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# Unified Protocol for Fe-Based Catalyzed Biaryl Cross Couplings between Various Aryl Electrophiles and Aryl Grignard Reagents

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# Unified Protocol for Fe-Based Catalyzed Biaryl Cross Couplings between Various Aryl Electrophiles and Aryl Grignard Reagents

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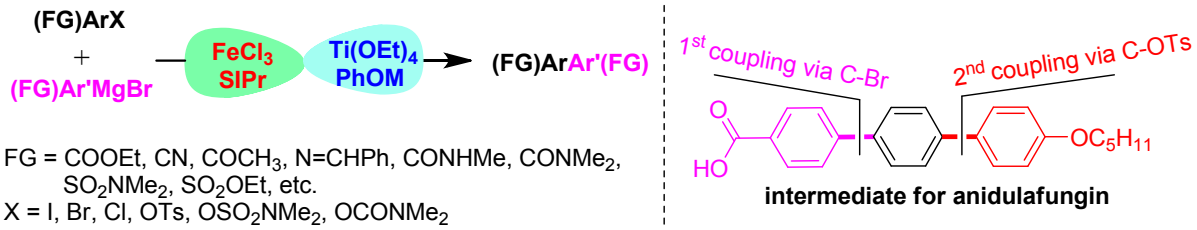
**RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)**

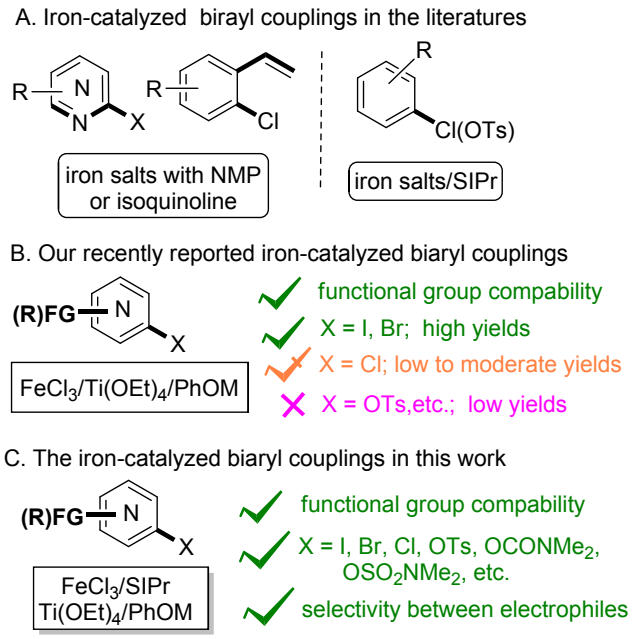



ABSTRACT. The combination of commonly used $FeCl_3$/SIPr with $Ti(OEt)_4$/PhOM enabled a highly general iron-based catalyst system which could efficiently catalyze the biaryl coupling reaction between various electrophiles (I, Br, Cl, OTs, $OCONMe_2$, $OSO_2NMe_2$) and common or functionalized aryl Grignard reagents with high functional group tolerance. Selective couplings of aryl iodides and bromides over the corresponding oxygen-based electrophiles have been achieved, and thus a terphenyl acid intermediate for anidulafungin was conveniently synthesized *via* an orthogonal coupling strategy.

## 1. INTRODUCTION

Iron is an ideal candidate for transition metal catalysts of various cross-couplings by virtue of its high abundance, low price and toxicity.[1] Although notable progresses have been made in Fe-catalyzed cross-couplings of Grignard reagents with various electrophiles between C($sp^2$) and C($sp^3$) centers,[2,3] yet there is still a big gap between the corresponding iron-catalyzed biaryl couplings and the Pd or Ni-catalyzed ones.[4,5] One main limitation which accounts for the gap is the fact that iron-catalyzed functional group tolerant biaryl couplings have been rather underdeveloped. Because of the inherent intolerance to functional group of Grignard reagents, Fe-catalyzed biaryl couplings of functionalized aryl halides with (functionalized) Grignard reagents remains a big challenge.[5] In contrast, Pd or Ni-catalyzed functional group tolerant biaryl couplings of (functionalized) Grignard reagents have made some progress due to their high catalytic activity based on well-designed ligands.[6,7] In addition to the coupling reactions of Grignard reagents, Pd or Ni catalyzed functional group tolerant biaryl couplings of other organometallic reagents such as boron (Suzuki coupling), zinc reagents (Negishi coupling) and *etc.* have been well developed;[4] however, the successful examples of Fe-catalyzed biaryl Suzuki or Negishi couplings are very rare. Only one Fe-catalyzed biaryl Negishi coupling reaction of 2-halopyridines or pyrimidines has been reported so far.[8] Meanwhile, until very recently, only one Fe-catalyzed substrate-directed (*N*-pyrrole 2-chlorobenzamides) biaryl Suzuki coupling reaction has been documented.[9]

Two main types of iron catalysts have been reported for the biaryl couplings of aryl Grignard reagents (Scheme 1A).[5,10] Iron salts in the presence of NMP or isoquinoline were mainly applicable to 2-(pseudo) halides of electron-deficient *N*-heteroarenes (pyridines or quinolones)[10a,e,f] and chlorostyrene.[10d] Instead, salts/SIPr could efficiently catalyze the biaryl couplings of common aryl chlorides or pseudohalides.[10b,c,g,h] For these two iron catalysts, aryl bromides and iodides (except 2-halopyridines or analogues[10a,e,f,11]) were incompatible substrates due to dehalogenation and consequent homocoupling side reactions.[9,10b,c,12] Thus, only a limited number of unfunctionalized aryl chlorides or pseudohalides were suited to the Fe-catalyzed biaryl cross couplings; this is another reason for the large gap between Fe catalysis and Pd or Ni catalysis in this area.



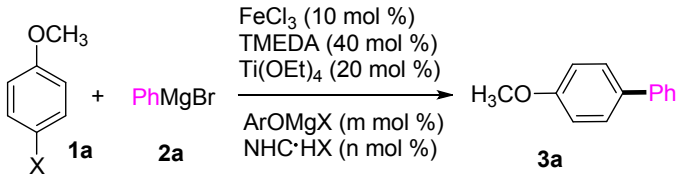

**Scheme 1.Variousiron-catalyzed biaryl couplings**

Recently, we have reported a phenolate mediated Fe/Ti cocatalyzed biaryl coupling reaction,[13] in which a variety of important functional groups in either coupling partner could be well tolerated in the absence of NHC or phosphine ligands, and various (functionalized) aryl halides could undergo the coupling reaction without dehalogenation (Scheme 1B). However, the reaction could not be applied to oxygen-based electrophiles such as ArOTs and *etc*.[14] Besides, the reactions of chlorides only gave low to acceptable yields. Herein, we report a highly general Fe/Ti cocatalyst system that can efficiently catalyze the biaryl couplings between various arylhalides as well as oxygen-based electrophiles and aryl Grignard reagents with high functional group tolerance (Scheme 1C). Since the present reaction could accommodate various aryl electrophiles and tolerate a variety of important functional groups, we expect that it will become a highly general protocol for Fe-based catalyzed biaryl couplings.

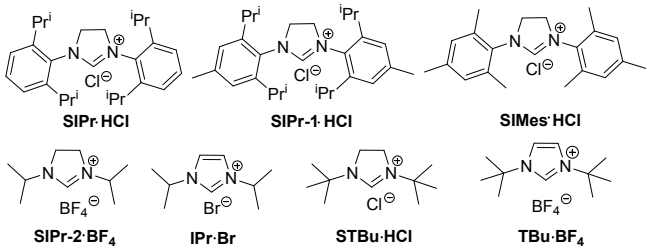
## 2. RESULTS AND DISSCUSSION

Our research started with an investigation of the phenolate mediated Fe/Ti cocatalyzed reaction of 4-$MeOC_6H_4X$ (**1a**) with PhMgBr (**2a**), and the results were outlined in Table 1. It could be seen that in the absence of NHC, the coupling of 4-$MeOC_6H_4Cl$ only gave 10% yield of the desired product

**Table 1. Reaction condition optimization**[a]




| entry | X | m | n | NHC | ArO | yield [%] |
|---|---|---|---|---|---|---|
| 1 | Cl | 20 | 0 | - | PhO | 10 |
| 2 | Cl | 10 | 0 | - | *p*-$C_6H_4O_2$ | 51 |
| 3 | Cl | 10 | 0 | - | *o*-$C_6H_4O_2$ | 45 |
| 4 | Cl | 10 | 0 | - | *m*-$C_6H_4O_2$ | 45 |
| 5 | Cl | 20 | 10 | SIPr[b,c] | PhO | 80 |
| 6 | Cl | 0 | 10 | SIPr | -- | 53 |
| 7 | Cl | 10 | 10 | SIPr | *p*-$C_6H_4O_2$ | 78 |
| 8 | Cl | 20 | 10 | SIPr-1 | PhO | 79 |
| 9 | Cl | 20 | 10 | SIMes | PhO | 39 |
| 10 | Cl | 20 | 10 | SIPr-2 | PhO | 48 |
| 11 | Cl | 20 | 10 | IPr | PhO | 35 |
| 12 | Cl | 20 | 10 | STBu | PhO | 42 |
| 13 | Cl | 20 | 10 | TBu | PhO | 61 |
| 14 | OTs | 20 | 0 | - | PhO | 12 |
| 15 | OTs | 20 | 10 | SIPr | PhO | 75(80)[d] |
| 16 | $OSO_2NMe_2$ | 20 | 0 | - | PhO | 7 |
| 17 | $OSO_2NMe_2$ | 20 | 10 | SIPr | PhO | 73(78)[d] |
| 18 | $OCONMe_2$ | 20 | 0 | - | PhO | 9 |
| 19 | $OCONMe_2$ | 20 | 10 | SIPr | PhO | 72(79)[d] |
| 20 | Br | 20 | 0 | - | PhO | 85 |
| 21 | Br | 20 | 10 | SIPr | PhO | 87 |
| 22 | I | 20 | 0 | - | PhO | 88 |
| 23 | I | 20 | 10 | SIPr | PhO | 89 |




[a]The reaction was carried on 2 mmol scale at 78 °C in THF/PhMe (3:1), and 1.5 equiv of PhMgBr was charged (10 mol % NHC·HCl was added) unless otherwise noted. [b]The optimization of the amount of NHC indicated that 5 mol % SIPr only gave a 45% yield; instead 20 mol % SIPr gave a 75% yield. [c]Below was a list of NHC structures. [d]The yields in brackets were obtained with 2.0 equiv of PhMgBr.

