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Palladium-Catalyzed *ortho*-C-H Arylation of Acetophenone Oxime Ethers with Aryl Pinacol Boronic Esters

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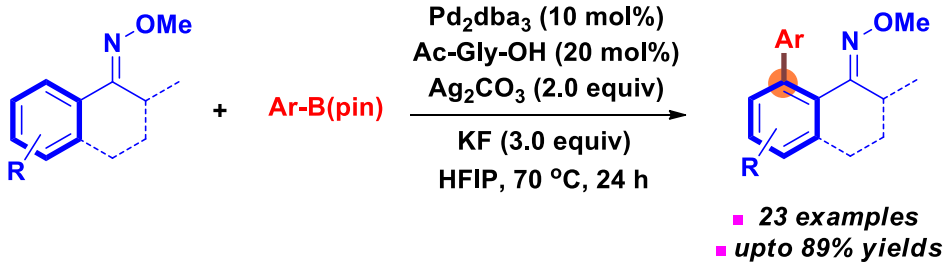


Abstract: We report an efficient palladium-catalyzed *ortho*-C-H arylation of acetophenone oxime ethers with aryl pinacol boronic esters, leading to the synthesis of biaryl derivatives in good yields. Sequential process of iridium-catalyzed C-H borylation and palladium-catalyzed *ortho* C-H arylation directed to access functionalized arenes.

Introduction

In recent years, direct C-H functionalization has emerged as an elegant pathway to construct precise and complicated natural scaffolds, and synthetic structural entities.[1] The sp^2 and sp^3 C-H bond activation interface with subsequent C-C bond formation reactions catalyzed by ruthenium, rhodium, palladium, iridium, and other metal complexes have been demonstrated.[2] Owing to this, recently many potential synthetic efforts have been made to pursue this goal.[3,4] In particular, *O*-methyl oximyl group has been applied in this field for *ortho*-acetoxylation and amination.[5] Synthesis of biaryl compounds[6] has consistently been of great interest in organic synthesis, due to their wide array of applications in pharmaceuticals and agrochemicals.[7] Various directing groups has been employed for palladium-catalyzed arylation of *ortho*-aromatic C-H bonds to synthesize biaryl motifs.[8] Direct C-H arylation of *O*-methyl oximyl group has also been accomplished by using aryl iodides,[9] aryldiazonium salts,[10] diaryliodonium salts,[11] acylperoxides,[12] and arenes as the coupling partners.[13]

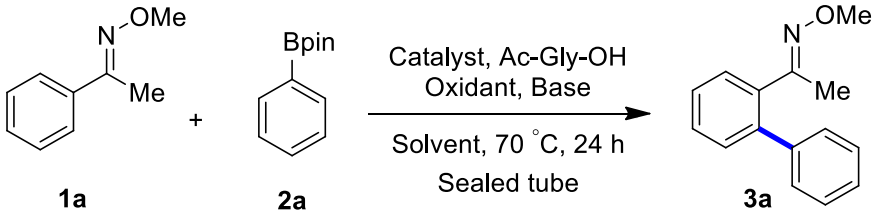
Indeed, aryl boronic acids[14] are extensively used as versatile precursors in transition-metal catalyzed cross-coupling reactions which include Suzuki-Miyaura cross-coupling reactions,[15] Cu-catalyzed C-O, C-N, C-S and C-Se coupling reactions,[16] Rh-catalyzed carbonyl conjugate addition reactions,[17] and very few examples of *O*-methyl oximyl group directed C-H arylation with aryl boronic acids as coupling reagents.[18]

The impact on stability of aryl pinacol boronates facilitate ease to handle and exhibits them to use under a variety of reaction conditions. To the best of our knowledge, the synthetic approach to biaryl products through Pd-catalyzed directed C-H arylation of *O*-methyl oximyl group with arylboronic esters has not been developed. Herein, we report a palladium-catalyzed *ortho*-C-H arylation of acetophenone oxime ethers with aryl pinacol boronic esters for the synthesis of biaryl derivatives. To our delight, this protocol shows remarkable mono-arylation selectivity. We also have achieved sequential cross-coupling with arenes *via meta*-C-H borylation followed by direct *ortho*-C-H arylation of acetophenone oxime ethers to afford functionalized biaryl skeletons.

Results and Discussion

Initially, we have conducted reaction with the combination of 1-phenyl-ethanone-*O*-methyl-oxime (**1a**), 3.0 equiv. of phenyl pinacol boronate (**2a**), 10 mol% of $Pd(OAc)_2$ as catalyst, 20 mol% of Ac-Gly-OH (*N*-acetyl glycine) as ligand, 2.0 equiv. of Ag_2CO_3 as oxidant and 3.0 equiv. of KF as base in 1,1,1,3,3,3-hexafluoropropanol (HFIP) as solvent at 70 °C for 24 h. The desired product (**3a**) was obtained in 39% yield (Table 1, entry 1). The reaction required excess amount of phenyl pinacol boronate (**2a**), because it was observed the formation of biphenyl as by-product *via* homo-coupling of phenyl pinacol boronate (**2a**) under these reaction conditions. Double transmetallation of active Pd-catalyst with phenyl pinacol boronate leads to the formation of diphenylpalladium (II) species, which underwent reductive elimination to give oxidative homo-coupling biphenyl by-product. Encouraged by this result, we attempted to further optimize the reaction conditions. Different solvents were tested first, and no desired product (**3a**) was obtained when DMSO, 1,2-dichloroethane (DCE) and 2-propanol were used as solvents (Table 1, entries 2-4).

Table 1. Screening of Reaction Conditions[a]



