixture of $CoCl_2$ (3.9 mg, 0.03 mmol) and DMPU (38.4 mg, 0.3 mmol) in THF (5 mL) was added in one portion. The Ar atmosphere was changed into O_2 atmosphere (applied by a balloon filled with dioxygen). The thus obtained mixture was stirred at −10 °C until completion of the reaction (monitored by TLC). The reaction was quenched with saturated aqueous Na_2CO_3 solution and diluted with CH_2Cl_2. After being filtered, the mixture was extracted with CH_2Cl_2 (50 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated to yield the crude compound, which was purified by column chromatography to yield the desired product **7bn** as a whitish solid (538 mg, 79% yield).

Note 1: The reactions of aryl Grignard reagents bearing amide groups were carried out at 0 °C.

Note 2: The reactions catalyzed by $FeCl_3$/TMEDA were performed according to the reported procedure.[11]

*2-Phenylpyridine (**4ab**).* The product was prepared as described in the typical procedure for **4dd** and isolated as a colorless oil in 90% yield (396 mg): R_f = 0.33 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 1592, 1565, 693; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 7.2 Hz, 2H), 7.67−7.66 (m, 2H), 7.46−7.40 (m, 2H), 7.38−7.36 (m, 1H), 7.17−7.13 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 157.4, 149.7, 139.4, 136.7, 129.0, 128.8, 127.0, 122.1, 120.5. Data was consistent with that reported in the literature.[24]

*2-(4-Methoxyphenyl)pyridine (**4bb**).* The product was prepared as described in the typical procedure for **4dd** and isolated as a whitish solid in 96% yield (516 mg): mp = 52.5−53.5 °C; R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 2926, 1609, 1587, 1516, 1462, 1040, 782, 744; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (dd, J = 5.0 Hz, J = 0.6 Hz, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.73−7.66 (m, 2H), 7.19−7.15 (m, 1H), 7.00 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 160.5, 157.1, 149.5, 136.7, 132.0, 128.2, 121.4, 119.8, 114.1, 55.3. Data was consistent with that reported in the literature.[25]

*3-(Naphthalen-1-yl)pyridine (**4cc**).* The product was prepared as described in the typical procedure for **4dd** and isolated as a pale yellow oil in 84% yield (517 mg): R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 3096, 2933, 2856, 1587, 1471, 1173, 1024, 797; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75−8.74 (m, 1H), 8.66 (dd, J = 4.9 Hz, J = 1.6 Hz, 1H), 7.89 (t, J = 8.0 Hz, 2H), 7.80−7.77 (m, 2H), 7.54−7.50 (m, 2H), 7.46−7.43 (m, 1H), 7.41−7.38 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.5, 148.5, 137.4, 136.5, 136.3, 133.9, 131.5, 128.62, 128.56, 127.5, 126.6, 126.2, 125.5, 125.3, 123.3. Data was consistent with that reported in the literature.[26]

*2-Methoxy-5-(thiophene-2-yl)pyridine (**4dd**).* The product was isolated as a pale yellow solid in 75% yield (430 mg): mp = 72 °C; R_f = 0.43 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 2923, 1601, 1493, 1285, 1020, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.2 Hz, 1H), 8.22 (dd, J = 5.0 Hz, J = 1.9 Hz, 1H), 7.91 (dd, J = 8.6 Hz, J = 2.4 Hz, 1H), 7.65 (dd, J = 7.3 Hz, J = 1.9 Hz, 1H), 7.04 (dd, J = 7.3 Hz, J = 5.0 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 4.03 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.6, 144.5, 137.1, 128.1, 126.9, 124.7, 122.9, 117.2, 111.1, 53.6. Data was consistent with that reported in the literature.[27]

*6-Methoxy-3,3′-bipyridine (**4 cd**).* The product was prepared as described in the typical procedure for **4dd** and isolated as a white solid in 85% yield (576 mg): mp = 46−48 °C; R_f = 0.43 (petroleum ether/ethyl acetate =10:1); IR (cm^{-1}, KBr) 2924, 1604, 1583, 1456, 1374, 1285, 1022, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (m, 1H), 8.60 (d, J = 4.8 Hz, 1H), 8.39 (d, J = 2.5 Hz, 1H), 7.84−7.77 (m, 2H), 7.40−7.37 (m, 1H), 7.39 (dd, J = 7.9 Hz, J = 4.9 Hz, 1H), 3.99 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.2, 146.4, 147.6, 145,1, 137.3, 134.1, 133.7, 126.7, 123.7, 111.3, 53.7. Data was consistent with that reported in the literature.[27]

*2-Bromo-5-(4-chlorophenyl)pyridine (**4ee**).* 6-Bromopyridin-3-yl magnesium bromide was prepared via bromine−magnesium exchange from 2,5-dibromopyridine using *i*-PrMgCl. The product was prepared as described in the typical procedure for **4dd** and isolated as a light yellow solid in 70% yield (564 mg): mp = 112 °C; R_f = 0.55 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 3034, 1588, 1546, 1452, 1427, 1350, 1084, 997; ^1H NMR (400 MHz, $CDCl_3$) δ 8.0 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.1, 147.8, 135.8, 135.2, 134.5, 129.4, 129.1, 128.2, 128.1. Data was consistent with that reported in the literature.[28]