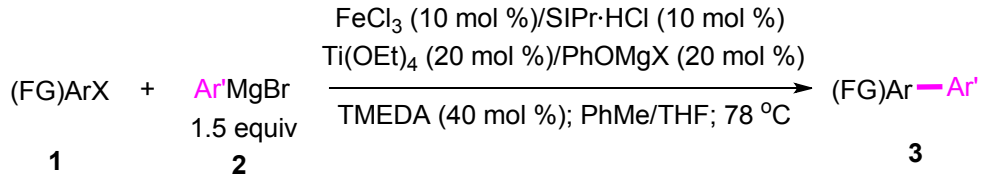
(entry1).[13] The use of salts of benzenediol instead of PhOMgBr could raise the yields up to 51% (entries 2-4). To our delight, the combination of commonly used $FeCl_3$/SIPr[10b,c,g,h] with $Ti(OEt)_4$/PhOM could promote the coupling in 80% yield (entry 5). In contrast, the absence of phenolate only gave 53% yield

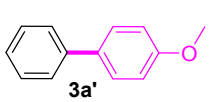
(entries 5-7). For the present $FeCl_3$/SIPr/$Ti(OEt)_4$/ArOM catalyst system, the use of *p*-$C_6H_4(OMgBr)_2$ instead of PhOMgBr did not improve the yield of **3a**. Among the tested NHC ligands (entries 8-13), SIPr and SIPr-1 gave the best yields while the other NHCs could only result in low to moderate yields.[15] Meanwhile, this catalyst could catalyze the couplings of 4-$MeOC_6H_4OTs$, 4-$MeOC_6H_4OSO_2NMe_2$, 4-$MeOC_6H_4OCONMe_2$ with the yields of 75%, 73% and 72% respectively, whereas in the absence of SIPr, the corresponding yields were rather low (entries 14 *vs* 15; 16 *vs* 17 and 18 *vs* 19). We also found that the increase of the amount of Grignard reagents to 2.0 equivalents could further raise the yields of these oxygen-based electrophiles to nearly 80% without observable side reactions (entries 15, 17 and 19). It should be noted that in previously reported Fe-catalyzed biaryl couplings, iron salts/NHC used to result in dehalogenation and consequent side homocoupling with aryl bromide and iodide substrates.[9,10b,c,12] In sharp contrast, our present catalysts could still promote the couplings of the bromide and iodide in high yields with those side reactions being well suppressed (entries 20-23). Thus, to best of our knowledge, the present iron-based catalyst system proves to be most general for various electrophiles until now.

With the optimal reaction conditions at hand, we then investigated the scope of this reaction. Initially, various aryl electrophiles including those bearing sensitive functional groups were tested with different common aryl Grignardreagents and the results were outlined in Scheme 2 (**3a′-o**). In general, various iodides and bromides could still couple well to furnish the biaryl products in high yields without observable dehalogenation and homocoupling side reactions. Although the presence of SIPr did not significantly affect the yields of iodides (**3e** and **3f**), it could raise the yields of bromides by about 10% in most cases (**3c-o**). The yields of the chlorides had been improved significantly under the present conditions (**3a-o**). On the other hand, various oxygen-based electrophiles such as ArOTs, $ArOSO_2NMe_2$, $ArOCONMe_2$ could hardly undergo the biaryl cross coupling in the absence of NHC ligands, however, they could participate in the couplings to afford the desired products in the yields ranged from 46% to 78% (**3a-o**) under the catalysis of the present catalyst system. Their yields seemed

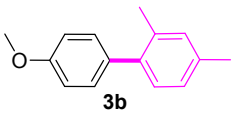
comparable to those of chlorides. For the reactions of chlorides and oxygen-based electrophiles, the increase of the amount

**Scheme 2. Biaryl couplings of various electrophiles with Common Grignard reagents**[a]

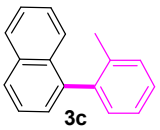


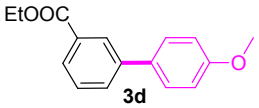

I: 90%; Br: 88%
Cl: 77% (33%)[b]
OTs: 70%
$OSO_2NMe_2$: 68%
$OCONMe_2$: 78%



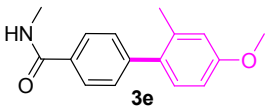

Br: 88%
Cl: 79% (19%)[b]
OTs: 71%
$OSO_2NMe_2$: 66%
$OCONMe_2$: 73%



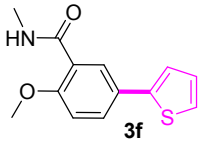

Br: 78% (61%)[b]
OTs: 69%; 74%[c]
$OSO_2NMe_2$:46%; 67%[c]
$OCONMe_2$: 62%; 71%[c]



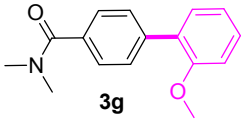

Br: 88% (76%)[b]
Cl: 68% (56%)[b]
OTs: 71%
$OSO_2NMe_2$: 67%
$OCONMe_2$: 78%



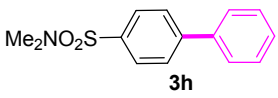

[d]I: 89% (88%)[b]
[d]Br: 82% (71%)[b]
[d]Cl: 70% (53%)[b]



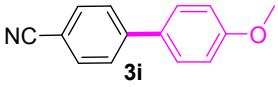

[d]I: 84% (85%)[b]
[d]Br: 77% (65%)[b]
[d]Cl: 62% (34%)[b]



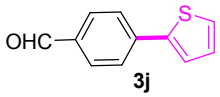

Br: 85% (75%)[b]
Cl: 67% (34%)[b]
OTs:69%
$OCONMe_2$: 72%



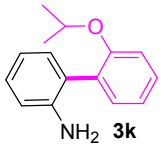

Br: 90%
Cl: 80% (71%)[b]



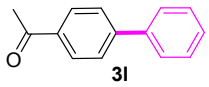

Br: 88% (76%)[b]
Cl: 78% (65%)[b]
OTs: 71%
$OCONMe_2$: 69%



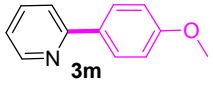

[e]Br: 71%;(62%)[b]
[e]Cl: 59% (40%)[b]



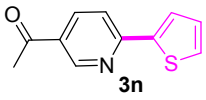

[f]Br: 81% (75%)[b]
[f]Cl: 65% (43%)[b]



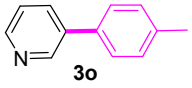

Br: 73% (60%)[b]
Cl: 59% (23%)[b]
OTs: 58%; 71%[c]
$OCONMe_2$: 42%; 61%[c]




Br: 90% (88%)[b]
Cl: 89% (80%)[b]
OTs: 69%
$OSO_2NMe_2$: 68%




Br: 83%
Cl: 81% (62%)[b]



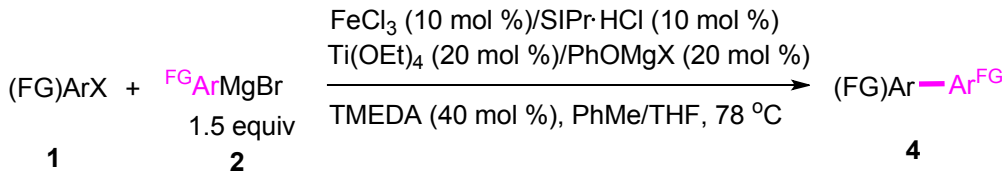

Br: 90% (85%)[b]
Cl: 89% (80%)[b]
OTs: 66%
$OSO_2NMe_2$: 67%

[a]The reaction was carried on 2 mmol scale at 78 °C. [b]The yields in the parentheses were obtained without SIPr·HCl. [c]The yields were obtained with 2.0 equiv of ArMgX. [d]One more equivalent of ArMgX was added. [e]$C_6H_5N{=}CHC_6H_4X$ was used as an electrophile. [f]ArX was $C_6H_5CH{=}NC_6H_4X$.

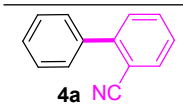
of ArMgX could further raise the yields of the desired biaryls (**3c** and **3l**). Notably, various sensitive functional groups including easily enolizable ketone (**3l** and **3n**), ester (**3d**), nitrile (**3k**), amide (**3e-3g**), sulfamide (**3h**) and aldimine (**3j** and **3k**) groups could be well tolerated and no noticeable products resulted from the addition of Grignard reagents to these groups were found. Besides, the cross-couplings for sterically hindered biaryls could also be achieved smoothly (**3b**, **3c** and **3k**). Heteroaryl Grignard

reagents and electrophiles were well compatible with this biaryl coupling reaction, and provided the heteroaryl-containing biaryls in good yields (**3f**, **3j**, **3m**, **3n** and **3o**).

