Studies on Syntheses of Polyfunctionalized Heteroarenes by Transition Metal Catalyses

Eiji Yamaguchi

2011

Contents

Chapter 1. General Introduction 1

Chapter 2. Synthesis of 1,3-Diarylated Imidazo[1,5-*a*]pyridines *via* Conventional Cross-Coupling Strategies 15

- 2.1. Introduction 16
- 2.2. Halogenation of imidazo[1,5-*a*]pyridines 18
  - 2.2.1. Iodination 18
  - 2.2.2. Bromination 20
  - 2.2.3. Chlorination 21
  - 2.2.4. Fluorination 22
- 2.3. Cross-coupling reactions 22
  - 2.3.1. Kumada-Tamao-Corriu coupling reaction 22
  - 2.3.2. Suzuki-Miyaura coupling reaction 27
- 2.4. Photophisycal properties of 1,3-diarylated imidazo[1,5-*a*]pyridines 28
- 2.5. Summary 31
- 2.6. Experimental 31
- References and notes 47

Chapter 3. Introduction of Planar π-Conjugated System to Imidazo[1,5-*a*]pyridines by Means of Palladium Catalysis 51

- 3.1. Introduction 52
- 3.2. Synthesis of 1-alkynylated imidazo[1,5-*a*]pyridines 53
- 3.3. Synthesis of 1-alkynylated imidazo[1,5-*a*]pyridines 59
- 3.4. Photophysical properties of imidazo[1,5-*a*]pyridine derivatives 61
- 3.5. Summary 67
- 3.5. Experimental 68
- References and notes 87

Chapter 4. Direct Arylation Reaction of Heteroarenes Catalyzed by Palladium Complex Bearing Diimine-Type Ligand 89

- 4.1. Introduction 90
- 4.2. Direct arylation reaction of imidazo[1,5-*a*]pyridines 90
- 4.3. Direct arylation reaction of benzazoles 96
- 4.4. Direct arylation reaction of 5-membered-heteroarenes 101

4.5. Mechanistic studies of direct arylation reaction 103
4.6. Summary 104
4.7. Experimental 105
References and notes 120

Chapter 5. A Sequential Direct Arylation Reaction of Azoles Catalyzed by Phenanthroline-modified Palladium Complexes 123
5.1. Introduction 124
5.2. One-pot multiple C–H direct arylation of azoles 126
5.3. Sequential arylation of azoles 128
  5.3.1. C5-arylation of *N*-methylimidazole 128
  5.3.2. C2-arylation of *N*-methylimidazole 131
  5.3.3. C4-arylation of *N*-methylimidazole 135
  5.3.4. Sequential Arylation of Thiazole 138
5.4. Mechanistic studies on direct arylations 139
5.5. Direct synthesis of Tie2 Tyrosine Kinase Inhibitor 143
5.6. Summary 145
5.7. Experimental 146
References and notes 163

List of publication 165

Acknowledgement 167

Chapter 1

General Introduction

1.1. Polyfunctionalyzed heteroaromatics

Heteroaromatic moieties containing nitrogen, oxygen and sulfur atoms are frequently found as fundamental structures in natural products, pharmaceuticals and functional materials, and a tremendous amount of methods for construction of the motifs have been established. Indeed, polyfunctionalized heteroaromatics show various bioactive properties[1] and absorption-emission and redox behavior owing to their electronic and structural properties.[2] Moreover, the derivatives have acted not only as ligands for transition metals,[3] but also as a precursor of stabilized carbenes.[4] Owing to the importance of their utilities, extensive efforts are still paid to develop efficient synthetic routes to these structures. In previous cases, most of the procedures were developed based on condensation-cyclizations strategy.[5] However, a variety of derivatives are hardly obtained by using these approach since repeating multistep syntheses are usually needed to prepare less commonly available starting materials. Therefore, more straightforward procedures to develop polyfunctionalized heteroaromatics from commercially available or readily prepared starting materials have been strongly demanded.

1.1.1. Cross-coupling reaction of heteroaromatics leading to polyfunctionalized heteroaromatics

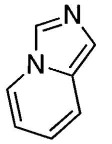
Of particular interest was the cross-coupling reactions[6] such as Suzuki-Miyaura, Kumada-Tamao-Corriu, Negishi, Hiyama, Stille, Heck and Sonogashira reactions since these are well-established as a dependable process applicable to many substrates. However, at the outset of the author's studies in this area, the preparation and use of electron-rich heteroaryl metal species or use of electron-rich heteroaryl halides as a coupling partner in the cross-coupling is hard to achieve. In general, heteroatoms such as a nitrogen atom in heteroaromatics readily bind to metal center resulting in inhibition of catalytic cycles (e.g. oxidative addition and transmetallation), and electron-rich heteroaryl species hardly undergoes oxidative addition. In addition, electron-rich heteroaryl metal species is usually unstable and readily decomposed *via* protodemetallation process owing to their high nucleophilicity.[7] Therefore, there have been tremendous efforts to resolve this issue to provide polyfunctionalized heteroaromatics.