1a 2a 3a

entry	catalyst	base	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	KF	Ag_2CO_3	HFIP	39
2	$Pd(OAc)_2$	KF	Ag_2CO_3	DMSO	0
3	$Pd(OAc)_2$	KF	Ag_2CO_3	DCE	0
4	$Pd(OAc)_2$	KF	Ag_2CO_3	IPA	0
5	$Pd(OAc)_2$	KF	Ag_2CO_3	TFE	27
6	$Pd(OAc)_2$	$NaHCO_3$	Ag_2CO_3	HFIP	0
7	$Pd(OAc)_2$	CsOAc	Ag_2CO_3	HFIP	0
8	$Pd(OAc)_2$	Cs_2CO_3	Ag_2CO_3	HFIP	24
9	$Pd(OAc)_2$	Li_2CO_3	Ag_2CO_3	HFIP	22
10	$Pd(OAc)_2$	CsF	Ag_2CO_3	HFIP	35
11	$Pd(OAc)_2$	KF	AgOAc	HFIP	0
12	$Pd(OAc)_2$	KF	AgF	HFIP	trace
13	$Pd(OAc)_2$	KF	$AgSbF_6$	HFIP	trace
14	$Pd(OAc)_2$	KF	Ag_2O	HFIP	trace
15[c]	$Pd(OAc)_2$	KF	Ag_2CO_3	HFIP	0
16[d]	$Pd(OAc)_2$	KF	Ag_2CO_3	HFIP	0
17[e]	$Pd(OAc)_2$	KF	Ag_2CO_3	HFIP	0
18[f]	$Pd(OAc)_2$	KF	Ag_2CO_3	HFIP	29
19	$Pd(TFA)_2$	KF	Ag_2CO_3	HFIP	43
20	$Pd(dba)_2$	KF	Ag_2CO_3	HFIP	47
21	**$Pd_2(dba)_3$**	**KF**	**Ag_2CO_3**	**HFIP**	**68**
22[g]	$Pd_2(dba)_3$	KF	Ag_2CO_3	HFIP	50
23[h]	$Pd_2(dba)_3$	KF	Ag_2CO_3	HFIP	0
24[i]	$Pd_2(dba)_3$	KF	Ag_2CO_3	HFIP	66
25[j]	$Pd_2(dba)_3$	KF	Ag_2CO_3	HFIP	35
26[k]	$Pd_2(dba)_3$	KF	Ag_2CO_3	HFIP	0

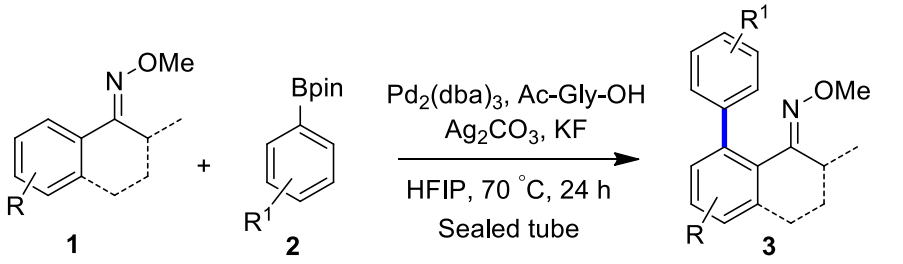
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv.), catalyst (10 mol%), Ligand (20 mol%), oxidant (2.0 equiv.), base (3.0 equiv.), and solvent (2.0 mL) in a sealed tube at 70 °C for 24 h. [b]Isolated yield. [c]1,10-Phenanthroline was used as ligand. [d]DPPE was used as ligand. [e]TMEDA was used as ligand. [f]PPh_3 was used as ligand. [g]5 mol% $Pd_2(dba)_3$ was used as catalyst. [h]$PhB(OH)_2$ instead of PhB(pin). [i]Phenyl hexylene glycol boronate instead of PhB(pin). [j]Phenyl neopentylglycol boronate instead of PhB(pin). [k]$PhBF_3K$ instead of PhB(pin).

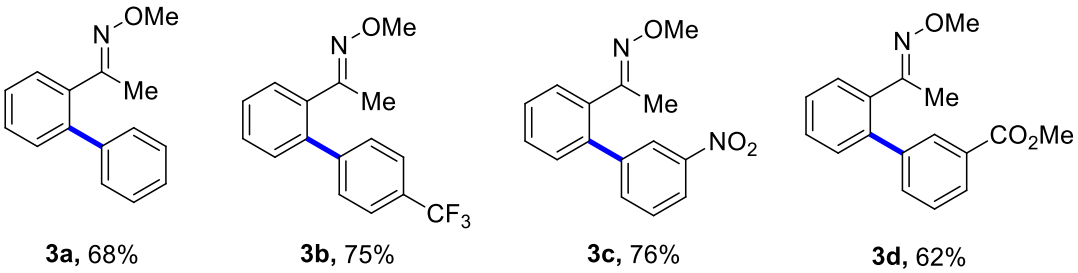
When the reaction was performed in CF_3CH_2OH (TFE), the product was obtained in lower yield as we compared with HFIP (Table 1, entry 5). These above results clearly demonstrate that fluorinated solvent plays a key role in this transformation.

We next examined the reaction using different bases and the result shows that no product was formed when $NaHCO_3$ and CsOAc were used. However, other bases such as Cs_2CO_3 and Li_2CO_3 could afford the product in lower yields (Table 1, entries 6-9). Replacing KF with CsF could not improve the yield of the product (Table 1, entry 10). No desired product or trace amount of product was observed, when AgOAc, AgF, $AgSbF_6$ and Ag_2O were used as oxidants (Table 1, entries 11-14). The choice of ligand was crucial in this transformation. The use of bidentate ligands such as 1,10-phenanthroline, 1,2-bis(diphenylphosphino)ethane (dppe) and TMEDA instead of Ac-Gly-OH failed to give the product (Table 1, entries 15-17). When PPh_3 was used as ligand, the product was obtained in 29% yield (Table 1, entry 18). Next, we tested the reaction with other Pd-catalysts such as $Pd(TFA)_2$, $Pd(dba)_2$, $Pd_2(dba)_3$ (Table 1, entries 19-21). Interestingly, $Pd_2(dba)_3$ gave a better result (68% yield) when compared with other Pd-catalysts (Table 1, entry 21). When the catalyst loading was reduced to 5 mol%, lower yield of the product was observed (Table 1, entry 22). The reactivity of various phenyl boronic sources [phenylboronic acid (**4**), phenyl hexylene glycol boronate (**5a**), phenyl neopentylglycol boronate (**5b**) and potassium phenyltrifluoroborate (**6**)] was also investigated (Table 1, entries 23-26). The output of these results revealed that phenyl pinacol boronate (**2a**) was best for this transformation.

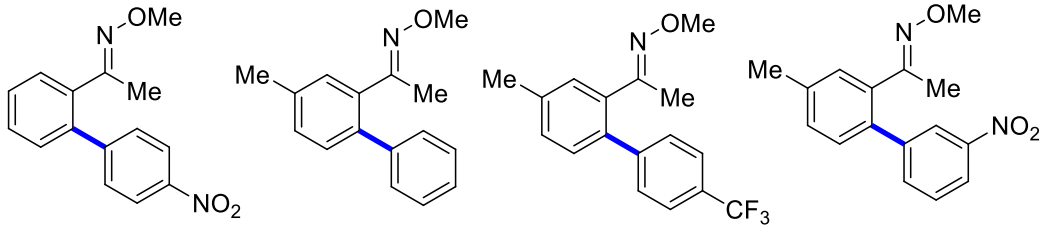
With these optimized conditions in hand, we examined the various scopes of the substrate (Table 2). In addition to the phenyl pinacol boronate (**2a**), other substituted phenyl pinacol boronates were also tested to couple with 1-phenyl-ethanone-*O*-methyl-oxime (**1a**). 4-Trifluoromethylphenyl (**2b**), 3-nitrophenyl (**2c**), 3-(methoxycarbonyl)phenyl (**2d**), and 4-nitrophenyl (**2e**) pinacol boronates were coupled well with 1-phenyl-ethanone-*O*-methyl-oxime (**1a**), and it provided the corresponding biaryl derivatives (**3b**-**3e**) in good yields.