**Scheme 3. Biaryl couplings of various electrophiles with Functionalized Grignard reagents**[a]

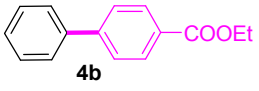



**1** **2** **4**



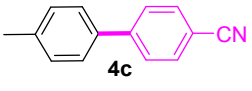

**4a**

I: 90%; Br: 86%
Cl: 71% (40%)[b]
OTs: 74%; 78%[c]
$OSO_2NMe_2$: 65%
$OCONMe_2$: 63%



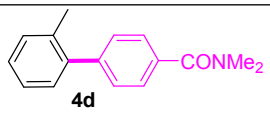

**4b**

I: 87% (79%)[b]
Br: 85% (83%)[b]
Cl: 67% (38%)[b]
OTs: 62%; 71%[c]



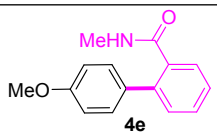

**4c**

I: 80% (70%)[b]
Br: 79% (63%)[b]
Cl: 62% (30%)[b]
$OCONMe_2$: 63%; 72%[c]



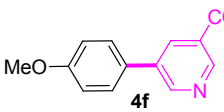

**4d**

I: 80% (78%)
Br: 75% (60%)[b]
Cl: 62% (30%)
OTs: 64%
$OSO_2NMe_2$: 72%



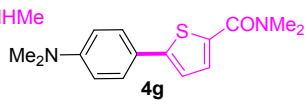

**4e**

I: 81% (70%)[b]
Br: 74%
Cl: 67% (43%)[b]
OTs: 57%;69%[c]



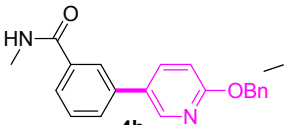

**4f**

I: 81%
Br: 74%
Cl: 63% (32%)[b]



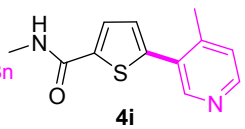

**4g**

I: 79%
Br: 68% (51%)[b]
Cl: 57% (21%)[b]



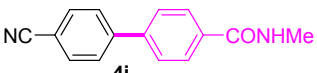

**4h**

[d]I: 85%
[d]Br: 82%
[d]Cl: 69% (42%)[b]



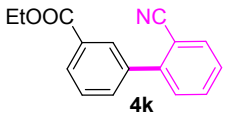

**4i**

[d]Br: 81% (70%)[b]



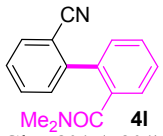

**4j**

Br: 80% (76%)[b]
Cl: 68% (31%)[b]
$OCONMe_2$: 66%
$OSO_2NMe_2$: 63%



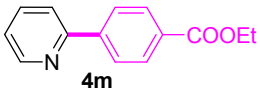

**4k**

Br: 72% (31%)[b]
OTs: 66%
$OSO_2NMe_2$: 63%



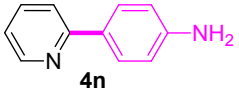

**4l**

Cl: 78% (53%)[b]
OTs: 74%
$OCONMe_2$: 75%



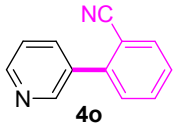

**4m**

Br: 88%
Cl: 84% (80%)[b]
OTs: 72%




**4n**

[e]Br: 79%
[e]Cl: 69%
[e]OTs: 65%




**4o**

Br: 78%
Cl: 67% (32%)[b]
OTs: 68%

[a]The reaction was carried on 2 mmol; the functionalized Grignard reagents were prepared by I/Mg exchange using *i*-PrMgCl·LiCl and the concomitant *i*-PrI was removed. [b]The yields in the parentheses were obtained without SIPr. [c]The yields were obtained with 2.0 equiv of ArMgX. [d]One more equivalent of ArMgX was added. [e]Grignard reagent was $C_6H_5CH{=}NC_6H_4MgCl{\cdot}LiCl$.

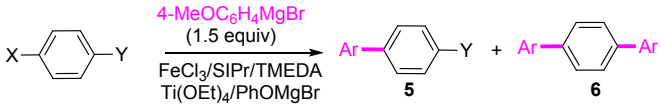
The couplings of Knochel-type functionalized Grignard reagents were also investigated using the present protocol, and the results were summarized in Scheme 3 (**4a-o**). It can be seen that although the functionalized aryl Grignard reagents were only stable at low temperature,[7,16] yet under the current reaction conditions they could still undergo the desired coupling reaction at elevated temperature as we previously reported.[13] Besides, although the Fe salts/SIPr catalyzed biaryl couplings of ArCl, ArOTs

and $ArOSO_2NMe_2$ had been reported,[10h,17] to the best of our knowledge, the couplings with sensitive functional group(s) in ether partners have been elusive to date. Our experiments clearly showed that these previously challenging couplings could be well realized under our present conditions. Once again, the present catalytic system was efficient for various aryl electrophiles. The yields of the iodides and bromides were good in most cases in the absence of NHC (**4a-o**). Upon addition of SIPr ligand, the yields of both the iodides and the bromides were further increased, demonstrating clearly that the present combination of Fe salts with SIPr did not result in dehalogenation as previously reported.[9,10b,c,12] In our previous reports,[13] the yields of couplings between aryl chlorides and functionalized Grignard reagents were rather low without SIPr. Under the present conditions, the yields of aryl chlorides were significantly improved (**4a-m**). Similarly, the couplings of various oxygen-based electrophiles such as ArOTs, $ArOSO_2NMe_2$, $ArOCONMe_2$ could be also achieved with Knochel-type functionalized Grignard reagents (**4a-m**). On the whole, the yields of the couplings of ArOTs, $ArOCONMe_2$ and $ArOSO_2NMe_2$ compared to those of the corresponding aryl chlorides. Besides, increasing the amount of Grignard reagents could increase the yields of the reactions with these oxygen-based electrophiles (**4a-e**).

Functionalized heteroaryl Grignard reagents could undergo the biaryl coupling well (**4f-i**). Besides, the reaction continued to proceed smoothly even if functional groups were present on both coupling substrates, and thus bifunctional biphenyls were conveniently furnished (**4j-m**). It should be noted that the unprotected amide groups (CONHMe), after neutralized by a Grignard reagent, had a strong complexation with iron, and thus often acted as a directing group for Fe-catalyzed *ortho* C-H activation.[18] Up to date, the Fe-catalyzed couplings of the arylmagnesium reagents bearing this function at 3 or 4-position remains elusive, probably due to the facts that the strong binding with iron might inhibit the catalytic reaction or result in *ortho* C-H activation as a side reaction. Our experiments clearly showed that these challenging Fe-catalyzed couplings of such Grignard reagents could be well achieved under the present conditions (**4e**, **4f** and **4j**). Additionally, functionalized aryl pyridines (**4m-o**) were

also assembled through the couplings of pyridyl halides or sulphonates with functionalized Grignard reagents.

**Table 2 Reactivity comparison of the electrophiles**[a]



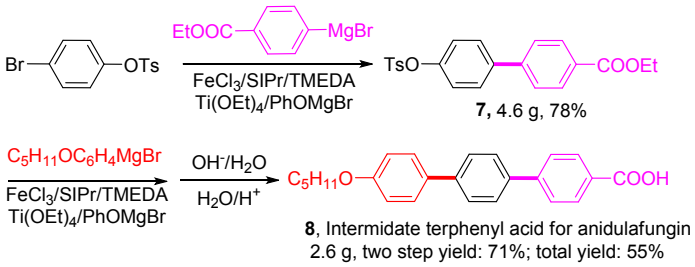

| Entry | X | Y | Yield (%) | |
|---|---|---|---|---|
| | | | **5** | **6** |
| 1 | I | Br | **5a**, 88 | **6**, trace |
| 2 | Br | Cl | **5b**, 79 | **6**, 8 |
| 3 | I | p-TsO | **5c**, 85 | **6**, trace |
| 4 | Br | p-TsO | **5c**, 82 | **6**, trace |
| 5 | Cl | p-TsO | **5c**, 58 | **6**, 21 |
| 6 | I | $OCONMe_2$ | **5d**, 78 | **6**, 11 |
| 7 | Br | $OCONMe_2$ | **5d**, 63 | **6**, 25 |
| 8 | Cl | $OCONMe_2$ | **5d**, 56 | **6**, 31 |
| 9 | I | $OSO_2NMe_2$ | **5e**, 82 | **6**, 3 |
| 10 | Br | $OSO_2NMe_2$ | **5e**, 78 | **6**, 5 |
| 11 | Cl | $OSO_2NMe_2$ | **5e**, 59 | **6**, 17 |

[a]The reaction was carried on 2 mmol scale under the same conditions as noted in Scheme 2.

So far, Fe-catalyzed selective biaryl coupling reactions between different aryl electrophiles (e.g. ArI/ArBr *vs*ArOTs/$ArOSO_2NMe_2$) has not been reported,[19] probably because only rather limited types of aryl electrophiles could undergo Fe-catalyzed biaryl coupling reaction under the previously reported conditions.[10] Our protocol is suitable for various electrophiles, and at the same time, aryl iodides and bromides seemed to exhibit higher reactivity (Scheme 2 and 3), therefore we believe that a selective coupling between different electrophiles can be realized. In order to achieve this goal, the reactivity of various electrophiles under the present conditions was compared and the results were outlined in Table 2. Obviously, the reactivity of aryl iodides and bromides was higher than that of the corresponding oxygen-based electrophiles under the present conditions, and the highly selective couplings of iodide over Br, Cl, OTs, $ArOCONMe_2$ and $ArOSO_2NMe_2$ could be well achieved (Table 2, entries 1, 3, 6, 9). Similarly, the bromide could also undergo the biaryl coupling preferentially to the chloride and oxygen-

based electrophiles (Table 2, entries 2, 4, 7, 10). Since the reactivity of the chloride was only slightly higher than that of ArOTs, $ArOCONMe_2$ and $ArOSO_2NMe_2$, it seemed difficult to achieve a selective coupling between these electrophiles (Table 2, entries 5, 9, 11).