1.1.2. Direct arylation of heteroaromatics leading to polyarylated heteroaromatics

During the past decades, C-H bond direct arylation reaction[8] has emerged as an attractive alternative to traditional cross-coupling reactions. According to the strategy, polyarylated heteroaromatics can be directly prepared from a variety of simple heteroaromatics and aryl (heteroaryl) halides. In addition, direct arylation reactions through cleavage of ubiquitous carbon-hydrogen bonds represent an environmentally and economically attractive strategy. Although a variety of methods for functionalizations of heteroaromatics have been reported, a selective and sequential protocol for multiple C-H bonds in heteroarenes to achieve polyarylated products is limited.[9]

In this thesis, the author describes syntheses of polyfunctionalized heteroarenes by transition metal catalyses such as cross-coupling reaction and C-H direct arylation of heteroaromatics.

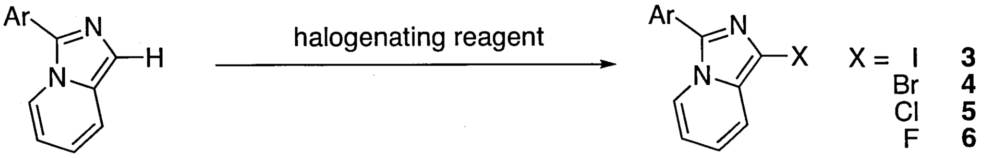
1.2. Functionalization of imidazo[1,5-*a*]pyridines by means of traditional cross-coupling strategy



1

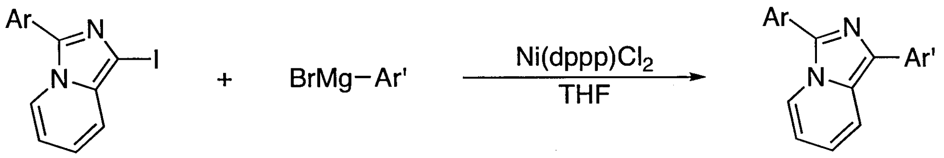
imidazo[1,5-*a*]pyridine

Imidazo[1,5-*a*]pyridines **1** are attractive classes of skeletons due to potentially applicable to photo- and electronic-functional materials such as organic light emitting diodes (OLEDs),[10] organic thin-layer field effect transistors (FETs),[11] as well as precursors of *N*-heterocyclic carbenes (NHCs).[12] In addition, owing to their bioactive properties, imidazo[1,5-*a*]pyridines have been applied to pharmaceuticals such as HIV-protease inhibitors,[13] cardio tonic agents,[14] aromatase inhibitors in estrogen-dependent diseases[15] and thromboxane A2 synthetase inhibitors.[16] Recently, a number of methods for the synthesis of substituted imidazo[1,5-*a*]pyridines *via* condensation-cyclization reactions have been reported.[17-19] As a part of the author's recent interest in the synthesis of imidazo[1,5-*a*]pyridine families to explore photo-functional materials, he focused on developing methods for synthesizing a series of imidazopyridines involving π-conjugated systems such as aryl, alkynyl and alkenyl groups by transition-metal-catalyzed cross coupling reactions. In chapter 2, first of all, the author has described syntheses of 1-halogenated imidazo[1,5-*a*]pyridines as a platform of coupling reactions. Halogenation of variety of imidazo[1,5-*a*]pyridines **2** proceeded with iodine, bromine, *N*-chlorosuccinimide and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as halogenating reagents and gave the corresponding 1-halogenated imidazopyridines **3-6** in good yields (scheme 1).



Scheme 1. Halogenation reaction of imidazopyridines

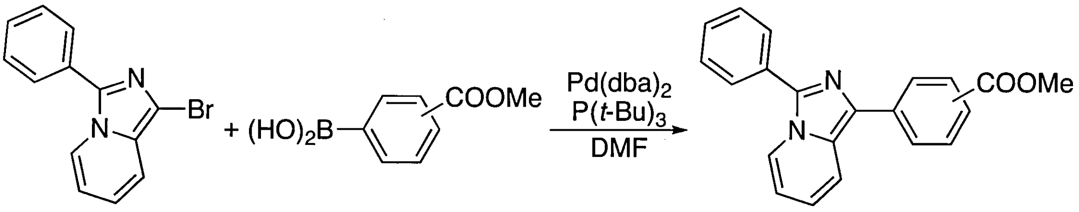
Then, arylations for the obtained halogenated imidazopyridines **3** and **4** are described. First, the author investigated nickel-catalyzed Kumada-Tamao-Corriu (KTC) coupling reaction using **3** and a variety of Grignard reagents **7** (scheme 2).



3 **7** **8**

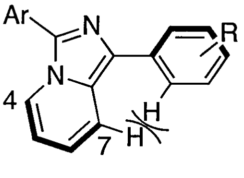
Scheme 2. KTC coupling of **3** with **7**

Although KTC coupling reaction succeeded by using 3-iodoimidazopyridines with Grignard reagents, some issues still remains for the compatibility of the substituents under the conditions (e.g. use of substrates bearing carbonyl group). Thus, Suzuki-Miyaura coupling of **3** with aryl boronic acid bearing ester was then investigated (scheme 3). Using 3-bromoimidazopyridine **4** as a substrate, the coupling of **4** and **9** proceeded smoothly to give 1,3-diarylimidazopyridine bearing ester group (**8’**) in good yield. To the best of the author’s knowledge, these results are the first examples for catalytic transformation of halogenated imidazopyridines.