Table 2. Substrate Scope with *O*-methyl oximes and Arylboronic esters[a,b]

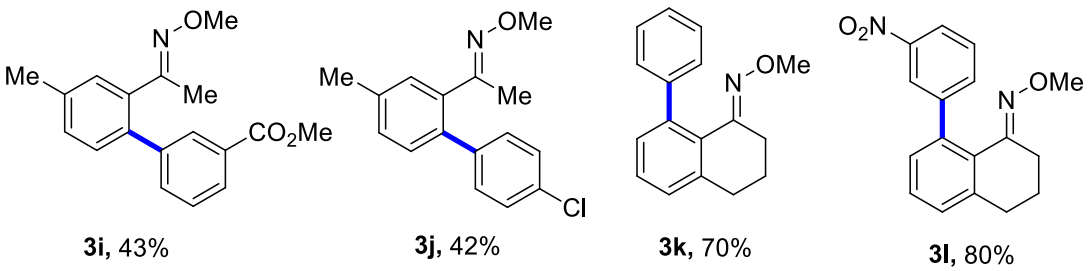




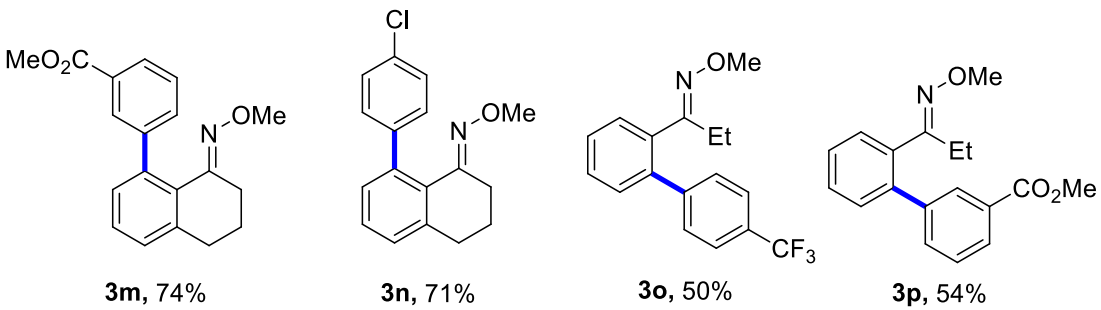
3a, 68% **3b**, 75% **3c**, 76% **3d**, 62%



3e, 74% **3f**, 80% **3g**, 65% **3h**, 70%



3i, 43% **3j**, 42% **3k**, 70% **3l**, 80%



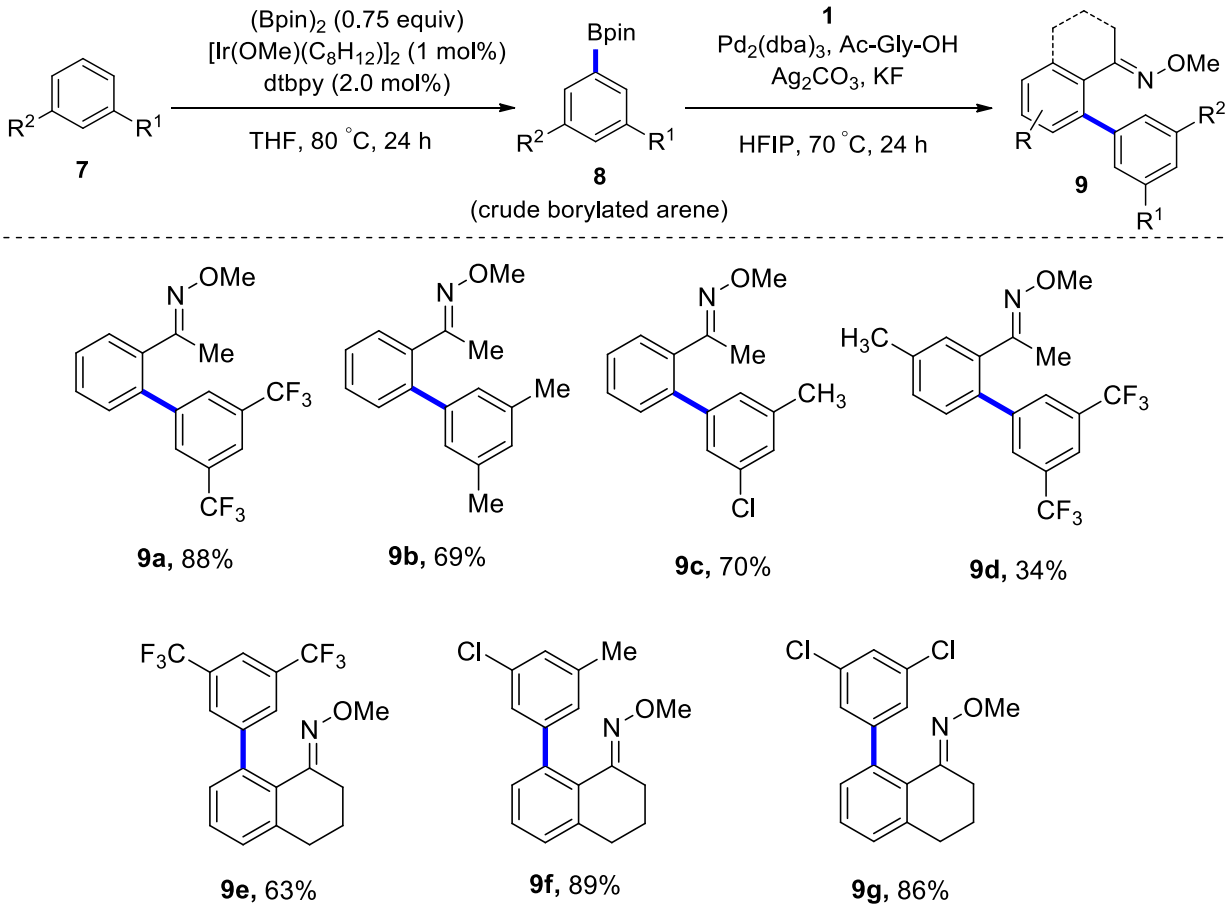
3m, 74% **3n**, 71% **3o**, 50% **3p**, 54%

[a]Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv.), $Pd_2(dba)_3$ (10 mol%), Ac-Gly-OH (20 mol%), Ag_2CO_3 (2.0 equiv.), KF (3.0 equiv.), and HFIP (2.0 mL) in a sealed tube at 70 °C for 24 h. [b]Isolated yield.