*3-Bromo-5-(p-tolyl)pyridine (**4ff**).* 5-Bromopyridin-3-yl magnesium bromide was prepared via bromine−magnesium exchange from 3,5-dibromopyridine using *i*-PrMgCl. The product was prepared as described in the typical procedure for **4dd** and isolated as a white solid in 83% yield (583 mg): mp = 90 °C; R_f = 0.56 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 2920, 1614, 1515, 1472, 1384, 1026, 796, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.56 (d, J = 4.2 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.9, 145.4, 138.1, 134.8, 134.3, 129.8, 126.9, 123.6, 115.5, 21.1. Data was consistent with that reported in the literature.[29]

*2-(Naphthalen-1-yl)quinoline (**4cg**).* 2-Quinoline metal reagent was prepared from quinoline using $BF_3{\cdot}Et_2O$ and TMPMgCl·LiCl[16,30] and combined with the titanium reagent at −40 °C. The magnesium reagents and titanium reagent were mixed at −40 °C, and then the temperature was raised to 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**. The product was isolated

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as a pale yellow solid in 73% yield (557 mg): mp = 95−96 °C; R_f = 0.46 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3316, 2949, 2866, 1604, 1489, 1385, 1303, 1225, 1033, 789, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08−8.08 (m, 1H), 7.97−7.95 (m, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.69−7.66 (m, 1H), 7.55−7.54 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.36−7.32 (m, 2H), 7.18−7.13 (m, 2H), 6.88 (m, 2H), 6.43 (d, J = 7.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.9, 150.1, 148.0, 143.1, 136.0, 132.5, 130.0, 129.4, 129.1, 128.4, 127.5, 127.0, 126.1, 125.5, 124.9, 123.2, 121.9, 117.0, 114.0. Data was consistent with that reported in the literature.[31]

*2-(4-Fluorophenyl)quinoline (**4gg**).* The coupling was conducted as described for **4cg**. The product was isolated as a pale yellow solid in 77% yield (515 mg): mp = 94−96 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2957, 2924, 2854, 1602, 1496, 1385, 1225, 1157, 822, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22−8.14 (m, 2H), 7.82 (d, J = 8.7 Hz, 1H), 7.54−7.45 (m, 4H), 7.20 (t, J = 8.6 Hz, 1H), 7.14−7.12 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.4, 161.5, 156.3, 148.2, 136.9, 136.4, 129.7 (d, J = 19.3 Hz), 129.4 (d, J = 8.2 Hz), 128.7 (q, J = 7.9 Hz), 127.3 (q, J = 58.3 Hz), 126.4, 118.6, 115.7 (q, J = 9.3 Hz). Data was consistent with that reported in the literature.[32]

*1-(4-Methylphenyl)isoquinoline (**4fh**).* 1-Isoquinoline metal reagent was prepared from isoquinoline using TMPMgCl·LiCl[33] and combined with the titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**. The product was isolated as a pale yellow solid in 80% yield (526 mg): mp = 70−72 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3064, 2955, 1604, 1550, 1502, 1387, 1257, 1177, 1022, 833, 770; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 5.7 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 7.57 (t, J = 8.2 Hz, 1H), 7.35 (d, J = 7.7 Hz, 2H), 6.97 (d, J = 7.0 Hz, 2H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.8, 154.5, 141.2, 138.8, 137.0, 130.4, 129.8, 129.1, 127.9, 127.4, 126.9, 120.3, 115.4, 21.3. Data was consistent with that reported in the literature.[34]

*2-(2-(Thiophene-2-yl)phenyl)pyridine (**4di**).* 2-(Pyridin-2-yl)phenyl magnesium reagent was prepared from 2-phenylpyridine using TMPMgCl·LiCl[33] and combined with titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**, and the product was isolated as a pale yellow oil in 77% yield (466 mg): R_f = 0.15 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 3058, 1585, 1466, 1420, 1260, 1022, 848, 745, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 5.3 Hz, 1H), 7.67−7.63 (m, 1H), 7.57−7.55 (m, 1H), 7.48−7.46 (m, 1H), 7.25−7.22 (m, 1H), 7.20−7.18 (m, 2H), 6.92−6.88 (m, 1H), 6.81 (d, J = 7.7 Hz, 2H), 6.71 (dd, J = 3.5 Hz, J = 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 159.1, 149.3, 142.8, 139.6, 135.7, 133.1, 130.7, 130.5, 128.6, 128.1, 127.1, 127.0, 125.8, 125.1, 121.9. Data was consistent with that reported in the literature.[35]

*2′-(Pyridin-2-yl)[1,1′-biphenyl]-2-carbonitrile (**4hi**).* The product was prepared as described in **4di** and isolated as a pale yellow solid in 81% yield (622 mg): mp = 138−140 °C; R_f = 0.11 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 2922, 2223, 1589, 1467, 1010, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.61−7.55 (m, 2H), 7.53−7.52 (m, 1H), 7.47−7.43 (m, 1H), 7.35−7.28 (m, 1H), 7.21−7.19 (m, 1H), 7.11 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 6.98−6.96 (m, 1H), 6.87−6.83 (m, 1H), 6.78 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.7, 149.2, 145.0, 141.6, 139.8, 136.2, 133.6, 133.0, 130.6, 130.3, 129.8, 129.3, 128.3, 124.5, 124.0, 122.6, 117.7, 112.3; HRMS calcd for $C_{18}H_{13}N_2^+$ $[M + H]^+$ 257.1079, found 257.1074.