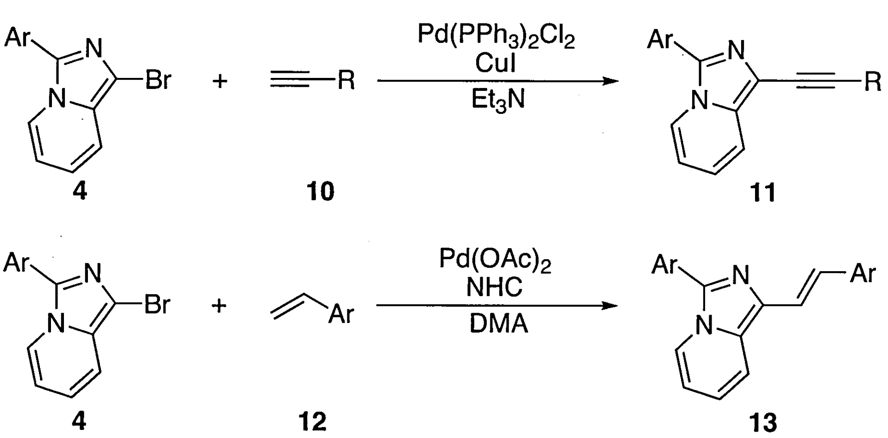
4 **9** **8'**

Scheme 3. Suzuki-Miyaura coupling reaction of **4** with **9**



8

The obtained π-expanded imidazopyridine derivatives **8** and **8'** emitted a variety of fluorescence. The quantum yields of 1,3-diarylated imidazopyridines were greatly improved when compared with those of the parent 3-monosubstituted compounds. Meanwhile, a series of derivatives obtained were found to form distorted π-conjugated systems due to steric repulsion of hydrogen atom at 4- or 7-position of imidazo[1,5-*a*]pyridines **8** and substituted aromatic rings by X-ray analyses and DFT calculations.[18c] In chapter 3, the author describes syntheses of a series of imidazopyridines bearing alkynyl groups to achieve planar π-conjugated systems using Sonogashira coupling reaction (scheme 4, upper). In addition, an alkenyl group was also introduced by using Heck reaction (scheme 4, lower).

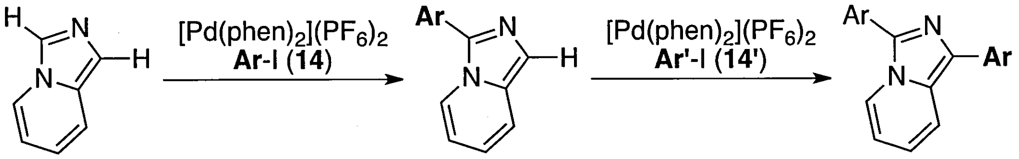


Scheme 4. Sonogashira coupling and Heck reaction of **4**

As expected, alkynyl substituents greatly influenced to absorption and emission maxima (λ_{abs} and λ_{em}) and fluorescent quantum yields, comparing with the both 3-arylated imidazopyridine **2** and 1,3-diarylated imidazopyridines **8**. In the case of alkene introduced **13**, fluorescent quantum yields decreased due to inhibition of forming suitable conjugated system by twisted olefin moiety, which was indicated by DFT calculations.[20]

1.3. Direct functionalization of Imidazo[1,5-*a*]pyridines using a Pd complex

Finally, in chapter 4 is described synthesis of 1,3-diarylimidazopyridine **8** by using C-H direct arylation reaction of **1**. During the studies on C-H bond direct arylation at 1-position of 3-arylimidazopyridines **2**, the author found the palladium complex bearing 1,10-phenanthroline as a ligand shows a high catalytic activity for direct arylation of imidazopyridines at 1-position. The result encouraged the author to investigate direct arylation reaction at 3-position of **1** using Pd-phenanthroline system to achieve direct synthesis of 1,3-diarylimidazopyridine from **1** by sequential arylation reaction (scheme 5).



1 **2** **8**

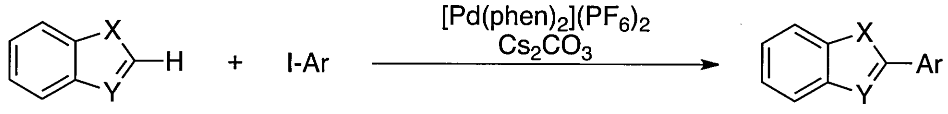
Scheme 5. Sequential arylation reaction of **1** leading to **8**

As a result, C3 arylation of imidazo[1,5-a]pyridine **1** was successful in the reaction with a variety of aryl iodides **14** to give monoarylated imidazole **2** in a selective fashion.

Following C1 arylation gave 1,3-diarylimidazoles **8** in good to high yields.

1.4. Direct arylation of heteroaromatics: benzazoles, thiophene, pyrrole and azoles using a Pd complex

Direct arylation reactions of benzazoles, thiophenes, pyrrole and azoles are also described in chapter 4. The author set benzazoles **15** as the first choice of the direct arylation of simple azoles with aryl iodides **14** using $[Pd(phen)_2](PF_6)_2$ as a catalyst. (scheme 6).