It is worthy to mention here that aryl pinacol boronates with electron-rich substituents such as 4-methyl and 4-methoxy groups failed to give the desired coupling products with 1-phenyl-ethanone-*O*-methyl-oxime (**1a**) as like phenylboronic acid and potassium phenyl trifluoroborate, whereas aryl

pinacol boronates with electron with-drawing substituents such as CF_3, NO_2 and CO_2Me gave better results in this transformation. Increasing the electron density in the aryl system of boronic esters, preferentially underwent homo-coupling over cross-coupling (coupling with other substrate). It was already clearly observed in case of phenylboronic acid and potassium phenyltrifluoroborate (Table 1) which are more electron-rich when compared with corresponding aryl boronic esters. 4-Methyl and 4-methoxy aryl boronic esters are also more electron rich substrates as like phenylboronic acid and potassium phenyltrifluoroborate when compared with other aryl boronic esters which contain electron with-drawing groups.

Table 3. Cross-Coupling of Acetophenone Oxime Ethers with 1,3-Disubstituted Arenes[a,b]



[a]Reaction conditions: step 1: **4** (1.0 mmol), Ir-catalyst (1.0 mol%) and dtbpy (2.0 mol%) in THF (2.0 mL) at 80 °C for 24 h; step 2: **1** (0.2 mmol), crude borylated arene as such, $Pd_2(dba)_3$ (10 mol%), Ac-Gly-OH (20 mol%), Ag_2CO_3 (2.0 equiv.), KF (3.0 equiv.), and HFIP (2.0 mL) in a sealed tube at 70 °C for 24 h. [b]Isolated yield.

The generality of this coupling reaction was further demonstrated by using aryl boronic esters with various ketoxime ethers, such as 1-(3-methylphenyl)-ethanone-*O*-methyl-oxime (**1b**),

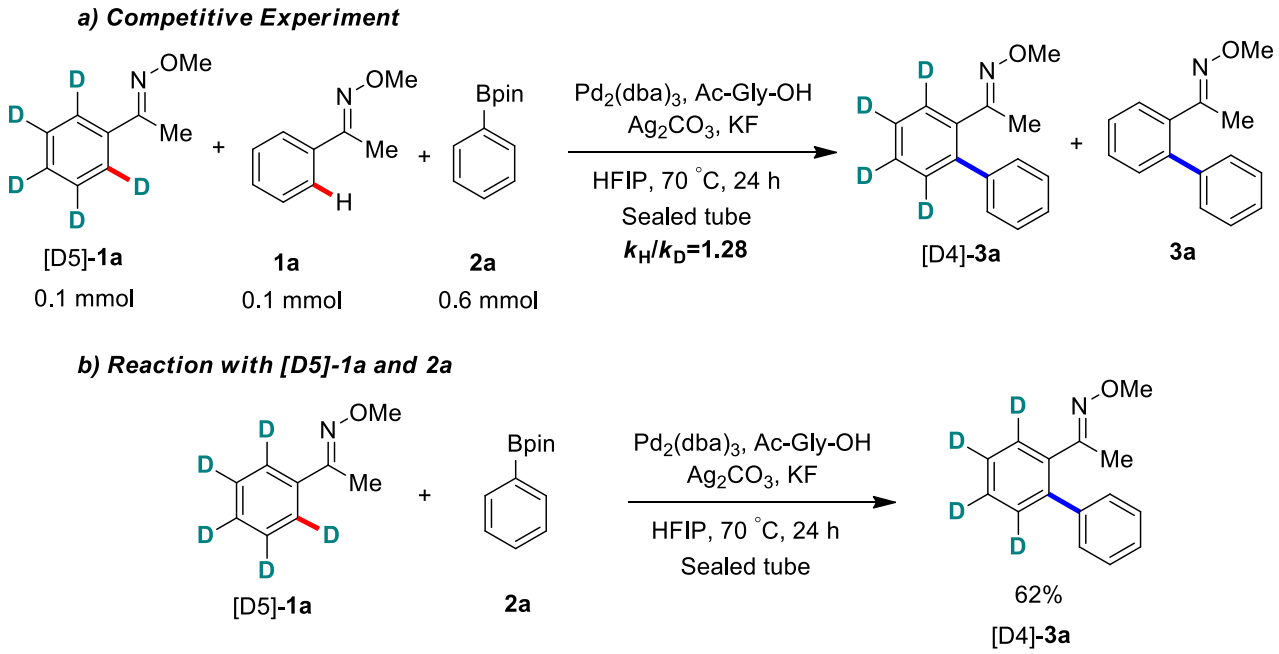
3,4-dihydro-2*H*-naphthalen-1-one-*O*-methyl-oxime (**1c**) and 1-phenyl-propan-1-one-*O*-methyl-oxime (**1d**) which afforded the corresponding biaryl derivatives (**3f-3p**) in moderate to good yields. Interestingly, we observed only mono-arylated products selectively at less steric hindrance site, and no double C-H arylation products were detected. The formation of mono-arylated products can be explained on the basis of availability of less steric hindrance sites in the substrate. Moreover, this protocol showed good functional group tolerance with trifluoromethyl, nitro and ester moieties.

Iridium-catalyzed C-H borylation is a powerful method to form aryl pinacol boronic esters with exclusive *meta*-selectivity. Stretching this strategy, iridium-catalyzed C-H borylation has been utilized as an intermediate for one-pot chemical transformations.[19,20] Inspired by this method, we next turned our attention towards the cross-coupling of acetophenone oxime ethers (**1**) with 1,3-disubstituted arenes (**7**) via sequential *meta*-C-H borylation followed by direct *ortho*-C-H arylation of acetophenone oxime ethers (Table 3). In this regard, 1,3-bis(trifluoromethyl)benzene (**7a**) was selected as a model substrate for iridium-catalyzed borylation, and it was executed under optimal reaction condition. After the reaction, the resultant reaction mixture was subjected to filtration, and the filtrate was concentrated under vacuum to remove the volatile components. Then, the existing crude borylated product (**8a**) was directly used as coupling partner for *ortho*-C-H arylation of acetophenone oxime ethers to attain the desired product (**9a**) in 88% yield. In addition to 1,3-bis(trifluoromethyl)benzene (**7a**), other arenes such as *meta*-xylene (**7b**), 3-chlorotoluene (**7c**) and 1,3-dichlorobenzene (**7d**) have also been applied for the iridium-catalyzed borylation followed by *ortho*-arylation with 1-phenyl-ethanone -*O*-methyl-oxime (**1a**), 1-(3-methylphenyl)-ethanone-*O*-methyl-oxime (**1b**) and 3,4-dihydro-2*H*-naphthalen-1-one-*O*-methyl-oxime (**1c**) to give the functionalized biaryls (**9a**-**9g**) in moderate to high yields. Trifluoromethyl and chloro functional group patterns were well tolerated in this sequential process.