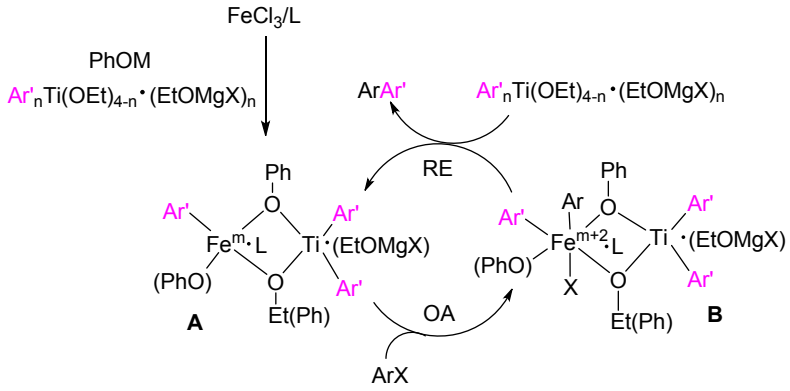
**Scheme 4 Synthesis of terphehyl acid 8**




Based on these findings, we believed that diarylation or polyarylation could be achieved using the present Fe-catalyzed biaryl reaction through an orthogonal coupling strategy. As outlined in Scheme 4, a terphenyl intermediate **8** for anidulafungin was facilely synthesized on a multi-gram scale through selective iterative biaryl couplings. The synthesis started with readily available 4-$BrC_6H_4OTs$, and the first bairyl coupling of C–Br bond using a Knochel-type functionalized Grignard reagent proceeded selectively over C–OTs, affording the compound **7** in 78% yield. Under the present conditions, the second coupling occurred with the sensitive ester group being untouched. After hydrolysis, the desired compound **8** was obtained in 71% two-step yield from **7** (55% total yield). As far as we know, our synthesis represents the first application example of Fe-catalyzed selective biaryl coupling between C-X and oxygen-based electrophiles. Besides, the previous synthesis of this compound used to utilize Pd-catalyzed Suzuki coupling to construct functionalized biaryl structural unit,[20] however, the high price of Pd catalysts and the worrying residual of Pd metal always bother their industrial applications in pharmaceuticals. Our synthesis only used two low price and nontoxic metal (Fe and Ti), thus the above problems of Pd catalysis have been well solved.

Mechanistically, we believe thata Fe/Ti bimetallic cooperativity assisted by phenolate coordination plays an important role in the present reaction because our experiments have clearly demonstrated that

the combination of Fe salt, $Ti(OEt)_4$ and ArOM was crucial to the success of this Fe-catalyzed biaryl cross-coupling (Table 1 entries 2-4, 21 and 22; for more details, see: Table s1 in ref 13). We propose a tentative Fe/Ti bimetallic cooperativity mechanism *via* an Fe(II)/Fe(IV) or Fe(I)/Fe(III) catalytic cycle as illustrated inScheme 5.[10c,21] We think that the Fe(II)/Fe(IV) or Fe(I)/Fe(III) cycle[10c] is more reasonable than the Fe(0)/Fe(II) cycle[10h] under our conditions because the Fe(0) species is easily oxidized by the Ti(IV) compounds and therefore difficult to exist. Besides, we also found that the present reaction was not inhibited by the addition of a radical scanvengner (TEMPO), indicating that this Fe catalytic cycle consists of double-electron processes. Thus, the catalytic cycle started with bimetallic complex **A** formed from $Ar'_nTi(OEt)_{4-n}\cdot(EtOMgX)_n$, PhOM, $FeCl_3$ and ligand (NHC or




L = NHC and TMEDA; m = 1 or 2; n = 1, 2, 3
RE = reductive elimination; OA = oxidative addition

**Scheme 5 Tentative bimetallic cooperativity mechanism**

TMEDA). Obviously, this complex prevented the formation of $Ar'_2Fe(I)MgX$, $Ar'_2Fe(II)$ or $ArAr'_2Fe(II)MgX$, and thus deiodination/debromiantion and the homocoupling side reactions were well suppressed. We also considered that the formation of bimetallic complex **A** had altered the reactivity of Fe species in oxidative addition to the C–X bond of ArX. For example, in the absence of NHC ligand, the oxidative addition of Fe salts could hardly occur on the C–Cl bond of aryl chlorides bearing an electron-donating group (e.g. $MeOC_6H_4Cl$),[10b-d] whereas this oxidative addition took place in our Fe catalyst system (Table 1, entries 2-4; scheme 2, **3b**). Subsequently, complex **A** underwent oxidative addition with ArX to form a bimetallic Fe(IV) or Fe(III) complex **B**. This high-valent **B** with high

coordination number is liable to undergo the final reductive elimination reaction to release the product. Besides, the bimetallic cooperativity can also function as a bidentate ligand, and thus promote the reductive elimination process to a certain extent. Thus, by postulating the catalytic cycle consisting of two bimetallic complexes **A** and **B**, the fact that the deiodination/debromiantion and the homocoupling side reactions were well suppressed in our reaction has been reasonably explained. Nevertheless, the exact mode of bimetallic synergy is not clear at present, and polynuclear complexes (such as macrocyclic or clathrate complex) can't be excluded, especially when the salts of catechol or hydroquinone was used. Further studies for the structures of Fe/Ti bimetallic complexes and mechanistic details are underway in our laboratories.

## 3. CONCLUSION

In conclusion, we reported a new iron-based catalyst system, a combination of the commonly used $FeCl_3$/SIPr with $Ti(OEt)_4$/PhOM, which enabled a highly general and chemoselective biaryl cross coupling between various electrophiles and Grignard reagents. To the best of our knowledge, this is the first iron-based catalytic system that can be applied to all common aryl electrophiles (ArX, X = I, Br, Cl, OTs, $OCONMe_2$, $OSO_2NMe_2$) with high tolerance to important functional groups. By virtue of the high generality of this iron-based catalytic system, the highly selective couplings between ArI or ArBr and ArOTs/$ArOCONMe_2$/$OSO_2NMe_2$ have been realized for the first time, which enabled a Fe-catalyzed facile synthesis of a terphenyl intermediate for anidulafungin. Because Fe-catalyzed functional group tolerant biaryl coupling reaction of aryl Grignard reagents remains a challenge, and at the same time, Fe-catalyzed Negishi and Suzuki biaryl couplings are rather underdeveloped, we expect that the present protocol provides a practical solution to this long-standing problem and narrows the gap between iron catalysis and palladium or nickel catalysis in this regard. Moreover, the Fe/Ti synergistic catalysis also provides implications for us to develop Fe-catalyzed Negishi and Suzuki biaryl couplings, which are currently under the way in our laboratories.

## 4. EXPERIMENTAL SECTIONS

**General Information**IR spectra were recorded using a FTIR spectrophotometer. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on 400, 500 or 600 MHz spectrometer (100, 125 or 150 MHz for $^{13}C$ spectroscopy) using TMS as an internal standard. High resolution mass spectra (HRMS) were obtained with a microTOF (ESI).Melting points recorded on a microscopic instrument and areuncorrected.

All reagents and solvents used for aryl magnesium reagents or lithium reagents and reactions were freshly dehydrated and distilled before use. $Ti(OEt)_4$ was distilled under vacuum before use. The corresponding glassware was oven dried (120 $^{o}C$) and cooled under a stream of argon gas. Aryl Grignard reagents such as phenyl magnesium or 4-methoxyphenyl magnesium were prepared according to standard procedure. Pyridyl Grignard reagents were prepared *via* bromine-magnesium exchange using *i*-PrMgCl while functionalized aryl Grignard reagents such as 2-cyanophenylmagnesium chloride or 4-(ethoxycarbonyl)phenylmagnesium chloride were prepared *via* iodine-magnesium exchange using *i*-PrMgCl·LiCl according to Knochel's method.[22] All the Grignardreagents were titrated before use.[23]

**Representative procedure for the biaryl cross couplings of common Grignard reagents (3a')**

Under Ar atmosphere, $Ti(OEt)_4$ (91.4 mg; 0.4 mmol) and phenol (37.7 mg; 0.4 mmol) were added to 3 mL THF, and stirred at room temperature for 20 to 30 min. A solution of 4-$MeOC_6H_4MgBr$ (3.4 mmol, 1.0 M in THF) was added dropwise through a syringe to the resulting mixture during 10 - 15 min, and then stirred at room temperature for 30 to 40 min.

To another three-necked round-bottom flask was added $C_6H_5Br$ (314 mg, 2 mmol) and 3 mL THF. Under stirring, $FeCl_3$ (32.5 mg; 0.2 mmol) and SIPr·HCl (68.2 mg; 0.2 mmol) were added to the resulting solution and stirred for 5 min at room temperature. Then TMEDA (92.8 mg, 0.8 mmol) was added and stirred for 5 min at room temperature. The above-prepared solution of titanate, phenolate and Grignard reagent was then added dropwise through a syringe during 10 - 15 min. After addition, 3 mL toluene was added (THF/$CH_3Ph$ = 3:1) and the mixture was heated to reflux under stirring (about 78 $^{o}C$). The progress of the reaction was monitored by TLC, and after the reaction finished (about 6 - 8 hr), the reaction was quenched by adding 30 mL distilled water. After being filtered, the solid and filtrate were

extracted with $CH_2Cl_2$. 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 **3a'** (324 mg, 88% yield).