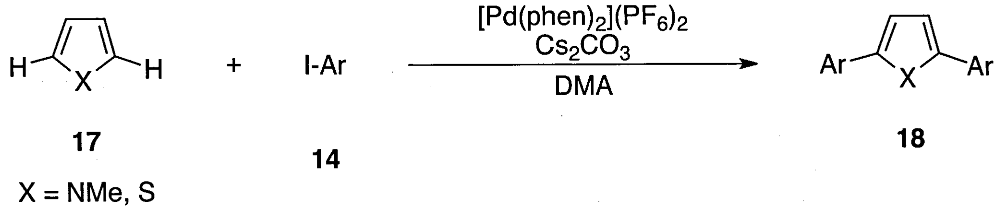


15 **14** **16**

X = NMe, O, S
Y = N, CH

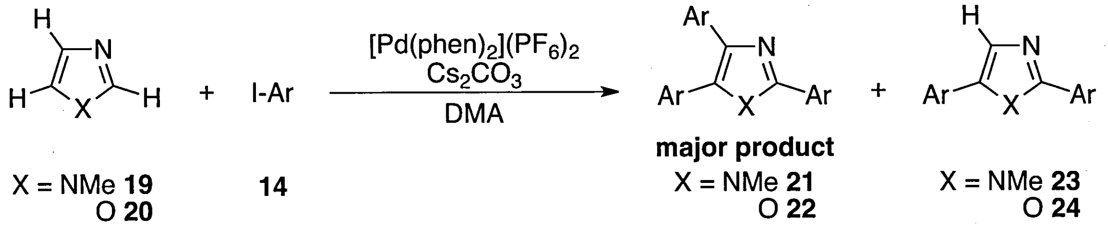
Scheme 6. Direct arylation of **15** with **14**

The reaction proceeded smoothly to give the corresponding arylated products in high yields regardless of electronic and steric properties of aryl iodides **14**. Encouraged by this result, the author investigated reaction of further heteroaromatics such as thiophene and pyrrole under the proposed reaction conditions (scheme 7).



Scheme 7. Direct diarylation of **17** with **14**

In this case, direct diarylation reaction took place at once to give **18** in good yields and no monoarylated product was observed. This catalysis can be applied to simple azoles **19** and **20**, which have potentially transformable three carbon-hydrogen bonds (scheme 8).



Scheme 8. Direct tri- or diarylation reaction of **19, 20** with **14**

Interestingly, triarylation reaction took place at once and gave the corresponding 2,4,5-triarylated azoles **21** and **22** as major products. Notably, no triarylated product was observed under previously reported direct arylation reaction conditions such as $Pd(OAc)_2/P(t\text{-}Bu)_3$ system. Instead, 2,5-diarylated products were yielded as major products in moderate yields.

1.5. Sequential direct functionalization of azoles using $[Pd(phen)_2](PF_6)_2$ complex

Generally, reactivity for the C-H bond direct arylations of 5-membered heteroaromatics are usually governed by π-nucleophilicity or C-H acidity as shown in Figure 1.

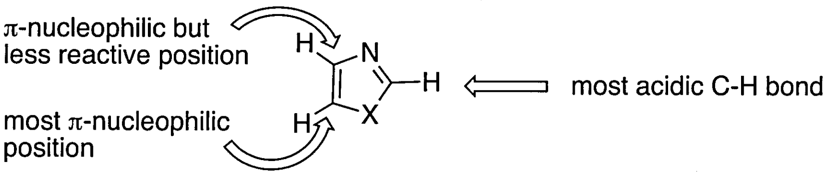


Figure 1. Reactivity of azoles

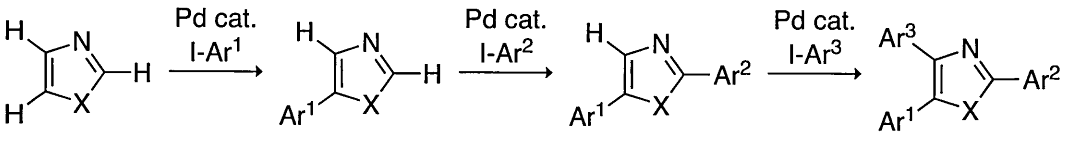
In the case of azoles, the C5 position shows high reactivity toward electrophilic substitution, and the C2 position have the most acidic C-H bond, and in recent studies, regioselective C2 or C5 arylation of azoles, were achieved by using these respects.[21] Meanwhile, a high yielding C4 direct arylation has not been established. In previous examples of regioselective arylation including C4 position leading to triarylated azoles, the each of syntheses used a special mean as follows:

(1) introducing directing groups into starting azoles[9a]

(2) using preactivated starting materials such as azole *N*-oxide[9c, 9e]

(3) protection and deprotection of nitrogens with SEM-group to switch its orientation[9f]

Meanwhile, as shown in scheme 8, C4 arylation products could be obtained by using the catalytic system, which the author developed in this thesis, in moderate to good yields. This observation encouraged the author to investigate sequential arylations of azoles using Pd-phenanthroline system. In chapter 5 is described syntheses of triaryl azoles from simple azoles by means of sequential arylation reaction using Pd-phenanthroline catalyst (scheme 9).