*2-(4-Methoxyphenyl)quinoxaline (**4bj**).* Quinoxalin-2-yl magnesium chloride was prepared from quinoxaline using $TMP_2Mg·LiCl_2$[36] and combined with the titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**, and the product was isolated as a pale yellow solid in 85% yield (602 mg): mp = 94−95 °C; R_f = 0.52 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2934, 1602, 1584, 1286, 1252, 1176, 1028, 763; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.19−8.17 (m, 2H), 8.14 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 8.11 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 7.80−7.70 (m, 2H), 7.10−7.07 (m, 2H), 3.90 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.5, 151.6, 142.8, 142.3, 130.5, 129.4, 129.3, 129.1, 128.7, 116.2, 114.8, 114.6, 55.8. Data was consistent with that reported in the literature.[37]

*2-(Quinoxalin-2-yl)benzonitrile (**4hj**).* The product was prepared as described in **4bj** and isolated as a pale yellow solid in 76% yield (527 mg): mp = 158−160 °C; R_f = 0.38 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2225, 1544, 1487, 1246, 1155, 1091, 958, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 8.0 Hz, J = 1.1 Hz, 1H); 8.31 (d, J = 8.2 Hz, 1H), 8.25−8.23 (m, 1H), 7.83−7.79 (m, 1H), 7.64−7.60 (m, 1H), 7.52−7.49 (m, 1H), 7.33−7.29 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.1, 153.7, 147.8, 144.3, 137.3, 133.6, 132.9, 131.8, 130.6, 129.8, 129.2, 124.9, 122.8, 117.5, 112.5; HRMS calcd for $C_{15}H_{10}N_3^+$ $[M + H]^+$ 232.0875, found 232.0871.

*2-(4-Fluorophenyl)-1-methyl-1H-benzoimidazole (**4gk**).* Benzoimidazole lithium reagent was prepared from *N*-methylbenzimidazole using TMPLi at 0 °C and combined with the titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**, and the product was isolated as a pale yellow solid in 80% yield (542 mg): mp = 95−97 °C; R_f = 0.45 (ethyl acetate); IR (cm^{-1}, KBr) 2941, 2875, 1604, 1509, 1384, 1221, 1157, 1052, 836; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22−8.19 (m, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.41−7.39 (m, 3H), 7.11−7.03 (m, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.8, 142.9, 136.6, 130.2, 129.7, 129.5, 128.7, 122.8, 122.4, 119.8, 109.6, 31.7. Data was consistent with that reported in the literature.[38]

*1-Methyl-2-(thiophene-2-yl)-1H-imidazole (**4da**).*[39] The coupling reaction was conducted as described in **4gk**, and the product was isolated as a pale yellow oil in 86% yield (423 mg): R_f = 0.15 (ethyl acetate); IR (cm^{-1}, KBr) 3103, 1655, 1560, 1508, 1471, 1406, 1285, 1140, 849, 716; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 5.1 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.08 (t, J = 3.9 Hz, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.1, 136.7, 128.2, 127.5, 126.5, 125.7, 122.6, 34.6.

*1-Methyl-2-(3-(trifluoromethyl)phenyl)-1H-imidazole (**4ia**).* The product was prepared as described in **4da** and isolated as a pale yellow oil in 78% yield (529 mg): R_f = 0.24 (ethyl acetate); IR (cm^{-1}, KBr) 2950, 1619, 1472, 1328, 1167, 1125, 1069, 808, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.11 (s, 1H), 6.99 (s, 1H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.4 (d, J = 122.2 Hz), 131.6, 130.9, 129.2, 129.1, 128.4, 128.1, 125.2 (q, J = 3.7 Hz), 123.0, 122.5, 32.2; HRMS calcd for $C_{11}H_{10}F_3N_2^+$ $[M + H]^+$ 227.0796, found 227.0801.