The removal of directing group from resulting biaryl oxime (**3k**) was also performed using simple acid hydrolysis to give the corresponding ketone (**10**)[13] in 59% yield. To gain insight into mechanistic study of this C-H activation process, kinetic isotope effects (KIE) experiments were

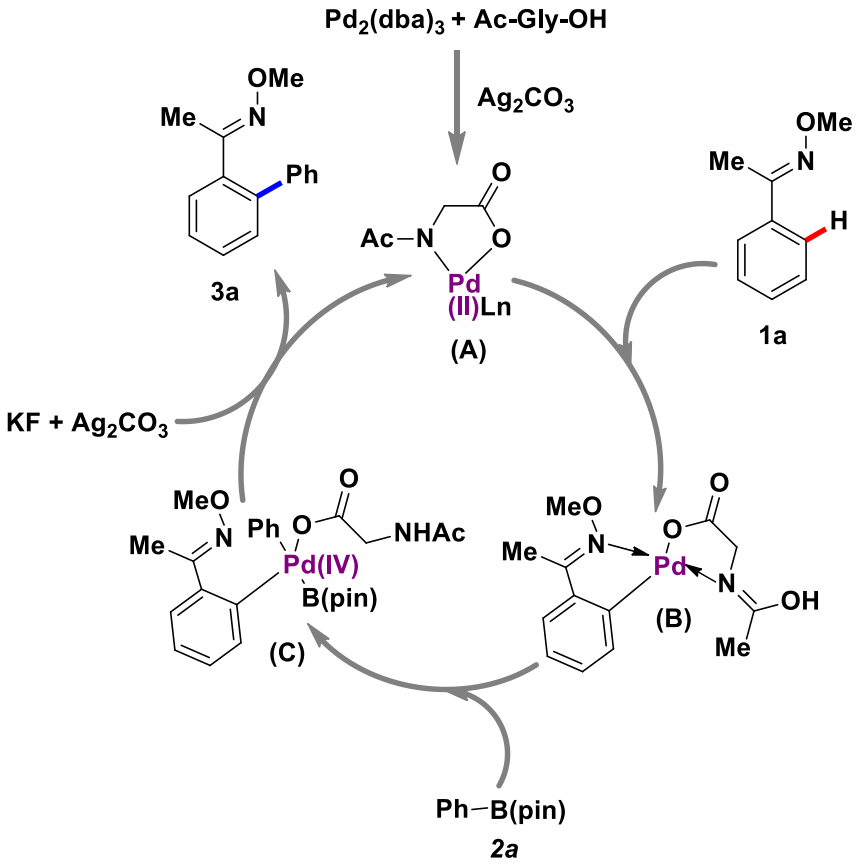
performed by using deuterated substrate [D5]-**1a**. Intermolecular H/D competition between [D5]-**1a** and **1a** with **2a** had a primary KIE value of 1.28, which indicated that the cleavage of C-H bond may not have considerable importance in the rate-determined step, although the initial step of oximyl-directing group assisted C-H(D) bond activation (Scheme 1a). To further probe the relevancy of C-H activation, a separate experiment was carried out between [D5]-**1a** and **2a** under identical reaction conditions, and product [D4]-**3a** was isolated in 62% yield (Scheme 1b).

Scheme 1. Kinetic Isotope Effects (KIE) Experiments



Although the mechanism of this transformation was not clear at this stage, based on experimental and literature[18,21] results we proposed a plausible mechanism for this work (Scheme 2). Initially, the active catalytic species **A** is formed from Pd-catalyst and the ligand Ac-Gly-OH in the presence of Ag_2CO_3, which then react with *O*-methyl ketoxime ether (**1a**) *via ortho* palladation to generate aryl Pd(II) species **B**. The species **B** further underwent transmetallation with arylpinacol boronate **2a** to produce diaryl Pd(IV) species **C**. Reductive elimination of **C** produced the desired *ortho*-arylated product **3a** and Pd(II) species to regenerate the catalytic cycle.

Scheme 2. Mechanistic proposal for Pd-Catalyzed Arylation



Conclusion

In summary, we have developed a palladium-catalyzed *ortho*-C-H arylation of acetophenone oxime ethers with aryl pinacol boronic esters leading to the formation of biaryl derivatives in moderate to good yields. Functionalized arenes can be prepared through sequential iridium-catalyzed C-H borylation followed by palladium-catalyzed *ortho*-C-H arylation.

Experimental Section

General Remarks

Experiments were performed under a dinitrogen atmosphere using standard Schlenk techniques unless otherwise stated. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). NMR spectra were recorded on a Varian Unity Inova-600 or a Varian Mercury-400 instrument using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Coupling constant (*J*) are reported in hertz (Hz). Standard abbreviations indicating

multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = double of doublet, q = quartet, m = multiplet, b = broad. Melting points (M.P.) were determined using a Büchi 535 apparatus and are reported uncorrected. GC-MS analyses were performed on a GC-MS analysis on Agilent Technologies 5977A GC equipped with Agilent 7890B MS. High-resolution mass spectra were carried out on a Jeol JMS-HX 110 spectrometer by the services at the National Chung Hsing University. All commercial chemicals were used as received except where noted. Aryl pinacol boronates[22] and ketoxime ethers[23] were all prepared through literature procedures.

Analysis: NMR spectra were recorded using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Coupling constant (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on 100 MHz spectrometer using broadband proton decoupling. Standard abbreviations indicating multiplicity were used as follows: brs (broad singlet), s (singlet), d (doublet), t (triplet), dd (double doublet), q (quartet), m (multiplet). Melting points (m.p.) were determined using an apparatus and are reported uncorrected. High-resolution mass spectra (HRMS) were performed on an electron ionization time-of-flight (EI-TOF) mass spectrometer.

General Procedure for the preparation of compounds 3.