**Typical procedure for the biaryl cross couplings of functionalized Grignard reagents (4b)**

Under Ar atmosphere, the solution of 4-$IC_6H_4COOEt$ (939 mg, 3.4 mmol) in 3.4 mL THF was cooled to -40 °C under stirring. To this solution was added *i*-PrMgCl·LiCl (3.4 mmol, 1.0 M in THF) dropwise. The stirring was continued at that temperature until the exchange reaction was completed (monitored by TLC). Under Ar atmosphere, THF (3 mL); $Ti(OEt)_4$ (91.4 mg; 0.4 mmol) and phenol (37.7 mg; 0.4 mmol) were added to another round-bottom flask, and the mixture was stirred and cooled to -45 ~ -50 °C. To this solution, the above-prepared Knochel-type functionalized Grignard reagent was added dropwise through a syringe during 10-15 min with the temperature being kept below -40 °C. After the addition, the mixture was allowed to come to room temperature in 2 hr, and stirred at that temperature for 30 min. The solvent as well as *i*-PrI were removed under vacuum (about 10 mmHg) during which the temperature was below 20 °C until the mixture became a paste. THF (6 mL) was added to the paste and the stirring was continued until a solution was formed.

To another three-necked round-bottom flask was added $C_6H_5Br$ (312 mg, 2 mmol) and 3 mL THF. Under stirring, $FeCl_3$ (32.5 mg; 0.2 mmol) and SIPr·HCl (68.2 mg; 0.2 mmol) were added to the resulting solution and stirred for 5 min at room temperature. Then TMEDA (92.8 mg, 0.8 mmol) was added and stirred for 5 min at room temperature.The above-prepared solution of titanate, phenolate and Grignard reagent was added dropwise during 10-15 min. After addition, 3 mL toluene was added (THF/$CH_3Ph$ = 3:1) and the mixture was heated to reflux under stirring (about 78 °C). The progress of the reaction was monitored by TLC, and after the reaction finished (about 6-8 hr), the reaction was quenched by adding 30 mL distilled water. After being filtered, the solid and filtrate were extracted with $CH_2Cl_2$. 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 **4b** (385 mg, 85% yield).

*4-Methoxy-1,1'-biphenyl* (**3a** and **3a'**). The product was prepared as described in the typical

procedure for **3a'** and isolated through flash chromatography using petroleum ether as a white solid in 88% yield (324 mg for **3a'**, X = Br): m.p. 85-86 °C (lit., 85-87 °C); $R_f$ = 0.55 (petroleum ether); IR ($cm^{-1}$, KBr): 1606, 1488, 834; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.53-7.47 (m, 4H), 7.39-7.36 (m, 2H), 7.26 (t, $J$ = 5.6 Hz, 1H), 6.95-6.92 (m, 2H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 159.1, 140.8, 133.8, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. Data was consistent with that reported in the literature.[24]

*4'-Methoxy-2,4-dimethyl-1,1'-biphenyl* (**3b**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a yellow oil in 88% yield (374 mg for **3b**, X = Br): $R_f$ = 0.43 (petroleum ether/ethyl acetate = 50/1); IR ($cm^{-1}$, KBr): 2952, 2924, 1247, 910, 807; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.25-7.22 (m, 2H), 7.13-7.03 (m, 3H), 6.96-6.92 (m, 2H), 3.85 (s, 3H), 2.36 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 158.5, 138.8, 136.7, 135.4, 134.4, 131.1, 130.4, 130.4, 130.4, 130.4, 129.9, 126.5, 113.5, 113.5, 113.5, 100.0, 55.4, 21.1, 20.5. Data was consistent with that reported in the literature.[25]

*1-(o-Tolyl)naphthalene* (**3c**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a white solid in 78% yield (341 mg for **3c**, X = Br): m.p. 64.1-65.7 °C (lit., 65-66 °C); $R_f$ = 0.44 (petroleum ether/ethyl acetate = 50/1); IR ($cm^{-1}$, KBr): 3057, 2360, 2345, 1394, 1017, 802, 778, 758; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.93-7.87 (m, 2H), 7.56-7.47 (m, 3H), 7.41-7.25 (m, 6H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 140.3, 139.8, 136.8, 133.6, 132.0, 130.4, 129.9, 128.2, 127.6, 127.5, 126.7, 126.1, 126.0, 125.8, 125.6, 125.4, 20.1. Data was consistent with that reported in the literature.[26]

*Ethyl 4'-methoxy-[1,1'-biphenyl]-3-carboxylate* (**3d**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a yellow oil in 88% yield (451 mg for **3d**, X = Br): $R_f$ = 0.40 (petroleum ether/ethyl acetate = 50/1); IR ($cm^{-1}$, KBr): 2980, 1770, 1608, 1510, 1435, 1365, 1298, 1244, 1180, 1106, 1040, 1030, 831,

745, 571;$^{1}$H NMR ($CDCl_3$, 400 MHz)$\delta$ (ppm) 8.23 (t, $J$ = 1.6 Hz, 1H), 7.97 (dt, $J$ = 8.0 Hz, $J$ = 1.6 Hz, 1H), 7.74-7.71(m, 1H), 7.58-7.55 (m, 2H), 7.47 (t, $J$ = 7.6 Hz, 1H),7.01-6.98 (m, 2H), 4.40 (q, $J$ = 7.6 Hz, 2H), 3.85 (s, 3H), 1.41 (t, $J$ = 6.8 Hz, 3H); $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 166.8, 159.6, 141.1, 132.8, 131.1, 131.0, 131.0, 128.8, 127.9, 127.8, 114.4, 61.1, 55.5, 14.4. Data was consistent with that reported in the literature.[27]

*4'-Methoxy-N,2'-dimethyl-[1,1'-biphenyl]-4-carboxamide* (**3e**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a white solid in 82% yield (419 mg for **3e**, X = Br): m.p. 155-157 °C (lit., 156.2-157.8 °C); $R_f$ = 0.32 (petroleum ether/ethyl acetate = 3/1); IR (cm$^{-1}$, KBr): 3338, 3308, 2933, 2911, 2366, 1644, 1636, 1618, 1542, 1495, 1300, 1280, 1164, 1050, 858, 814, 759; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.78 (d, $J$ = 8.4 Hz, 2H), 7.34 (d, $J$ = 7.6 Hz, 2H), 7.13 (d, $J$ = 8.0 Hz, 1H), 6.81-6.78 (m, 2H), 6.24 (s, 1H), 3.82 (s, 3H), 3.03 (d, $J$ = 4.4 Hz, 3H), 2.24 (s, 3H); $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 168.2, 159.1, 144.9, 136.7, 133.5, 132.7, 130.7, 129.6, 126.4, 115.9, 111.3, 55.3, 26.9, 20.7. Data was consistent with that reported in the literature.[13]

*2-Methoxy-N-methyl-5-(thiophen-2-yl)benzamide* (**3f**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 3/1 as a brown oil in 77% yield (381 mg for **3f**, X = Br): $R_f$ = 0.25 (petroleum ether/ethyl acetate = 1/1); IR (cm$^{-1}$, KBr): 3342, 3103, 2978, 1677, 1149, 871; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.67-7.27 (m, 2H), 7.21-6.70 (m, 4H), 5.39 (s, 1H), 3.85 (s, 3H), 2.70 (s, 3H); $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 155.6, 134.0, 131.9, 129.4, 129.1, 126.9, 126.7, 125.8, 116.1, 112.8, 111.2, 56.3, 26.6; MS (HRMS) m/z Calcd for $C_{13}H_{14}NO_2S^+$ $[M+H]^+$ 248.0740, found 248.0738.

*2'-Methoxy-N,N-dimethyl-[1,1'-biphenyl]-4-carboxamide* (**3g**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a yellow oil in 85% yield (434 mg for **3g**, X = Br): $R_f$ = 0.31 (petroleum ether/ethyl acetate = 3/1); IR (cm$^{-1}$, KBr): 2939, 2858, 2835, 1650, 1610, 1483, 1390, 1261, 1236, 1082,

1026, 754, 738; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.56-7.54 (m, 2H), 7.46-7.44 (m, 2H), 7.35-7.29 (m, 2H), 7.04-6.97 (m, 2H), 3.80 (s, 3H), 3.09 (s, 6H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 161.7, 156.5, 150.2, 142.8, 131.3, 130.0, 122.4, 120.8, 115.5, 111.2, 109.3, 55.6, 40.6, 35.4; MS (HRMS) m/z Calcd for $C_{16}H_{18}NO_2^+$ $[M+H]^+$ 256.1327, found 256.1329.