*2-(4-Fluorophenyl)benzothiazole (**4gl**).* Benzothiazol-2-yl magnesium bromide was prepared from benzothiazole using EtMgBr at 10−15 °C.[40] The thus obtained mixture was combined with the titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**, and the product was isolated as a light yellow solid in 80% yield (550 mg): mp = 100−101 °C; R_f = 0.34 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 2966, 1669, 1601, 1454, 1288, 1216, 1160, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−8.10 (m, 3H), 7.95 (d, J = 8.0 Hz, 1H), 7.57−7.53 (m, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.25−7.21 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.8, 165.5, 163.5, 154.0, 135.0, 129.5 (d, J = 8.4 Hz), 126.5, 125.3, 123.2, 121.7, 116.2 (d, J = 22.0 Hz). Data was consistent with that reported in the literature.[41]

*5-(4-Methoxyphenyl)-2-phenyloxazole (**4am**).* The product was prepared as described for **4da** and isolated as a light yellow solid in 82% yield (617 mg): mp = 78−79 °C; R_f = 0.28 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3022, 2965, 2823, 1625, 1501, 1244, 1176; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 7.9 Hz, J = 2.4 Hz, 2H), 7.89 (dd, J = 8.6 Hz, J = 2.4 Hz, 1H), 7.50−7.47 (m, 4H), 7.38 (s, 1H), 6.85 (d, J = 8.6 Hz, 1H), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 164.0, 161.2, 148.9, 143.0, 134.8, 130.5, 128.9, 126.3, 122.7, 117.9, 111.4, 58.5. Data was consistent with that reported in the literature.[42]

*Ethyl 2-(1,3,7-Trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)benzoate (**4jn**).* The Grignard reagent of caffeine was prepared as follows: to a solution of caffeine (480 mg, 3 mmol, 1 equiv) in THF

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(10 mL) was added dropwise TMPMgCl·LiCl (3.6 mmol, 1.2 equiv) at −10 °C and the mixture stirred for 2 h at this temperature. The Grignard reagent of caffeine was combined with the titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**, and the product was isolated as a white solid in 79% yield (811 mg): mp = 174−175 °C; R_f = 0.22 (ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2919, 2851, 1714, 1659, 1284, 1102, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 4.62 (q, J = 7.1 Hz, 2H), 4.09 (s, 3H), 3.64 (s, 3H), 3.44 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.2, 155.6, 151.7, 150.9, 148.4, 132.5, 132.3, 130.0, 129.1, 109.0, 60.9, 34.0, 29.8, 28.0, 14.0. Data was consistent with that reported in the literature.[43]

*4,4-Dimethyl-2-(2-(thiophene-2-yl)phenyl)-4,5-dihydrooxazole (**6da**).* 2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl magnesium chloride was prepared from 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole using TMPMgCl·LiCl at 0 °C for 4 h and combined with titanium reagent at 0 °C. The coupling reaction was conducted as described in the typical procedure for **4dd**, and the product was isolated as a pale yellow solid in 80% yield (617 mg): mp = 213-214 °C; R_f = 0.23 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3063, 1648, 1585, 1462, 1425, 725, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 1.8 Hz, 1H), 8.44 (dd, J = 4.7 Hz, J = 1.2 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.24−7.20 (m, 2H), 6.80 (d, J = 8.9 Hz, 1H), 6.73−6.71 (m, 1H), 2.93 (s, 2H), 1.28 (d, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 163.5, 142.3, 134.2, 130.6, 130.4, 130.3, 128.4, 127.6, 127.1, 126.1, 125.8, 79.7, 67.7, 28.1. Data was consistent with that reported in the literature.[44]

*2-(4′-Fluoro[1,1′-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**6ga**).*[45] The compound was prepared as described in **6da** and isolated as a colorless yellow oil in 75% yield (605 mg): R_f = 0.12 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2952, 2833, 1640, 1510, 1454, 1234, 1179, 826, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.6 Hz, 1H), 7.53 (td, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.43 (dd, J = 7.5 Hz, J = 1.2 Hz, 1H), 7.41−7.37 (m, 3H), 7.14−7.09 (m, 2H), 3.87 (s, 2H), 1.34 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 163.5 (d, J = 62.5 Hz), 161.3, 140.6, 137.1 (d, J = 3.4 Hz), 130.6, 130.2 (d, J = 8.1 Hz), 130.0 (d, J = 7.8 Hz), 128.1 (q, J = 8.1 Hz), 127.3, 115.0, 114.9, 79.6, 67.5, 28.0.

*2-(5-Methoxy-4′-methyl[1,1′-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**6fb**).* The compound was prepared as described in **6da** and isolated as a light yellow oil in 77% yield (682 mg): R_f = 0.40 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 2967, 2839, 1644, 1610, 1513, 1256, 1172, 1083, 1029, 839; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.02 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.79 (s, 1H), 4.13 (s, 2H), 3.81 (s, 3H), 2.56 (s, 3H), 1.39 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 163.1, 162.4, 158.0, 156.1, 153.8, 152.3, 130.3, 129.3, 119.6, 115.9, 113.9, 79.4, 67.3, 55.5, 28.4, 20.6. Data was consistent with that reported in the literature.[46]

*4,4-Dimethyl-2-(2-(naphthalen-1-yl)phenyl)-4,5-dihydrooxazole (**6ca**).* The compound was prepared as described in **6da** and isolated as a pale yellow oil in 72% yield (555 mg): R_f = 0.10 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3057, 1653, 1589, 1462, 1435, 1259, 735; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89−7.85 (m, 2H), 7.83 (d, J = 8.2 Hz, 1H); 7.60 (d, J = 8.5 Hz, 1H), 7.54 (dd, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.51−7.49 (m, 1H), 7.48−7.42 (m, 4H), 7.41−7.38 (m, 1H), 3.47 (d, J = 8.0 Hz, 1H), 3.19 (d, J = 8.0 Hz, 1H), 1.0 (s, 3H), 0.95 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 163.5, 140.2, 139.4, 133.3, 131.9, 131.3, 130.5, 129.7, 129.3, 128.1, 127.6, 127.5, 126.4, 126.0, 125.9, 125.6, 125.2, 79.3, 67.0, 27.72, 27.69; HRMS calcd for $C_{21}H_{20}NO^+$ $[M + H]^+$ 302.1539, found 302.1551.