To a mixture of *O*-methylacetophenoneoximes (0.2 mmol), $Pd_2(dba)_3$ (0.02 mmol, 10 mol%), arylboronic ester (0.6 mmol, 3.0 equiv), Ac-Gly-OH (0.04 mmol, 20 mol%), Ag_2CO_3 (0.4 mmol, 2 equiv) and KF (0.6 mmol, 3 equiv) was added HFIP (2 mL), and the resulting suspension was heated in a sealed tube at 70 °C for 24 h. After 24 h, the reaction mixture was cooled down to room temperature, and was filtered through a pad of silica gel and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (ether/hexane=1/99).

1-(Biphenyl-2-yl)ethanone *O*-methyloxime (3a):[24] Pale yellow oil; (0.031g, 68% yield); R_f = 0.75 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 3H), 3.96 (s, 3H), 7.32-7.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 61.7, 127.2, 127.4, 128.4, 128.9, 129.0, 129.2, 130.3, 136.8, 140.4, 141.0, 158.3.

1-(4'-Trifluoromethylbiphenyl-2-yl)ethanone *O*-methyloxime (3b): Pale yellow oil; (0.044g, 75% yield); R_f = 0.71 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.66 (s, 3H), 3.93 (s, 3H), 7.35-7.48 (m, 4H), 7.51 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 61.8, 124.2 (q, J = 270.5 Hz), 125.3 (q, J = 3.8 Hz), 128.2, 129.0, 129.3, 129.37, 129.41 (q, J = 23.5 Hz), 129.5, 130.2, 136.9, 138.9, 144.8, 157.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.46 (CF_3); HRMS (EI) calcd for $C_{16}H_{14}NOF_3$ $[M]^+$ 293.1027, found 293.1033.

1-(3'-Nitrobiphenyl-2-yl)ethanone *O*-methyloxime (3c): Pale yellow oil; (0.041g, 76% yield); R_f = 0.50 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 3.91 (s, 3H), 7.38-7.41 (m, 1H), 7.42-7.50 (m, 3H), 7.55-7.60 (m, 1H), 7.72 (dd, J = 7.8 Hz & 0.8 Hz, 1H), 8.19-8.23 (m, 1H), 8.29-8.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 61.8, 122.0, 123.8, 128.5, 129.1, 129.2, 129.4, 130.1, 135.1, 136.8, 137.8, 142.8, 148.1, 156.6; HRMS (EI) calcd for $C_{15}H_{14}N_2O_3$ $[M]^+$ 270.1004, found 270.1011.

1-(3'-Methoxycarbonylbiphenyl-2-yl)ethanone *O*-methyloxime (3d):[25] Pale yellow oil; (0.035g, 62% yield); R_f = 0.50 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 7.37-7.41 (m, 2H), 7.43-7.49 (m, 3H), 7.57-7.60 (m, 1H), 8.01-8.04 (m, 1H), 8.11-8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 52.2, 61.8, 127.8, 128.38, 128.41, 129.0, 129.2, 130.0, 130.2, 130.3, 133.5, 136.8, 139.3, 141.4, 157.6, 166.9; HRMS (EI) calcd for $C_{17}H_{17}NO_3$ $[M]^+$ 283.1208, found 283.1212.

1-(4'-Nitrobiphenyl-2-yl)ethanone *O*-methyloxime (3e): Pale yellow solid; m.p. 100-102 °C; (0.040g, 74% yield); R_f = 0.50 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 3H), 3.91 (s, 3H), 7.36-7.39 (m, 1H), 7.43-7.50 (m, 3H), 7.54-7.58 (m, 2H), 8.25-8.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 61.9, 123.6, 128.7, 129.1, 129.5, 129.8, 130.1, 136.8, 138.1, 146.9, 148.0, 156.7; HRMS (EI) calcd for $C_{15}H_{14}N_2O_3$ $[M]^+$ 270.1004, found 270.0994.

1-(4-Methylbiphenyl-2-yl)ethanone *O*-methyloxime (3f):[26] Pale yellow oil; (0.038g, 80% yield); R_f = 0.78 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 3H), 2.40 (s, 3H), 3.97 (s, 3H), 7.23-7.28 (m, 3H), 7.30-7.34 (m, 1H), 7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 21.0, 61.7, 127.0, 128.3, 128.9, 129.6, 129.8, 130.2, 136.5, 137.2, 137.6, 141.0, 158.6.

1-(4'-Trifluoromethyl-4-methylbiphenyl-2-yl)ethanone *O*-methyl oxime (3g): Pale yellow oil; (0.040g, 65% yield); R_f = 0.71 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 3H), 2.42 (s, 3H), 3.95 (s, 3H), 7.26 (s, 3H), 7.50 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 21.0, 61.8, 124.2 (q, J = 270.5 Hz), 125.2 (q, J = 3.4 Hz), 129.1 (q, J = 32.3 Hz), 129.2, 129.8, 130.0, 130.1, 136.1, 136.7, 138.1, 144.8, 157.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.45 (CF_3); HRMS (EI) calcd for $C_{17}H_{16}ONF_3$ $[M]^+$ 307.1184, found 307.1182.

1-(4-Methyl-3'-nitrobiphenyl-2-yl)ethanone *O*-methyloxime (3h): Pale yellow oil. (0.040g, 70% yield); R_f = 0.53 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 3H), 2.43 (s, 3H), 3.93 (s, 3H), 7.28 (s, 3H), 7.53-7.58 (m, 1H), 7.68-7.72 (m, 1H), 8.17-8.21 (m, 1H), 8.28-8.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 21.0, 61.8, 121.9, 123.8, 129.2, 129.9, 130.0, 130.1, 135.0, 135.1, 136.7, 138.6, 142.8, 148.2, 157.0; HRMS (EI) calcd for $C_{16}H_{16}N_2O_3$ $[M]^+$ 284.1161, found 284.1164.

1-(3'-Methoxycarbonyl-4-methylbiphenyl-2-yl)ethanone *O*-methyloxime (3i): Pale yellow solid; m.p. 77-80 °C; R_f = 0.44 (Et_2O/Hexanes, 1:99 v/v); (0.026g, 43% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 3H), 2.41 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 7.22-7.32 (m, 3H), 7.43-7.47 (m, 1H), 7.55-7.60 (m, 1H), 7.98-8.03 (m, 1H), 8.09-8.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 21.0, 52.2, 61.8, 128.2, 128.4, 129.7, 129.8, 130.0, 130.2, 130.3, 133.5, 136.5, 136.6, 137.7, 141.3, 158.0, 167.0; HRMS (EI) calcd for $C_{18}H_{19}NO_3$ $[M]^+$ 297.1365, found 297.1361.