X = NMe **19**
S **25**

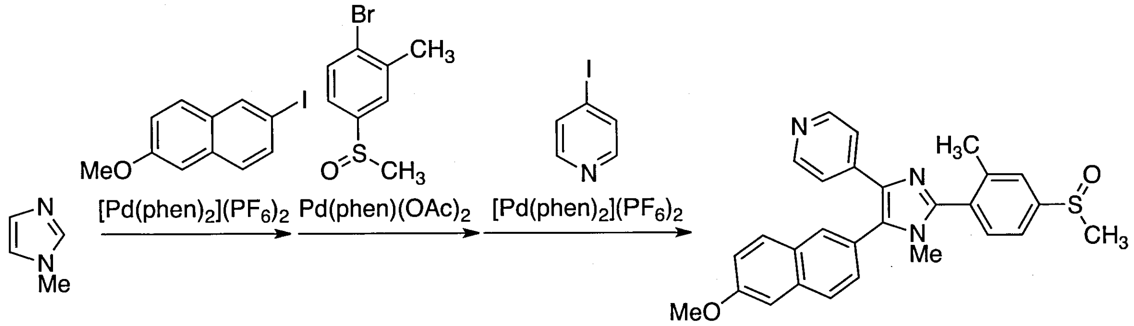
X = NMe **26**
S **27**

X = NMe **28**
S **29**

X = NMe **30**
S **31**

Scheme 9. Sequential arylation of **19** and **25**

The C5 and following C2 selective arylation were achieved under controlled reaction conditions, respectively. Finally, the present catalytic system showed high compatibility with C4 arylation reaction to give the product **30** in excellent yields. Triarylated thiazoles **31** were also obtained from thiazole **25** under the catalytic system. To substantiate the synthetic utility of the present methodology, the author then carried out the synthesis of medicinal compound, the Tie-2 Tyrosine Kinase Inhibitor **32**[22] (scheme 10).



19

32

Overall yields of
3 steps of direct arylations: 29%
The longest liner 4 steps: 25%

Scheme 10 Synthesis of Tie2 Tyrosine Kinase Inhibitor

The target compound **32** was obtained in 29% overall yield by 3 steps from *N*-methylimidazole **19**. Finally, mechanistic study of C2 and C4 arylation was also investigated and is described in chapter 5.

Reference

(1) (a) Sohda, K.; Hiramoto, M.; Suzumura, K.; Takebayashi, Y.; Suzuki, K.; Tanaka, A. *J. Antibiot.* **2004**, *58*, 32. (b) Sohda, K.; Nagai, K.; Yamori, T.; Suzuki, K.; Tanaka, A. *J. Antibiot.* **2005**, *58*, 27. (c) Cummings, G. C.; Ross, T. N.; Katt, P. W.; Hamilton, D. A. *Org. Lett.* **2009**, *11*, 25. (d)

Lefranc, D.; Ciufolini, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4198. (e) Demirbas, A.; Sahin, D.; Demirbas, N.; Karaoglu, A. S. *Eur. J. Med. Chem.* **2009**, *44*, 2896. (f) Sarojini, K. B.; Krishna, B. G.; Darshanraj, C. G.; Bharath, R. B.; Manjunatha, H. *Eur. J. Med. Chem.* **2010**, *45*, 3490.

(2) Champagne, B.; Kirtman, B. in *Handbook of Advanced Electronic and Photonic Materials and Devices*, Nalwa, S. N. Eds., Nonlinear Optical Materials, vol. 9, Academic Press, San Diego, 2001.

(3) For reviews on P,N ligands with pyridyl donors see. Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471. (b) Alcock,N. W.; Brown, J. M.; Hulmes, D. I. *Asymmetry* **1993**, *4*, 743.

(4) For reviews for stabilized carbenes, see (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

(5) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Black Science: Oxford, U.K., 2000.

(6) For review for cross-coupling reaction, see: de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.

(7) For an example with arylboronic acid, see: Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(8) For recent reviews for C-H arylation reactions, see: (a) Alberico, D.; Scott, M.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. For Pd-catalyzed arylation of heterocycles: (b) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826–1834. Review on transition metal catalysis for the synthesis of heteroaryl-heteroarenes: (c) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310.

(9) For recent examples for site selective arylation of azoles, see: (a) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron*, **2003**, *59*, 5685. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *131*, 3276. (d) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K.; *J. Org. Chem.* **2009**, *74*, 1826. (e) Campeau, L.-C.; Stuart, R. D.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (f) Joo, J. M.; Tour, B. B.; Sames, D. *J. Org. Chem.* **2010**, *75*, 4911.

(10) For examples of organic light-emitting diodes (OLED), see: (a) Nakatsuka, M.; Shimamura, T. Jpn. Kokai Tokkyo Koho JP 2001035664; *Chem. Abstr.* **2001**, *134*, 170632. (b) Tominaga, G.; Kohama, R.; Takano, A. Jpn. Kokai Tokkyo Koho JP 2001006877; *Chem. Abstr.* **2001**, *134*, 93136. (c) Kitazawa, D.; Tominaga, G.; Takano, A. Jpn. Kokai Tokkyo Koho JP 2001057292; *Chem. Abstr.* **2001**, *134*, 200276. (d) Salassa, L.; Garino, C.; Albertino, A.; Volpi, G.; Nervi, C.; Gobrtto, R.; Hardcastle, K. I. *Organometallics* **2008**, *27*, 1427.