*N,N-dimethyl-[1,1'-biphenyl]-4-sulfonamide* (**3h**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a white solid in 90% yield (470 mg for **3h**, X = Br): m.p. 89-91 °C (lit., 89-90 °C); $R_f$ = 0.33 (petroleum ether/ethyl acetate = 5/1); IR (cm$^{-1}$, KBr): 1596, 1480, 1332, 730, 697; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 7.87 (d, $J$ = 8.4 Hz, 2H), 7.77 (d, $J$ = 8.4 Hz, 2H), 7.63-7.61 (m, 2H), 7.52-7.49 (m, 2H), 7.46-7.43 (m, 1H), 2.77 (s, 6H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm)145.6, 139.3, 134.1, 132.4, 129.1, 128.3, 127.6, 127.3, 38.0. Data was consistent with that reported in the literature.[28]

*4'-Methoxy-[1, 1'-biphenyl]-4-carbonitrile* (**3i**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 50/1 as a white solid in 88% yield (368 mg for **3i**, X = Br): m.p. 102.1-104.4 °C (lit., 101.5-102.5 °C); $R_f$ = 0.43 (petroleum ether/ethyl acetate = 20/1); IR (cm$^{-1}$, KBr): 2962, 2357, 2320, 1635, 1604, 1257, 1030, 825, 759; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm) 7.79-7.78 (m, 2H), 7.70-7.69 (m, 2H), 7.45-7.43 (m, 2H), 6.97-6.95 (m, 2H), 3.88 (s, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 194.2, 163.4, 138.3, 136.6, 132.5, 131.2, 129.8, 128.5, 113.7, 55.5. Data was consistent with that reported in the literature.[24]

*4-(Thiophen-2-yl)benzaldehyde* (**3j**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 50/1 as a white solid in 71% yield (267 mg for **3j**, X = Br): m.p. 69.3-70.9 °C (lit. 69.0–69.5 °C); $R_f$ = 0.31 (petroleum ether/ethyl acetate = 10/1); IR (cm$^{-1}$, KBr): 3012, 1700, 1601, 1278, 791; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 9.99 (s, 1H), 7.87 (d, $J$ = 8.3 Hz, 2H), 7.79 (d, $J$ = 8.2 Hz, 2H), 7.49 (dd, $J$ = 3.6, 0.9 Hz, 1H), 7.43-7.42 (m, 1H), 7.13 (dd, $J$ = 5.0, 3.8 Hz, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm)

191.5, 142.7, 140.1, 135.1, 130.5, 128.5, 127.0, 126.1, 125.1. Data was consistent with that reported in the literature.[29]

*2'-Isopropoxy-[1,1'-biphenyl]-2-amine* (**3k**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 200/1 as a brown oil in 81% yield (368 mg for **3k**, X = Br): $R_f$ = 0.33 (petroleum ether/ethyl acetate = 100/1); IR ($cm^{-1}$, KBr): 3039, 3028, 2970, 2922, 2361, 2342, 1742, 1718, 1612, 1481, 1436, 1373, 1361, 1356, 1227, 1217, 1122, 1100, 950, 750; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.31-7.25 (m, 2H), 7.15-7.10 (m, 2H), 7.05-7.00 (m, 2H), 6.82-6.75 (m, 2H), 4.37-4.31 (m, 1H), 3.55 (s, 2H), 1.23 (d, $J$ = 18.0 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 132.3, 131.3, 130.6, 128.8, 128.3, 121.9, 116.5, 116.1, 72.1, 29.8, 22.2. Data was consistent with that reported in the literature.[13]

*1-([1,1'-Biphenyl]-4-yl)ethan-1-one* (**3l**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 50/1 as a white solid in 73% yield (287 mg for **3l**, X = Br): m.p. 121.1-123.4 °C (lit., 121-123 °C); $R_f$ = 0.50 (petroleum ether/ethyl acetate = 20/1); IR ($cm^{-1}$, KBr): 1683, 1602, 1267, 963, 766; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 8.06 (d, $J$ = 8.3 Hz, 2H), 7.71 (d, $J$ = 8.3 Hz, 2H), 7.66-7.65 (m, 2H), 7.52-7.49 (m, 2H), 7.44-7.43 (m, 1H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 197.8, 145.8, 139.9, 135.9, 129.0, 128.9, 128.3, 127.3, 127.2, 26.7. Data was consistent with that reported in the literature.[30]

*2-(4-Methoxyphenyl)pyridine* (**3m**).The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 20/1 as a yellow oil in 90% yield (333 mg for **3m**, X = Br): $R_f$ = 0.29 (petroleum ether/ethyl acetate = 10/1); IR ($cm^{-1}$, KBr): 3051, 3005, 2958, 1608, 1589, 1514, 1465, 1435, 1271, 1217, 1176, 781; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 8.66 (d, $J$ = 4.6 Hz, 1H), 7.97 (d, $J$ = 8.8 Hz, 1H), 7.69-7.63 (m, 2H), 7.16-7.13 (m, 1H), 7.00 (d, $J$ = 8.8 Hz, 2H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 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.[31]

*1-(6-(Thiophen-2-yl)pyridin-3-yl)ethan-1-one* (**3n**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 50/1 as a yellow oil in 83% yield (337 mg for **3n**, X = Br): $R_f$ = 0.30 (petroleum ether/ethyl acetate = 10/1); IR ($cm^{-1}$, KBr): 3246, 3101, 2978, 2926, 1575, 1456, 1089, 1020, 912, 702; $^1H$ NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm) 8.28 (d, $J$ = 2.0 Hz, 1H), 7.64 (dd, $J$ = 5.6, 1.6 Hz, 1H), 7.35 (d, $J$ = 5.6 Hz, 1H), 7.18 (d, $J$ = 3.2 Hz, 1H), 6.87-6.84 (m, 2H), 1.91 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) $\delta$ (ppm) 151.9, 147.7, 142.6, 140.7, 136.3, 127.5, 126.9, 125.7, 124.6, 73.2, 32.1; MS (HRMS) m/z Calcd for $C_{11}H_9NNaOS^+$ $[M+Na]^+$ 226.0303, found 226.0304.

*3-(p-Tolyl)pyridine* (**3o**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 50/1 as a white solid in 90% yield (305 mg for **3o**, X = Br): m.p. 38.2-39.5 °C (lit., 38-39 °C); $R_f$ = 0.32 (petroleum ether/ethyl acetate = 10/1); IR ($cm^{-1}$, KBr): 2924, 2852, 2350, 1636, 1501, 1458, 1276, 796, 713; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.8 (s, 1H), 8.6 (s, 1H), 7.85-7.82 (m, 1H), 7.48-7.46 (m, 2H), 7.34-7.32 (m, 1H), 7.28-7.26 (m, 2H), 2.40 (d, $J$ = 2.4 Hz, 3H);$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 148.2, 138.1, 136.8, 135.0, 134.2, 129.9, 127.1, 123.7, 21.2. Data was consistent with that reported in the literature.[32]

*[1,1'-Biphenyl]-2-carbonitrile* (**4a**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a yellow oil in 86% yield (308 mg for **4a**, X = Br): $R_f$ = 0.39 (petroleum ether/ethyl acetate = 50/1); IR ($cm^{-1}$, KBr): 3045, 2369, 2345, 2323, 1653, 1559, 1539, 1507, 1457, 1270, 759, 699; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 7.79 (d, $J$ = 7.7 Hz, 1H), 7.67 (t, $J$ = 7.7 Hz, 1H), 7.60-7.58 (m, 2H), 7.55-7.51 (m, 3H), 7.49-7.46 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 145.5, 138.2, 133.8, 132.8, 130.1, 128.8, 128.7, 127.5, 118.7, 111.3. Data was consistent with that reported in the literature.[33]

*Ethyl [1,1'-biphenyl]-4-carboxylate* (**4b**). The product was prepared as described in the typical procedure and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a yellow oil in 85% yield (385 mg for **4b**, X = Br): $R_f$ = 0.41 (petroleum ether/ethyl acetate = 50/1); IR

(cm$^{-1}$, KBr): 3031, 2981, 1701, 1608, 1558, 1508, 1456, 1277, 1102, 858, 747, 697; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.12 (d, $J$ = 8.4Hz, 2H), 7.67-7.61 (m, 4H), 7.48-7.37 (m, 3H), 4.40 (q, $J$ = 6.8Hz, 2H), 1.41 (t, $J$ = 14.0Hz, 3H); $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 166.5, 145.5, 140.1, 130.1, 129.3, 128.9, 128.1, 127.3, 127.0, 61.0, 14.4. Data was consistent with that reported in the literature.[34]

*4'-Methyl-[1,1'-biphenyl]-4-carbonitrile* (**4c**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a white solid in 79% yield (305 mg for **4c**, X = Br): m.p. 112-115 °C (lit., 110-112 °C); $R_f$ = 0.52 (petroleum ether/ethyl acetate = 50/1); IR (cm$^{-1}$, KBr): 2352, 2344, 1645, 748, 653; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.69 (s, 1H), 7.67-7.64 (m, 5H), 7.62-7.60 (m, 2H), 2.43 (s, 3H); $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 195.4, 143.7, 136.8, 134.6, 131.6, 131.5, 130.3, 129.2, 127.3, 21.8. Data was consistent with that reported in the literature.[35]

*N, N, 2'-Trimethyl-[1,1'-biphenyl]-4-carboxamide* (**4d**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a whitish solid in 75% yield (359 mg for **4d**, X = Br): m.p. 97-98 °C (lit., 96-98 °C); $R_f$ = 0.45 (petroleum ether/ethyl acetate = 3/1); IR (cm$^{-1}$, KBr): 3015, 2913, 1620, 1390, 851, 774, 750; $^{1}$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 7.50-7.48 (m, 2H), 7.38-7.36 (m, 2H), 7.30-7.23 (m, 4H), 3.11 (s, 6H), 2.29 (s, 3H); $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 171.6, 143.3, 141.1, 135.3, 134.7, 130.4, 129.7, 129.2, 127.6, 127.0, 125.8, 39.7, 35.4, 20.4. Data was consistent with that reported in the literature.[13]

*4'-Methoxy-N-methyl-[1,1'-biphenyl]-2-carboxamide* (**4e**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a whitish solid in 74% yield (357 mg for **4e**, X = Br): m.p. 130.4-131.5 °C (lit., 130-132 °C); $R_f$ = 0.3 (petroleum ether/ethyl acetate = 3/1); IR (cm$^{-1}$, KBr): 3299, 2937, 1640, 1533, 1248, 843, 761; $^{1}$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 7.65-7.63 (m, 1H), 7.47-7.43 (m, 1H), 7.36-7.33 (m, 4H), 6.96-6.94 (m, 2H), 5.39(s, 1H), 3.85 (d, $J$ = 2.1 Hz, 3H), 2.71-2.69 (m, 3H); $^{13}$C{$^{1}$H} NMR

($CDCl_3$, 125 MHz) $\delta$ (ppm) 170.5, 159.3, 139.0, 135.6, 132.4, 130.1, 130.1, 129.8, 128.8, 127.2, 114.0, 55.3, 26.7. Data was consistent with that reported in the literature.[36]

*5-(4-Methoxyphenyl)-N-methylnicotinamide* (**4f**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 5/1 as a white solid in 74% yield (359 mg for **4f**, X = Br): m.p. 106.1-107.3 °C; $R_f$ = 0.3 (petroleum ether/ethyl acetate = 1/1); IR ($cm^{-1}$, KBr): 3255, 3034, 2971, 2906, 2360, 2345, 2324, 1734, 1635, 1558, 1518, 1473, 1249, 1180, 1041, 1022, 829, 729, 576, 527; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.37 (s, 1H), 8.27 (d, $J$ = 5.2 Hz, 1H), 7.17-7.15 (m, 2H), 7.06 (d, $J$ = 5.2 Hz, 1H), 6.79-6.76 (m, 2H), 6.69-6.67 (m, 1H), 3.68-3.67 (m, 3H), 2.55 (d, $J$ = 4.4 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 168.4, 160.3, 150.3, 149.0, 146.7, 131.3, 129.6, 129.3, 124.0, 114.3, 55.3, 26.6; MS (HRMS) m/z Calcd for $C_{14}H_{15}N_2O_2^+$ $[M+H]^+$ 243.1128, found 243.1131.