1-(4'-Chloro-4-methylbiphenyl-2-yl)ethanone *O*-methyloxime (3j): Pale yellow oil; (0.023g, 42% yield); R_f = 0.72 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 3H), 2.40 (s, 3H), 3.96 (s, 3H), 7.22-7.27 (m, 3H), 7.31 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 21.0, 61.8, 128.5, 129.7, 129.9, 130.1, 130.2, 133.2, 136.3, 136.5, 137.6, 139.5, 158.1; HRMS (EI) calcd for $C_{16}H_{16}ClNO$ $[M]^+$ 273.0920, found 273.0923.

8-Phenyl-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (3k):[27] Pale yellow oil; (0.035g, 70% yield); R_f = 0.71 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.81-1.87 (m, 2H), 2.68-2.72 (m, 4H), 3.40 (s, 3H), 7.13-7.15 (m, 1H), 7.17-7.19 (m, 1H), 7.24-7.28 (m, 4H), 7.31-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 25.0, 30.8, 61.4, 125.8, 127.0, 127.6, 128.0, 129.0, 129.3, 129.5, 141.3, 142.2, 143.7, 153.1.

8-(3-Nitrophenyl)-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (3l): Pale yellow solid; m.p 87-89 °C; (0.047g, 80% yield); R_f = 0.56 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.82-1.89 (m, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.74 (t, J = 6.0 Hz, 2H), 3.36 (s, 3H), 7.13-7.15 (m, 1H), 7.21-7.26 (m, 1H), 7.29-7.33 (m, 1H), 7.46-7.50 (m, 1H), 7.57-7.59 (m, 1H), 8.13-8.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 25.0, 61.5, 120.8, 124.1, 128.2, 128.3, 129.1, 129.3, 135.4, 138.6, 142.3, 145.7, 147.8, 152.9; HRMS (EI) calcd for $C_{17}H_{16}N_2O_3$ $[M]^+$ 296.1161, found 296.1162.

8-(3-Methoxycarbonylphenyl)-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (3m): Pale yellow oil; (0.046g, 74% yield); R_f = 0.50 (Et_2O/Hexanes, 1:99 v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.82-1.88 (m, 2H), 2.68-2.73 (m, 4H), 3.36 (s, 3H), 3.91 (s, 3H), 7.15-7.18 (m, 2H), 7.26-7.29 (m, 1H), 7.36-7.42 (m, 1H), 7.43-7.46 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 25.0, 30.8, 52.0, 61.4, 127.1, 127.48, 127.53, 128.1, 129.2, 129.5, 130.1, 133.8, 140.2, 142.1, 144.2, 153.0, 167.3; HRMS (EI) calcd for $C_{19}H_{19}NO_3$ $[M]^+$ 309.1365, found 309.1360.

8-(4-Chlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (3n): Pale yellow oil; (0.041g, 71% yield); R_f = 0.72 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82-1.87 (m, 2H), 2.68-2.71 (m, 4H), 3.45 (s, 3H), 7.11-7.20 (m, 4H), 7.22-7.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 25.0, 30.8, 61.5, 127.4, 127.7, 127.8, 128.1, 129.2, 129.4, 130.3, 130.8, 131.8, 140.0, 142.3, 142.3, 153.0; HRMS (EI) calcd for $C_{17}H_{16}ClNO$ $[M]^+$ 285.0920, found 285.0922.

1-(4'-Trifluoromethylbiphenyl-2-yl)propanone *O*-methyl oxime (3o): Pale yellow oil; (0.031g, 50% yield); R_f = 0.66 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J =7.6 Hz, 3H), 2.10 (q, J = 7.6 Hz, 2H), 3.92 (s, 3H), 7.35-7.46 (m, 4H), 7.54 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 22.9, 61.8, 124.2 (q, J = 270.6 Hz), 125.2 (q, J = 3.8 Hz), 128.1, 128.3, 128.97 (q, J = 32.2 Hz), 129.0, 129.8, 130.0, 135.5, 139.0, 144.7, 162.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.45 (CF_3); HRMS (EI) calcd for $C_{17}H_{16}ONF_3$ $[M]^+$ 307.1184, found 307.1187.

1-(3'-Methoxycarbonylbiphenyl-2-yl)propanone *O*-methyl oxime (3p): Pale yellow oil; (0.032g, 54% yield); R_f = 0.44 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, J = 7.6 Hz, 3H), 2.09 (q, J = 7.6 Hz, 2H), 3.93 (s, 6H), 7.36-7.42 (m, 3H), 7.44-7.49 (m, 2H), 7.61-7.63 (m, 1H), 8.00-8.03 (m, 1H), 8.14-8.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 22.9, 52.2, 61.7, 127.7, 128.3, 128.4, 128.9, 129.9, 130.1, 130.2, 130.2, 133.6, 135.5, 139.3, 141.2, 162.9, 166.9; HRMS (EI) calcd for $C_{18}H_{19}NO_3$ $[M]^+$ 297.1365, found 297.1373.

General Procedure for Sequential *meta*-C-H borylation[28] and *ortho*-C-H arylation 9.

A mixture of arenes (1.0 mmol), $[Ir(OMe)(cod)]_2$ (1 mol%), B_2pin_2 (0.75 mmol, 1.5 equiv.) and 4,4′-Di-*tert*-butyl-2,2′-dipyridine (2 mol%), combined in THF (2 mL) was in schlenk tubes with nitrogen. The tubes were heated at 80°C for 24 h. Then the reaction mixture was filtered through a pad of silica gel and the filtrate was concentrated under vacuum. Then the resulting crude boronate was

transferred to a sealed tube which contains $Pd_2(dba)_3$ (0.02 mmol, 10 mol%), Ac-Gly-OH (0.04 mmol, 20 mol%), Ag_2CO_3 (0.4 mmole, 2 equiv) and KF (0.6 mmole, 3 equiv). To this mixture was added HFIP (2 mL) and heated at 70 °C for 24 h. After cooling down to room temperature, the reaction mixture was filtered through a pad of silica gel and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (ether/hexane=1/99).

1-[3', 5'-Bis(trifluoromethyl)biphenyl-2-yl]ethanone *O*-methyl oxime (9a): Pale yellow oil; (0.064g, 88% yield); R_f = 0.71 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 3H), 3.87 (s, 3H), 7.38-7.40 (m, 1H), 7.46-7.49 (m, 3H), 7.87-7.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 61.8, 120.8 (q, J = 3.4 Hz), 123.3 (q, J = 271.4 Hz), 128.9, 129.2, 129.3 (q, J = 3.4 Hz), 130.1, 131.5 (q, J = 33.4 Hz), 137.0, 137.3, 143.2, 156.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.93 (CF_3); HRMS (EI) calcd for $C_{17}H_{13}NOF_6$ $[M]^+$ 361.0901, found 361.0899.