(11) For an example of organic thin-layer field effect transistor (FET), see:Nakamura, H.; Yamamoto, H. PCT Int. Appl. WO 2005043630; *Chem. Abstr.* **2005**, *142*, 440277.

(12) For examples of *N*-heterocyclic carbenes precursors, see: (a) Alcarazo, M.; Roseblade, S. J.;

Cowley, A. R.; Fernañdez, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290. (b) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207. (c) Hahn, F. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1348.

(13) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.

(14) Davey, D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337.

(15) Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E. *J. Med. Chem.* **1991**, *34*, 725.

(16) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. *J. Med. Chem.* **1985**, *28*, 164.

(17) Bower, J. D.; Ramage, C. R. *J. Chem. Soc.* **1955**, 2834.

(18) For recent advances in the synthesis of imidazo[1,5-*a*]pyridines via an oxidative pathway, see: (a) Bluhm, M. E.; Ciesielski, M.; Gorls, H.; Döring, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2962. (b) Bluhm, M. E.; Folli, C.; Pufky, D.; Kröer, M.; Walter, O.; Döring, M. *Organometallics* **2005**, *24*, 4139. (c) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621. (d) Ostermeier, M.; Limberg, C.; Ziemer, B.; Karunakaran, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5329. (e) Shibahara, F.; Sugiura, R.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *J. Org. Chem.*, **2009**, *74*, 3566. (f) Arvapalli, S. V.; Chen, G.; Kosarev, S.; Tan, E. M.; Xie, D.; Yet, L. *Tetrahedron Lett.* **2010**, *51*, 284, and references cited therein.

(19) For recent advances in the synthesis of imidazo[1,5-*a*]pyridines via an acid-mediated condensation pathway, see:(a) Wang, J.; Mason, R.; VanDerveer, K.; Feng, D.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415. (b) Dyers, J. W. L., Jr.; Mason, R., Jr.; Amoyaw, P.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353. (c) Siddiqui, S. A.; Potewar, T. M.; Lahoti, R. J.; Srinivasan, K. V. *Synthesis* **2006**, *17*, 2849. (d) Crawforth, J. M.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916 and references cited therein.

(20) See chapter 3.

(21) For recent reports for C2 arylation, see: (a) Hoarau, C.; Du Fou de Kerdaniel, A.; Bracq, N.; Grandclaudon, P.; Couture, A.; Marsais, F. *Tetrahedron Lett.* **2005**, *46*, 8573. (b) Derridj, F.; Djebbar, S.; Benali-Baitich, O.; Doucet, H. *J. Organomet. Chem.* **2008**, *693*, 135. (c) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383. (d) Strotman A. N.; Chobanian, H, R.; Guo,Y.; He, J.; Wilson, E. J. *Org. Lett.* **2010**, *12*, 3578. For recent reports for C5 arylation, see: (a) Bellila, F.; Cauteruccio, S.; Di Fiore, A.; Rossi, R. *Eur. J. Org. Chem.* **2008**, 5436. Joo, M. J.; Toure, B. B.; Sames, D.; *J. Org. Chem.* **2010**, *75*, 4911.

(22) (a) Semones, M.; Feng, Y.; Johnson, N.; Adams, J. L. *Bio. Med. Chem. Lett.* **2007**, *17*, 4756; (b) Johnson, N. W.; Semones, M.; Adams, J. L.; Hansbury, M.; Winkler, J. *Bio. Med. Chem. Lett.* **2007**, *17*, 5514.

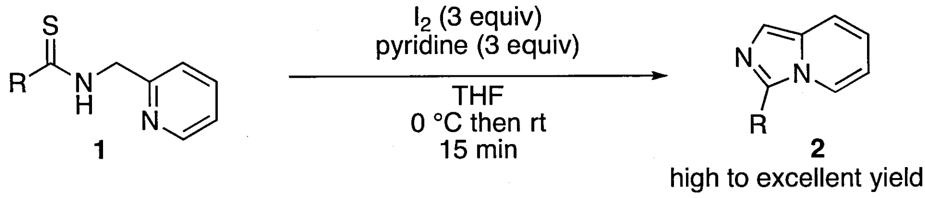
Chapter 2

Synthesis of 1,3-diarylated Imidazo[1,5-*a*]pyridines *via* Conventional Cross-Coupling Strategies

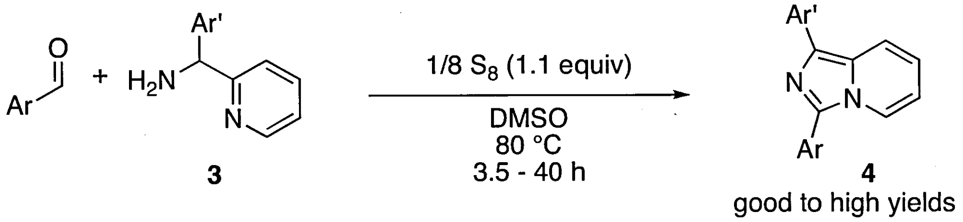
The halogenation of 3-arylimidazo[1,5-*a*]pyridines was carried out with iodine, bromine, *N*-chlorosuccinimide, and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as halogenating agents to give selectively halogenated products 1-halo-3-arylimidazo[1,5-*a*]pyridines in good to excellent yields. Kumada-Tamao-Corriu cross-coupling of the obtained 1-iodo-3-arylimidazo[1,5-*a*]pyridines and aryl Grignard reagents led to 1,3-diarylated imidazo[1,5-a]pyridines in good to excellent yields. Suzuki-Miyaura cross-coupling of the 1-bromo-3-phenylimidazo[1,5-*a*]pyridine and *p*- or *m*-methoxycarbonylphenylboronic acids furnished the coupling products in respective yields of 91% and 61%. The obtained 1,3-diarylated imidazo[1,5-*a*]pyridines showed a wide variety of fluorescent emissions with a wavelength range of 449–533 nm with improved quantum yields compared to monoarylated ones.