*2′-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5′-methoxy[1,1′-biphenyl]-2-carbonitrile (**6hb**).* The product was prepared as described in **6da** and isolated as a yellow solid in 67% yield (615 mg): mp = 215−220 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 2953, 2846, 2222, 1651, 1635, 1504, 1256, 1179, 1060, 1029, 845; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.02−6.98 (m, 2H), 6.91 (dd, J = 8.7 Hz, J = 2.7 Hz, 1H), 6.81−6.77 (m, 2H), 6.55 (d, J = 2.8 Hz, 1H), 3.70 (s, 3H), 3.49 (s, 2H), 1.16 (s, 3H), 1.12 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 160.4, 141.9, 134.2, 131.4, 130.2, 129.2, 128.9, 128.8, 126.8, 126.0, 124.6, 120.9, 120.7, 78.0, 68.7, 33.2, 19.3; HRMS calcd for $C_{19}H_{19}N_2O_2^+$ $[M + H]^+$ 307.1447, found 307.1444.

*2-(6-Fluoro[1,1′-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**6ac**).* The compound was prepared as described in **6da** and isolated as a yellow solid in 78% yield (629 mg): mp = 105−106 °C; R_f = 0.43 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2787, 2671, 1649, 1502, 1456, 1361, 1234, 1193, 1080, 829, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95−7.93 (m, 2H), 7.48−7.46 (m, 1H), 7.40−3.36 (m, 2H), 6.86−6.76 (m, 3H), 4.15 (s, 2H), 1.40 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 163.1, 157.5, 155.6, 153.2 (d, J = 1.5 Hz), 131.7, 128.5, 128.4, 127.3, 116.6 (d, J = 7.6 Hz), 115.8, 115.6, 79.3, 67.4, 28.3; HRMS calcd for $C_{17}H_{17}FNO^+$ $[M + H]^+$ 270.1294, found 270.1299.

*4,4-Dimethyl-2-(4′-methyl[1,1′-biphenyl]-3-yl)-4,5-dihydrooxazole (**6fd**).* 3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenylmagnesium chloride was prepared via iodine−magnesium exchange using *i*-PrMgCl·LiCl at −20 °C for 3 h and combined with titanium reagent at −20 °C. After that, the temperature was raised to 0 °C, and the coupling reaction was conducted as described in **6da**. The product was isolated as a white solid in 83% yield (660 mg): mp = 117−118 °C; R_f = 0.44 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2962, 2921, 2885, 1642, 1608, 1497, 1313, 1194, 1069, 809; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.63−7.61 (m, 2H) 7.53−7.51 (m, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 4.15 (s, 2H), 2.40 (s, 3H), 1.42 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 162.1, 143.9, 137.8, 137.3, 129.6, 128.7, 127.0, 126.7, 126.5, 79.6, 67.2, 28.4, 21.1; HRMS calcd for $C_{18}H_{20}NO^+$ $[M + H]^+$ 266.1545, found 266.1539.

*Ethyl 3′-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)[1,1′-biphenyl]-4-carboxylate (**6jd**).* The compound was prepared as described in **6fd** and isolated as a white solid in 80% yield (811 mg): mp = 158−160 °C; R_f = 0.38 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2966, 2926, 1723, 1649, 1560, 1350, 1305, 1076, 1053, 966, 714; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 2H), 7.95 (d, J = 7.7 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.42−7.40 (m, 2H), 4.41 (q, J = 7.0 Hz, 2H), 4.12 (s, 2H), 1.40 (s, 6H), 1.26 (q, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 166.3, 162.1, 144.3, 131.2, 130.2, 129.0, 128.3, 128.2, 128.0, 127.2, 126.4, 125.8, 79.1, 67.5, 61.1, 20.4, 14.3; HRMS calcd for $C_{20}H_{22}NO_3^+$ $[M + H]^+$ 324.1600, found 324.1597.

*2-(4′-Fluoro[1,1′-biphenyl]-4-yl)-4,4-dimethyl-4,5-dihydrooxazole (**6ge**).* The product was prepared as described in **6fd** and isolated as a white solid in 85% yield (686 mg): mp = 68−70 °C; R_f = 0.55 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2967, 2929, 1643, 1512, 1364, 1271, 1207, 1029, 961, 802; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 6.93−6.89 (m, 2H), 6.79−6.76 (m, 2H), 4.14 (s, 2H), 1.40 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 162.5, 157.6, 155.9, 152.6, 137.7, 129.9, 116.4, 115.9, 115.7, 79.5, 67.7, 28.3; HRMS calcd for $C_{17}H_{17}FNO^+$ $[M + H]^+$ 270.1294, found 270.1289.