1-(3',5'-Dimethylbiphenyl-2-yl)ethanone *O*-methyl oxime (9b): Light yellow oil; (0.035g, 69% yield); R_f = 0.66 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 3H), 2.33 (s, 6H), 3.98 (s, 3H), 6.98 (s, 1H), 7.01 (s, 2H), 7.31-7.36 (m, 2H), 7.39-7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 21.3, 61.7, 126.9, 127.1, 128.8, 128.8, 129.1, 130.2, 136.6, 137.7, 140.6, 140.9, 158.6. HRMS (EI) calcd for $C_{17}H_{19}NO$ $[M]^+$ 253.1467, found 253.1469.

1-(3'-Chloro-5'-methylbiphenyl-2-yl)ethanone *O*-methyl oxime (9c): Pale yellow oil; (0.038g, 70% yield); R_f = 0.72 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 3H), 2.36 (s, 3H), 3.96 (s, 3H), 7.08 (s, 1H), 7.15 (s, 1H), 7.20 (s, 1H), 7.34-7.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 21.2, 61.8, 126.1, 127.8, 127.9, 128.1, 128.9, 129.2, 130.1, 133.8, 136.7, 139.1, 139.7, 142.6, 157.8; HRMS (EI) calcd for $C_{16}H_{16}NOCl$ $[M]^+$ 273.0920, found 273.0918.

1-[3',5'-Bis(trifluoromethyl)-4-methylbiphenyl-2-yl]ethanone *O*-methyl oxime (9d): Pale yellow oil; (0.026g, 34% yield); R_f = 0.71 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s,

3H), 2.43 (s, 3H), 3.89 (s, 3H), 7.26-7.28 (m, 3H), 7.83-7.85 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 21.1, 61.8, 120.6 (q, J = 3.8 Hz), 123.3 (q, J = 271.0 Hz), 129.2, 129.9, 129.98, 130.0, 131.4 (q, J = 33.0 Hz), 134.4, 136.8, 139.0, 143.1, 156.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.94 (CF_3); HRMS (EI) calcd for $C_{18}H_{15}NOF_6$ $[M]^+$ 375.1058, found 375.1055.

8-[3,5-Bis(trifluoromethyl)phenyl]-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (9e): Pale yellow oil; (0.049g, 63% yield); R_f = 0.81 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82-1.89 (m, 2H), 2.69 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 3.36 (s, 3H), 7.12 (dd, J = 7.6 & 1.2 Hz, 1H), 7.23-7.25 (m, 1H), 7.29-7.33 (m, 1H), 7.72 (s, 2H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 24.9, 30.8, 61.4, 119.6 (q, J = 3.8 Hz), 123.6 (q, J = 271.3 Hz), 128.3, 128.7, 129.0, 129.3, 130.1, 130.5, 130.8, 131.1, 138.0, 142.3, 146.1, 152.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.78 (CF3); HRMS (EI) calcd for $C_{19}H_{15}NOF_6$ $[M]^+$ 387.1058, found 387.1055.

8-(3-Chloro-5-methylphenyl)-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (9f): Pale yellow oil; (0.053g, 89% yield); R_f = 0.81 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80-1.86 (m, 2H), 2.34 (s, 3H), 2.70 (t, J = 6.8 Hz, 4H), 3.47 (s, 3H), 6.96 (s, 1H), 7.06-7.15 (m, 4H), 7.23-7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.16, 21.21, 25.0, 30.8, 61.5, 126.3, 126.4, 127.5, 128.02, 128.04, 129.1, 129.4, 132.8, 138.8, 139.9, 142.1, 145.3, 152.9; HRMS (EI) calcd for $C_{18}H_{18}NOCl$ $[M]^+$ 299.1077, found 299.1070.

8-(3,5-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one-*O*-methyl oxime (9g): Pale yellow oil; (0.055g, 86% yield); R_f = 0.84 (Et_2O/Hexanes, 1:99 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80-1.87 (m, 2H), 2.68-2.73 (m, 4H), 3.50 (s, 3H), 7.08-7.10 (m, 1H), 7.14-7.20 (m, 3H), 7.25-7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 24.9, 30.8, 61.6, 125.7, 127.6, 128.11, 128.15, 129.0, 129.2, 133.7, 138.4, 142.2, 146.9, 152.7; HRMS (EI) calcd for $C_{17}H_{15}NOCl_2$$[M]^+$ 319.0531, found 319.0533.

Synthesis of [D4]-3a.

Compound **[D5]-1a** was synthesized according to the literature procedure.[29] To a mixture of **[D5]-1a** (0.2 mmol), $Pd_2(dba)_3$ (0.02 mmol, 10 mol%), phenylboronic ester **2a** (0.6 mmol, 3.0 equiv), Ac-Gly-OH (0.04 mmol, 20 mol%), Ag_2CO_3 (0.4 mmol, 2 equiv) and KF (0.6 mmol, 3 equiv) was added HFIP (2 mL), and the resulting suspension was heated in a sealed tube at 70 °C for 24 h. After 24 h, the reaction mixture was cooled down to room temperature, and was filtered through a pad of silica gel and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography to afford compound **[D4]-3a** as pale yellow oil in 62% yield (0.046g) (ether/hexane=1/99). R_f = 0.63 (Et_2O/Hexanes, 1:99 v/v); 1H NMR (400 MHz, CDCl3): δ 1.62 (s, 3H), 3.97 (s, 3H), 7.30-7.41 (m, 5H); 13C NMR (100 MHz, CDCl3): δ 16.5, 61.8, 127.2, 128.4, 128.9, 136.6, 140.3, 141.0, 158.3; HRMS (EI) calcd for C15H11D4NO [M]+ 229.1405, found 229.1401.

Synthesis of 8-phenyl-3,4-dihydronaphthalen-1(2*H*)-one (10).

The compound was readily obtained by hydrolysis of biphenyl *O*-methyl oxime **3k** following the literature procedure[29] with slight modification in 59% isolated yield. O-Methyl oxime **3k** (0.1 mmol), 12N HCl (0.5 mL) were added to a sealed tube. Then the mixture was stirred at 100 °C for 24 h. After completion of reaction, the reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were washed successively with saturated sodium bicarbonate and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuum. Then, the resulting residue was purified by silica gel flash chromatography to afford the desired product as a colorless solid (0.0131 mg, 59%). The spectral data were in accordance with the literature.[30]

ASSOCIATED CONTENT

Supporting information: ^{1}H and ^{13} NMR copies of compounds are available in supporting information file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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