2.1. Introduction

Imidazo[1,5-*a*]pyridines are an important class of compounds due to their unique photophysical and biological properties.[1] As a part of recent interest in the synthesis of this family to explore photo-functional materials, the author was interested in methods for synthesizing a series of imidazopyridines involving π-conjugated systems such as aryl and alkynyl groups.[2,3] During recent studies on the transformation of thioamides,[4] two methods for synthesis of imidazo[1,5-*a*]pyridine derivatives were reported as follow: 1) Thioamides **1** that bear a 2-pyridylmethyl group at a thioamide nitrogen undergo smoothly oxidative desulfurization–cyclization in the presence of iodine and pyridine (eq. 1).[5] The reaction gives a wide variety of 3-substituted imidazo[1,5-*a*]pyridines **2** in high to excellent yields. In addition, 2) oxidative condensation–cyclization of aldehydes and aryl-2-pyridylmethyl amines **3** using elemental sulfur as an oxidant gives 1,3-diarylated imidazopyridines **4** directly (eq. 2),[6] but less commonly available **3** must be prepared by a multistep synthesis from 2-pyridylcarboaldehyde.[3a] Thus, a more straightforward and efficient method for the synthesis of diverse 1,3-diarylated imidazo[1,5-*a*]pyridines is needed. Meanwhile, 3-arylated imidazo[1,5-*a*]pyridines **2**, which are readily obtained by the former method, were expected to be an expandable platform for 1,3-diarylated imidazo[1,5-*a*]pyridines by a selective halogenation–cross-coupling sequence.



(1)



(2)

The transition metal-catalyzed cross-coupling reaction of aryl halides and arylmetal reagents is one of the most straightforward synthetic strategies for obtaining a biaryl moiety, and many examples have been reported.[7-12] However, there are few reported examples in which electron-rich nitrogen-containing heteroaryls such as imidazopyridines are used as one or both of the coupling partners (e.g. heteroaryl halides and/or heteroaryl metals),[13] since the oxidative addition of electron-rich aryl halides to low-valence metals is usually sluggish, and an unprotected nitrogen moiety readily binds to metal catalysts to possibly inhibit the reaction (e.g. oxidative addition and transmetallation). In addition, electron-rich heteroaryl metal species are usually unstable and readily undergo protodemetalation due to their high nucleophilic character.[14] In fact, in most previous reports on cross-coupling with such a electron-rich nitrogen-containing heteroaryl substrates, the substrates were modified by attaching some electron-withdrawing groups directly to the heteroaryl moiety to reduce the electron density.[13] Therefore, it is important to investigate methods to achieve such a reaction with high efficiency but in the absence of electron-withdrawing groups. In this chapter, the selective halogenation of 3-arylimidazo[1,5-*a*]pyridines and transition metal-catalyzed cross-coupling reactions, with Kumada-Tamao-Corriu (KTC) and

Suzuki-Miyaura protocols, with electron-rich substrates are described. Under the optimal conditions, the cross-coupling reactions of the imidazopyridine substrates and arylmetal reagents proceeded with high efficiency in the absence of a protecting group on nitrogen moiety and an electron-withdrawing group.

2.2. Halogenation of imidazo[1,5-*a*]pyridines

Electrophilic substitution of indolizine-related compounds and electrophiles is expected to occur at the C1 or C3 position of the ring due to the electron rich character of the 5-membered ring moiety and the main mesomeric contributors that are stabilized by the formation of pyridinium moiety, as shown in Fig. 1.[1b] Thus, to obtain selective halogenated imidazopyridines **5-8**, conventional electrophilic halogenations were examined.

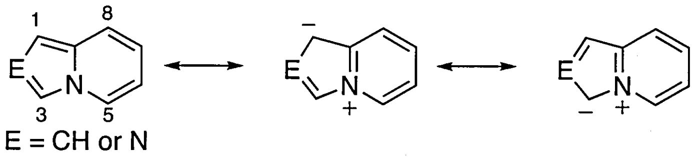
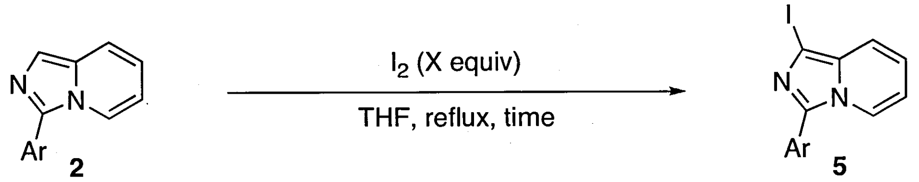