*[1,1′-Biphenyl]-2-carbaldehyde (**6af**).* The product was isolated as a colorless oil in 84% yield (458 mg): R_f = 0.55 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 2868, 2848, 1692, 1597, 1454, 1196, 1058, 750, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.03 (dd, J = 7.8 Hz, J = 1.1 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.48−7.44 (m, 4H), 7.40−7.37 (m, 2H), 7.33 (d, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 192.4, 146.0, 137.8, 133.6, 130.8, 130.1, 128.5, 128.2, 127.8, 127.6, 125.7. Data was consistent with that reported in the literature.[47]

*Ethyl 2′-Formyl[1,1′-biphenyl]-2-carboxylate (**6kf**).* The product was prepared as described in the typical procedure for **6af** and isolated as a white solid in 87% yield (662 mg): mp = 44−45 °C; R_f = 0.46 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 2980, 1712, 1598, 1443, 1365, 1290, 1256, 1132, 1082, 1049, 756, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.93 (dd, J = 7.8 Hz, J = 1.1 Hz, 1H), 7.90−7.88 (m, 1H), 7.84 (s, 1H), 7.58−7.54 (m, 3H), 7.47 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.36 (dd, J = 7.6 Hz, J = 0.9 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.02 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 192.2, 168.0, 142.7, 141.3, 136.2, 134.6, 131.5, 130.7,

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130.3, 129.7, 128.6, 128.4, 127.9, 127.1, 61.0, 13.8. Data was consistent with that reported in the literature.[48]

*Ethyl 4′-Formyl[1,1′-biphenyl]-4-carboxylate (**6jg**).*[11] The product was prepared as described in the typical procedure for **6af** and isolated as a light yellow solid in 82% yield (624 mg): mp = 62−63 °C; R_f = 0.45 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 2936, 1702, 1606, 1276, 1187, 1104, 771; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.16−8.14 (m, 3H), 7.92−7.88 (m, 2H), 7.71−7.68 (m, 2H), 7.65 (t, J = 7.7 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 192.0, 166.3, 143.9, 141.1, 137.1, 133.1, 130.3, 129.7, 128.2, 127.1, 61.1, 14.4.

*3′-(Trifluoromethyl)[1,1′-biphenyl]-2-amine (**6ih**).* The product was prepared as described in the typical procedure for **6af** and isolated as a light yellow oil in 79% yield (561 mg): R_f = 0.36 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 3456, 3390, 1610, 1509, 1475, 1456, 1340, 1168, 1133, 1095, 1074; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 5.2 Hz, J = 1.0 Hz, 1H), 7.28 (dd, J = 7.5 Hz, J = 1.3 Hz, 1H), 7.20 (dd, J = 3.5 Hz, J = 1.0 Hz, 1H), 7.15 (td, J = 7.9 Hz, J = 1.5 Hz, 1H), 7.11 (dd, J = 5.1 Hz, J = 3.2 Hz, 2H), 6.82−6.78 (m, 2H), 4.09 (br, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 143.2, 140.3, 132.5, 130.4, 130.2, 129.3, 129.2, 128.8, 126.1, 126.0 (q, J = 3.8 Hz), 124.0 (q, J = 3.7 Hz), 119.0, 115.0. Data was consistent with that reported in the literature.[49]

*2′-Methyl[1,1′-biphenyl]-2-amine (**6lh**).* The product was prepared as described in the typical procedure for **6af** and isolated as a light yellow oil in 78% yield (406 mg): R_f = 0.26 (petroleum ether/ethyl acetate = 10:1); IR (cm^{-1}, KBr) 3028, 1611, 1448, 1294, 1234, 908; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 1H), 7.47−7.46 (m, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.40−7.34 (m, 1H), 7.28−7.24 (m, 1H), 7.20 (d, J = 6.6 Hz, 1H), 7.17−7.14 (m, 1H), 7.11−7.10 (m, 1H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 143.2, 137.9, 134.5, 133.1, 131.2, 130.5, 130.4, 129.0, 128.9, 126.5, 119.0, 115.9, 18.5. Data was consistent with that reported in the literature.[49]

*4′-Chloro[1,1′-biphenyl]-4-amine (**6ei**).* The product was prepared as described in the typical procedure for **6af** and was isolated as a light yellow solid in 82% yield (499 mg): mp = 132−133 °C; R_f = 0.21 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3356, 3440, 1610, 1588, 1520, 1466, 1367, 1254, 1190, 1136, 1021, 789; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19−7.15 (m, 2H), 7.10−7.08 (m, 2H), 6.86−6.82 (m, 2H), 6.79 (d, J = 8.0 Hz, 2H), 4.00 (br, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 143.0, 137.8, 133.2, 130.5, 129.0, 126.6, 119.1, 116.0. Data was consistent with that reported in the literature.[50]