*5-(4-(Dimethylamino)phenyl)-N,N-dimethylthiophene-2-carboxamide* (**4g**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a white solid in 68% yield (373 mg for **4g**, X = Br): m.p. 169.7-170.1°C; $R_f$ = 0.35 (petroleum ether/ethyl acetate = 3/1); IR ($cm^{-1}$, KBr): 3601, 3554, 2916, 2906, 2854, 1520, 1388, 1197, 806, 734, 709; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 7.60-7.57 (m, 4H), 7.50-7.48 (m, 2H), 3.14-3.08 (m, 12H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 171.6, 128.3, 128.1, 127.8, 126.9, 126.4, 126.3, 122.5, 45.5, 39.7, 35.5, 29.3; MS (HRMS) m/z Calcd for $C_{15}H_{19}N_2OS^+$ $[M+H]^+$ 275.1213, found 275.1214.

*3-(6-(Benzyloxy)pyridin-3-yl)-N-methylbenzamide* (**4h**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 5/1 as a white solid in 82% yield (522 mg for **4h**, X = Br): m.p. 141-143 °C (lit., 143-144 °C); $R_f$ = 0.42 (petroleum ether/ethyl acetate = 2/1); IR ($cm^{-1}$, KBr): 2922, 2888, 2378, 2344, 2311, 1718, 1630, 1558, 1550, 1529, 1288, 1269, 1080, 829; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.44 (s, 1H), 8.00 (s, 1H), 7.89 (d, $J$ = 8.7 Hz, 1H), 7.71 (d, $J$ = 7.6 Hz, 1H), 7.66-7.64 (m, 1H), 7.53-7.49 (m, 3H), 7.41-

7.32 (m, 3H), 6.94 (d, $J$ = 8.6 Hz, 1H), 5.48 (s, 2H), 3.05 (d, $J$ = 4.8 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 162.8, 144.2, 138.4, 138.0, 136.7, 135.6, 129.7, 129.5, 129.3, 128.6, 128.1, 125.7, 125.5, 111.7, 68.7, 27.0. Data was consistent with that reported in the literature.[13]

*N-Methyl-5-(4-methylpyridin-3-yl)thiophene-2-carboxamide* (**4i**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 5/1 as a brown solid in 81% yield (376 mg for **4i**): m.p. 99.1-99.5 °C; $R_f$ = 0.30 (petroleum ether/ethyl acetate = 2/1); IR ($cm^{-1}$, KBr): 3448, 2953, 2923, 2361, 1602, 1589, 1533, 1500, 1488, 1455, 1392, 1265, 1219, 1203, 1035, 821, 808, 736; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.41 (s, 1H), 8.26 (s, 1H), 7.21-7.20 (m, 1H), 7.02-7.01 (m, 1H), 6.88-6.87 (m, 1H), 3.04 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 163.7, 149.7, 148.9, 145.0, 142.0, 138.7, 129.8, 129.5, 127.0, 125.5, 39.8, 20.3; MS (HRMS) m/z Calcd for $C_{12}H_{13}N_2OS^+[M+H]^+$ 233.0749, found 233.0753.

*4'-Cyano-N-methyl-[1,1'-biphenyl]-4-carboxamide* (**4j**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a white solid in 80% yield (378 mg for **4j**, X = Br): m.p. 130-131 °C (lit., 129-131 °C); $R_f$ = 0.30 (petroleum ether/ethyl acetate = 3/1); IR ($cm^{-1}$, KBr): 3385, 3311, 2361, 1647, 1635, 1541, 1317, 1276; $^1H$ NMR ($CDCl_3$, 400 MHz), $\delta$ (ppm): 7.88-7.81 (m, 3H), 7.78 (d, $J$ = 7.3 Hz, 1H), 7.63-7.59 (m, 1H), 7.51-7.47 (m, 2H), 6.41 (s, 1H), 3.05 (d, $J$ = 4.8 Hz, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz), $\delta$ (ppm): 167.5, 140.1, 138.0, 137.1, 133.0, 130.2, 130.1, 128.5, 126.9, 27.1. Data was consistent with that reported in the literature.[13]

*Ethyl 2'-cyano-[1,1'-biphenyl]-3-carboxylate* (**4k**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 40/1 as a white solid in 72% yield (362 mg for **4k**, X = Br): m.p. 96-98 °C; $R_f$ = 0.20 (petroleum ether/ethyl acetate = 20/1); IR ($cm^{-1}$, KBr): 2970, 2231, 1720, 1609, 1270, 767; $^1H$ NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm) 8.21 (t, $J$ = 1.6 Hz, 1H), 8.14 (d, $J$ = 7.8 Hz, 1H), 7.81-7.76 (m, 2H), 7.71-7.65 (m, 1H), 7.61-7.53 (m, 2H), 7.51-7.46 (m, 1H), 4.41 (q, $J$ = 7.1 Hz, 2H), 1.41 (t, $J$ = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR

($CDCl_3$, 150 MHz) $\delta$ (ppm) 166.2, 144.6, 138.5, 133.8, 133.1, 133.0, 131.3, 130.2, 130.0, 129.9, 128.9, 128.01, 118.4, 111.5, 61.3, 14.4. Data was consistent with that reported in the literature.[37]

*2'-Cyano-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide* (**4l**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a white solid in 78% yield (390 mg for **4l**, X = Cl): m.p. 101-102 °C (lit., 102.5-105.3 °C); $R_f$ = 0.35 (petroleum ether/ethyl acetate = 3/1); IR ($cm^{-1}$, KBr): 3063, 2930, 2351, 2320, 2224, 1633, 1506, 1489, 1471, 1395, 1269, 1076, 761, 748, 525; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.76-7.74 (m, 1H), 7.62-7.55 (m, 2H), 7.54-7.43 (m, 5H), 2.82 (s, 3H), 2.65 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 170.1, 143.5, 136.3, 135.1, 133.2, 132.4, 131.0, 130.4, 129.3, 129.1, 128.1, 127.3, 118.3, 111.7, 38.6, 34.6. Data was consistent with that reported in the literature.[13]

*Ethyl 4-(pyridin-2-yl)benzoate* (**4m**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 20/1 as a white solid in 88% yield (400 mg for **4m**, X = Br): m.p. 51-53 °C (lit., 50.5-52.0 °C); $R_f$ = 0.52 (petroleum ether/ethyl acetate = 5/1); IR ($cm^{-1}$, KBr): 3412, 3055, 2982, 2937, 2904, 2874, 1950, 1742, 1608, 1587, 1562, 1465, 1288, 1180, 1170, 866, 796, 750, 700, 617; $^1H$ NMR ($CDCl_3$, 400 MHz), $\delta$ (ppm) 8.68 (d, $J$ = 3.4 Hz, 1H), 8.10 (d, $J$ = 8.2 Hz, 2H), 8.02 (d, $J$ = 8.4 Hz, 2H), 7.73 (s, 2H), 7.24-7.21 (m, 1H), 4.36 (q, $J$ = 7.1 Hz, 2H); 1.36 (t, $J$ = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 166.3, 160.0, 149.8, 143.3, 136.8, 130.6, 129.9, 129.9, 126.7, 126.7, 122.8, 120.9, 61.0, 14.3. Data was consistent with that reported in the literature.[38]

*4-(Pyridin-2-yl)aniline* (**4n**). The product was prepared as described in the typical procedure for **4b**, and the post-treatment was adjusted as follows: the reaction was quenched by adding 20 mL 2N HCl solution, and the resuting mixture was stirred at 40 °C for 4 h. After cooled to rt, the mixture was extracted by $CH_2Cl_2$ (2 × 20 mL), and the thus-obtained aqueous phase was neutralized to pH = 8 with a saturated solution of $Na_2CO_3$. After being filtered, the solid and filtrate were extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated to yield the crude product.The compound was

purified through flash chromatography using petroleum ether/ethyl acetate = 10/1 as a brown solid in 79% yield (269 mg for **4n**, X = Br): m.p. 96-97 °C (lit., 95-97°C); $R_f$ = 0.30 (petroleum ether/ethyl acetate = 2/1); IR ($cm^{-1}$, KBr): 3458, 3316, 3036, 3007, 1636, 1585, 1420, 1188, 783; $^1H$ NMR ($CDCl_3$, 600 MHz), $\delta$ (ppm) 8.62-8.61 (m, 1H), 7.84-7.82 (m, 2H), 7.66-7.63 (m, 1H), 7.62-7.60 (m, 1H), 7.11-7.09 (m, 1H), 6.75-6.72 (m, 1H), 3.81 (s,2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) $\delta$ (ppm) 157.6, 149.5, 147.6, 136.7, 129.7, 128.1, 121.0, 119.4, 115.2. Data was consistent with that reported in the literature.[39]

*2-(Pyridin-3-yl)benzonitrile* (**4o**). The product was prepared as described in the typical procedure for **4b** and isolated through flash chromatography using petroleum ether/ethyl acetate = 20/1 as a yellow solid in 78% yield (281 mg for **4o**, X = Br): m.p. 87 °C (lit., 88-89 °C); $R_f$ = 0.32 (petroleum ether/ethyl acetate = 10/1); IR ($cm^{-1}$, KBr): 2921, 2361, 2224, 1591, 1475, 764; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.76 (d, $J$ = 2.4Hz, 1H), 8.69 (dd, $J$ = 4.8, 1.6Hz, 1H), 7.93 (dt, $J$ = 7.6, 1.6Hz, 1H), 7.81-7.79 (m, 1H), 7.69 (td, $J$ = 7.6, 1.2Hz, 1H), 7.53-7.49 (m, 2H), 7.45-7.41 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 149.9, 149.3, 141.8, 136.2, 134.0, 133.2, 130.0, 128.5, 123.4, 118.1, 111.6. Data was consistent with that reported in the literature.[40]

*4-Bromo-4'-methoxy-1,1'-biphenyl* (**5a**).The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether as a white solid in 88% yield (463 mg for **5a**, X = I): m.p. 142-143 °C ( lit., 143-145 °C); $R_f$ = 0.55 (petroleum ether); IR ($cm^{-1}$, KBr): 1602, 1558, 1496, 1261, 818; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm) 7.53 (d, $J$ = 8.5 Hz, 2H), 7.49 (d, $J$ = 8.7 Hz, 2H), 7.42 (d, $J$ = 8.4 Hz, 2H), 6.98 (d, $J$ = 8.7 Hz, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 159.4, 139.7, 132.5, 131.8, 128.3, 128.0, 120.8, 114.3, 55.4. Data was consistent with that reported in the literature.[41]

*4-Chloro-4'-methoxy-1,1'-biphenyl* (**5b**).The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether as a white solid in 79% yield (346 mg for **5b**, X = Br): m.p. 111-113 °C (lit., 111-113 °C); $R_f$ = 0.56 (petroleum ether); IR ($cm^{-1}$, KBr): 1554, 1489, 1263， 812; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.50-7.47 (m, 4H), 7.38 (d, $J$

= 7.8 Hz, 2H), 6.99-6.97 (m, 2H), 3.86 (s, 3H);$^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) $\delta$ (ppm) 159.3, 139.3, 132.7, 132.5, 128.8, 128.0, 127.9, 114.3, 55.4. Data was consistent with that reported in the literature.[42]

*4'-Methoxy-[1,1'-biphenyl]-4-yl 4-methylbenzenesulfonate* (**5c**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 30/1 as a white solid in 82% yield (581 mg for **5c**, X = Br): m.p. 133-135 °C (lit., 130-132 °C); $R_f$ = 0.29 (petroleum ether/ethyl acetate = 20/1);IR ($cm^{-1}$, KBr): 2988, 1558, 1375, 1175, 1092, 1040, 822; $^1H$ NMR ($CDCl_3$, 400 MHz), $\delta$ (ppm): 7.74 (d, $J$ = 8.3 Hz, 2H), 7.49-7.41 (m, 4H), 7.32 (d, $J$ = 8.1 Hz, 2H), 7.07-6.92 (m, 4H), 3.84 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm): 159.5, 148.6, 145.5, 139.9, 132.5, 132.3, 129.9, 128.7, 128.2, 127.8, 122.7, 114.4, 55.4, 21.8. Data was consistent with that reported in the literature.[43]

*4'-Methoxy-[1,1'-biphenyl]-4-yl dimethylcarbamate* (**5d**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a white solid in 63% yield (342 mg for **5d**, X = Br): m.p. 164-165 °C; $R_f$ = 0.40 (petroleum ether/ethyl acetate = 50/1); IR ($cm^{-1}$, KBr): 2967, 2936, 1719, 1170, 1035, 830; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.52 (dd, $J$ = 14.6, 8.7 Hz, 4H), 7.17 (d, $J$ = 8.6 Hz, 2H), 6.97 (d, $J$ = 8.7 Hz, 2H), 3.85 (s, 3H), 3.12 (s, 3H), 3.03 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 159.2, 155.1, 150.6, 138.0, 133.3, 128.2, 127.6, 122.1, 114.3, 55.4, 36.8, 36.6; MS (HRMS) m/z Calcd for $C_{16}H_{18}NO_3^+[M+H]^+$ 272.1287, found 272.1285.

*4'-Methoxy-[1,1'-biphenyl]-4-yl dimethylsulfamate* (**5e**). The product was prepared as described in the typical procedure for **3a'** and isolated through flash chromatography using petroleum ether/ethyl acetate = 100/1 as a white solid in 78% yield (480 mg for **5e**, X = Br): m.p. 163-164 °C; $R_f$ = 0.41 (petroleum ether/ethyl acetate = 50/1); IR ($cm^{-1}$, KBr): 2951, 1496, 1453, 1345, 824; $^1H$ NMR ($CDCl_3$, 600 MHz) $\delta$ 7.55 (d, $J$ = 8.8 Hz, 2H), 7.49 (d, $J$ = 8.8 Hz, 2H), 7.32 (d, $J$ = 8.7 Hz, 2H), 6.98 (d, $J$ = 8.8 Hz, 2H), 3.85 (s, 3H), 3.00 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 159.5, 149.2, 139.6,

132.6, 128.2, 128.0, 122.1, 114.4, 55.5, 38.9; MS (HRMS) m/z Calcd for $C_{15}H_{18}NO_4S^+[M+H]^+$ 308.0957, found 308.0953.

*4,4''-Dimethoxy-1,1':4',1''-terphenyl* (**6**). The product was isolated through flash chromatography using petroleum ether as a side product of the reaction of **5c** (Table 2, entry 5) as a white solid in 21% yield (121 mg for **6**): m.p. 272-273 °C (lit., 273-274 °C); $R_f$ = 0.17 (petroleum ether); IR ($cm^{-1}$, KBr): 2966, 1606, 1490, 1291, 1180, 832; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 7.61 (s, 4H), 7.57 (d, $J$ = 8.8 Hz, 4H), 6.99 (d, $J$ = 8.8 Hz, 4H), 3.86 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) $\delta$ (ppm) 159.3, 139.2, 133.4, 128.1, 127.1, 114.3, 55.4. Data was consistent with that reported in the literature.[44]

*Ethyl 4'-(tosyloxy)-[1,1'-biphenyl]-4-carboxylate* (**7**). The product was prepared as described in the typical procedure for **4b** on a 15 mmol scale and isolated through flash chromatography using petroleum ether/ethyl acetate = 40/1 as a white solid in 78% yield (4.64 g for **7**): m.p. 145-147 °C; $R_f$ = 0.21 (petroleum ether/ethyl acetate = 20/1); IR ($cm^{-1}$, KBr): 2988, 1701, 1342, 1277, 1179, 1094, 845, 773; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.11-8.08 (m,2H), 7.76-7.73 (m, 2H), 7.60-7.57 (m, 2H), 7.55-7.51 (m, 2H), 7.34-7.32 (m, 2H), 7.10-7.06 (m, 2H), 4.40 (q, $J$ = 7.1 Hz, 2H), 2.46 (s, 3H), 1.41 (t, $J$ = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm) 166.4, 149.7, 145.6, 144.1, 139.1, 132.5, 130.2, 129.9, 129.7, 128.6, 128.5, 127.0, 123.0, 61.2, 21.8, 14.4. Data was consistent with that reported in the literature.[45]

*4''-(Pentyloxy)-[1,1':4',1''-terphenyl]-4-carboxylic acid* (**8**). The product was prepared as described in the typical procedure for **3a'**on a 10 mmol scale. The terphenyl ester compound was hydrolyzed in a solution of KOH in 90% EtOH. When the hydrolysis completed, the poduct **8** was obtained as a white solid upon the acidification with concentrated HCl in 71% yield (2.56 g for **8**): m.p. > 300 °C (decomposed); $R_f$ = 0.33 (ethyl acetate/acetic acid = 100/1); IR ($cm^{-1}$, KBr) 2989, 1682, 1557, 1393, 1277, 916, 822, 773; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 8.00-7.98 (m, 2H), 7.82-7.80 (m, 2H), 7.78-7.76 (m, 2H), 7.72-7.70 (m, 2H), 7.64-7.62 (m, 2H), 7.01-6.99 (m, 2H), 3.98 (t, $J$ = 6.5 Hz, 2H), 1.74-1.67 (m, 2H), 1.42-1.36 (m, 2H), 1.35-1.28 (m, 2H), 0.87 (t, $J$ = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$,

150 MHz) $\delta$ (ppm) 167.7, 159.1, 144.4, 140.2, 137.7, 132.1, 130.5, 128.3, 127.9, 127.2, 127.1, 115.5, 68.1, 28.9, 28.3, 22.4, 14.4, 0.6. Data was consistent with that reported in the literature.[46]

## ASSOCIATED CONTENT

### Supporting Information

Copies of $^{1}$HNMR, $^{13}$C{$^{1}$H} NMR spectrafor all products. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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The authors declare the following competing financial interest(s): The authors have filed two patents on this technology.

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