*2′-Methoxy[1,1′-biphenyl]-4-amine (**6 mi**).* The product was prepared as described in the typical procedure for **6af** and isolated as a light yellow oil in 73% yield (436 mg): R_f = 0.27 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 3366, 1610, 1489, 1295, 1028, 820, 770; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.7 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 6.95−6.87 (m, 2H), 6.57 (d, J = 8.6 Hz, 2H), 3.90 (s, 3H), 3.66 (br, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 155.9, 145.7, 133.6, 132.0, 128.7, 121.9, 116.8, 112.2, 111.7, 110.0, 56.2. Data was consistent with that reported in the literature.[51]

*4′-Methoxy-N,N-dimethyl[1,1′-biphenyl]-4-amine (**7bn**).* The product was isolated as a white solid in 85% yield (579 mg): mp =155−156 °C; R_f = 0.15 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 2897, 1612, 1507, 1248, 1177, 1040, 810; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.44 (m, 4H), 6.94 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.97 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 158.3, 149.5, 133.9, 129.4, 127.4, 127.3, 114.2, 113.1, 55.4, 40.8. Data was consistent with that reported in the literature.[52]

*4-Methoxy-4′-methyl-1,1′-biphenyl (**7bf**).* The product was prepared as described in the typical procedure for **7bn** and isolated as a white solid in 86% yield (511 mg): mp = 102−104 °C; R_f = 0.48 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 3030, 2965, 1608, 1300, 1270, 1214, 1180, 1011; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58 (m, 2H), 7.54 (d, J = 6.4 Hz, 2H), 7.30 (d, J = 6.2 Hz, 2H), 7.05−7.04 (m, 2H), 3.91 (s, 3H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 159.0, 138.0, 136.4, 133.8, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1. Data was consistent with that reported in the literature.[53]

*4-Fluoro-4′-methoxy-1,1′-biphenyl (**7bg**).* The product was prepared as described in the typical procedure for **7bn** and isolated as a white solid in 81% yield (491 mg): mp = 87−88 °C; R_f = 0.65 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 1607, 1488, 1251, 833, 760, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.52 (m, 3H), 7.46 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 6.99−6.96 (m, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.3, 160.9, 159.2, 137.0, 132.8, 127.5(q), 115.5 (d), 114.3, 55.3. Data was consistent with that reported in the literature.[52]

*4′-Methyl-3-(trifluoromethyl)-1,1′-biphenyl (**7bi**).* The product was prepared as described in the typical procedure for **7bn** and isolated as a light yellow oil in 81% yield (605 mg): R_f = 0.57 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 2955, 1610, 1335, 1126, 798; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.59−7.48 (m, 4H), 7.27 (d, J = 7.9 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 141.9, 138.0, 131.3, 131.0, 130.2, 129.7, 129.2, 127.0, 124.7 (d), 124.0 (d), 123.7 (q), 21.1. Data was consistent with that reported in the literature.[25,54]

*N,N-Dimethyl-4-(naphthalen-1-yl)aniline (**7cn**).* The product was prepared as described in the typical procedure for **7bn** and was isolated as a white solid in 77% yield (571 mg): mp = 68−69 °C; R_f = 0.44 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 3383, 2991, 1606, 1504, 1394, 1242, 1175, 804, 781; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.3 Hz, J = 3.8 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.51−7.38 (m, 6H), 6.86 (d, J = 8.5 Hz, 2H), 3.02 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 149.8, 140.6, 134.0, 132.0, 130.9, 129.0, 128.3, 126.9, 126.8, 126.4, 125.8, 125.7, 125.6, 112.4, 40.8. Data was consistent with that reported in the literature.[54]

*4′-Chloro-3-(trifluoromethyl)-1,1′-biphenyl (**7ei**).* The product was prepared as described in the typical procedure for **7bn** and isolated as a white solid in 73% yield (560 mg): mp = 98−99 °C; R_f = 0.59 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 1485, 1440, 1338, 1275, 1132, 907, 702 ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.87 (d, J = 7.5 Hz, 2H), 7.70−7.68 (m, 2H), 7.66−7.62 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 141.2, 139.4, 131.3 (q, J = 32.0 Hz), 130.4, 129.4, 129.1 (d, J = 3.8 Hz), 128.3 (d, J = 5.6 Hz), 127.0, 124.3 (q, J = 3.5 Hz), 124.1 (q, J = 270.0 Hz), 123.9 (q, J = 3.7 Hz); HRMS calcd for $C_{13}H_9ClF_3^+$ $[M + H]^+$ 257.0345, found 257.0342.

*Ethyl 2′-Cyano[1,1′-biphenyl]-2-carboxylate (**7kh**).* Both Grignard reagents were prepared via iodine−magnesium exchange using *i*-PrMgCl·LiCl according to Knochel's method. The titanium reagent and the aryl magnesium reagent were mixed at −40 °C. After that, the temperature was raised to −10 °C, and the coupling reaction was conducted as described in the typical procedure for **7bn**. The product was isolated as a white solid in 83% yield (625 mg): mp = 68−70 °C; R_f = 0.59 (petroleum ether/ethyl acetate = 20:1); IR (cm^{-1}, KBr) 2988, 2223, 1719, 1614, 1485, 1301, 1276, 1107, 1028, 713; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 1H), 7.65−7.62 (m, 1H), 7.57−7.54 (m, 2H), 7.50−7.43 (m, 2H), 7.37−7.24 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 167.2, 143.3, 135.0, 132.3, 132.0, 131.3, 131.0, 130.2, 129.9, 129.5, 128.8, 127.5, 127.1, 112.4, 53.5, 13.7. Data was consistent with that reported in the literature.[55]

*N,N,2′-Trimethyl[1,1′-biphenyl]-2-carboxamide (**7lo**).* 2-(Dimethylcarbamoyl)phenyl magnesium chloride was prepared via iodine−magnesium exchange using *i*-PrMgCl·LiCl at −40 °C for 2 h. The titanium reagent was added to this mixture at −40 °C. After that, the temperature was raised to 0 °C, and the coupling reaction was conducted at this temperature as described in the typical procedure for **7bn**.

The product was isolated as a white solid in 78% yield (559 mg): mp = 58−60 °C; R_f = 0.44 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 2970, 1643, 1426, 1330, 1291, 1124, 796, 720; ^1H NMR (400 MHz, DMSO) δ 7.87 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H), 7.57 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H), 7.47 (td, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.35−7.33 (m, 1H), 7.29 (dd, J = 7.4 Hz, J = 1.0 Hz, 1H), 7.25 (dd, J = 7.8

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Hz, J = 1.8 Hz, 1H), 7.18−7.15 (m, 1H), 7.13−7.11 (m, 1H), 3.02 (s, 3H), 2.74 (s, 3H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (DMSO, 100 MHz) δ 170.0, 143.3, 139.1, 137.7, 132.5, 131.6, 130.6, 128.9, 128.3, 128.1, 127.5, 124.7, 93.4, 38.2, 34.5, 22.9; HRMS calcd for $C_{16}H_{18}NO^+$ $[M + H]^+$ 240.1388, found 240.1385.

*N-(2′-Methyl[1,1′-biphenyl]-2-yl)benzamide (**7lp**).* The product was prepared as described in **7lo** and isolated as a white solid in 76% yield (655 mg): mp = 123−125 °C; R_f = 0.33 (petroleum ether/ethyl acetate =5:1); IR (cm^{-1}, KBr) 3342, 2924, 1655, 1518, 1468, 1156, 753, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.3 Hz, 1H), 7.79 (br, 1H), 7.56−7.50 (m, 3H), 7.45−7.42 (m, 4H), 7.34 (d, J = 7.0 Hz, 1H), 7.30 (s, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 6.91−6.87 (m, 1H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 165.2, 137.0, 136.9, 135.3, 134.6, 131.9, 131.0, 130.8, 130.1, 129.7, 128.8, 128.7, 127.0, 126.7, 124.4, 120.6, 115.1, 19.8; HRMS calcd for $C_{20}H_{18}NO^+$ $[M + H]^+$ 288.1388, found 288.1383.

*N-(4′-Methyl[1,1′-biphenyl]-2-yl)benzamide (**7fp**).*[56] The compound was prepared as described in **7lo** and isolated as a white solid in 76% yield (654 mg): mp = 116−117 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 3266, 2886, 1667, 1582, 1522, 1469, 1310, 1242, 1114, 751; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (br, 1H), 7.94 (d, J = 7.3 Hz, 2H), 7.65 (d, J = 7.4 Hz, 1H), 7.62−7.60 (m, 2H), 7.57 (d, J = 7.6 Hz, 2H); 7.52 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 165.8, 153.7, 138.9, 138.1, 134.3, 132.4, 130.0, 129.5, 129.1, 128.5, 127.3, 126.9, 126.4, 122.1, 115.2, 20.6.

*N-Phenyl[1,1′-biphenyl]-2-carboxamide (**7aq**).* The compound was prepared as described in **7lo** and isolated as a white solid in 74% yield (606 mg): mp = 119−120 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 3322, 3041, 1664, 1602, 1537, 1422, 1323; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58 (m, 1H), 7.56−7.52 (m, 2H); 7.44−7.42 (m, 2H), 7.22−7.18 (m, 4H), 7.14 (d, J = 7.9 Hz, 1H), 6.90−6.87 (m, 2H), 6.78 (d, J = 7.7 Hz, 2H), 6.14 (br, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 159.3, 149.4, 142.9, 139.9, 135.6, 133.1, 130.7, 130.5, 128.5, 128.0, 127.1, 127.0, 125.7, 125.0, 121.8. Data was consistent with that reported in the literature.[57]

*N-([1,1′-biphenyl]-4-yl)benzamide (**7ar**).* The compound was prepared as described in **7lo** and isolated as a white solid in 85% yield (696 mg): mp = 226−227 °C; R_f = 0.43 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 3433, 3064, 1650, 1531, 1434, 1322, 1072, 760, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.49−7.46 (m, 3H), 7.40−7.37 (m, 3H), 7.24 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 166.2, 156.1, 137.8, 134.8, 132.0, 129.6, 129.1, 128.8, 127.1, 124.7, 120.5, 120.3, 115.4. Data was consistent with that reported in the literature.[58]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01787.

^1H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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