Figure 1. Three main mesomeric contributors of imidazopyridine family

2.2.1. Iodination

Initially, the iodination of imidazo[1,5-*a*]pyridines was carried out. When 3-phenylimidazo[1,5-*a*]pyridine (**2a**) was treated with 3 equiv of iodine in THF under reflux conditions for 2 h, as expected, the iodination proceeded selectively at the 1-position of imidazopyridine **2a** to give the desired product **5a** in 87% yield (Table 1, entry 1). In the presence of Lewis acid or base such as $AlCl_3$ or pyridine, no reaction took place.[15] Under similar conditions, the C1-selective iodination of imidazopyridines **2** bearing an electron-donating or electron-withdrawing substituent at the 4-position of the phenyl group on C3 was carried out. The iodination proceeded smoothly to give the desired products **5** in high to excellent yields (entries 2-6). Meanwhile, the reaction of imidazopyridine bearing a highly electron-rich 4-dimethylaminophenyl group **2g** consumed the starting material within 30 min but resulted in the formation of a complex mixture, maybe due to competitive iodination at the dimethylaminophenyl group. Interestingly, an internal pyridyl group did not inhibit the iodination, and the reaction of imidazopyridine bearing a 2-pyridyl group **2h** gave the corresponding iodination product **5h** in 86% yield.

Table 1. Iodination of 3-arylimidazo[1,5-*a*]pyridines **2**



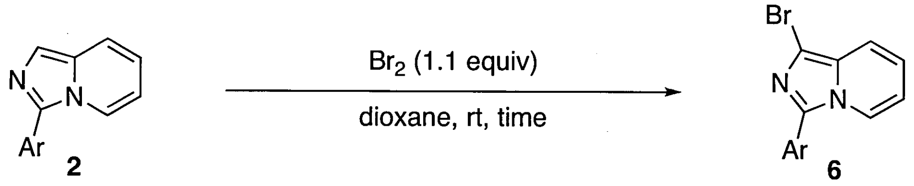
Entry	Ar		X (equiv)	Time (h)		Yield (%)[a]
1	Ph-	**2a**	3	2	**5a**	87
2	4-MeOC_6H_4-	**2b**	2	1	**5b**	99
3	4-FC_6H_4-	**2c**	3	1.5	**5c**	96
4	4-$CF_3C_6H_4$-	**2d**	3	0.5	**5d**	98
5	4-MeC_6H_4-	**2e**	3	1	**5e**	82
6	4-BrC_6H_4-	**2f**	3	0.6	**5f**	81
7	4-$Me_2NC_6H_4$-	**2g**	3	0.5	**5g**	complex mixture
8	2-pyridyl	**2h**	3	1	**5h**	86

[a] Isolated yields.

2.2.2. Bromination

Selective bromination with Br_2 as a bromine source was also investigated.[16] Although the reactions in THF or dichloromethane did not proceed at all, the product **6a** was obtained in 82% yield in dioxane (Table 2, entry 1). Other imidazopyridines were treated with Br_2 in dioxane. Bromination took place with **2** having not only an electron-donating or -withdrawing group, but also a basic 2-pyridyl group to give the desired products **6** in excellent yields (entries 2-4, 6 and 7), except for 3-(4-tolyl)imidazopyridine **2e** (entry 5). The reaction of **2e** gave **6e** in a significantly lower yield (56%), probably due to the competitive radical bromination at the benzylic position of the tolyl group.[17]

Table 2. Bromination of 3-arylimidazo[1,5-*a*]pyridines **2**



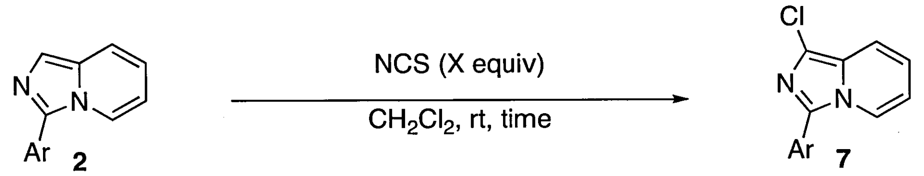
Entry	Ar		Time (h)	Yield (%)[a]	
1	Ph-	**2a**	1.5	**6a**	82
2	4-MeOC_6H_4-	**2b**	2	**6b**	97
3	4-FC_6H_4-	**2c**	1.5	**6c**	93
4	4-$CF_3C_6H_4$-	**2d**	2	**6d**	99
5	4-MeC_6H_4-	**2e**	0.5	**6e**	56
6	4-BrC_6H_4-	**2f**	1	**6f**	92
7	2-pyridyl	**2h**	1.5	**6h**	89

[a] Isolated yields.

2.2.3. Chlorination

Chlorination of **2** was also performed with *N*-chlorosuccinimide (NCS) in dichloromethane. The reactions of **2a,c-f** with a slight excess amount of NCS at room temperature afforded the desired products **7** in high yields (Table 3, entries 1, 3-6). Although the reaction required an excess amount (3 equiv) of NCS, 4-MeO-phenyl- and 2-pyridyl-substituted **2b** and **2h** were also chlorinated in isolated yields of 80% and 88%, respectively (entries 2, 7).

Table 3. Chlorination of 3-arylimidazo[1,5-*a*]pyridines **2**

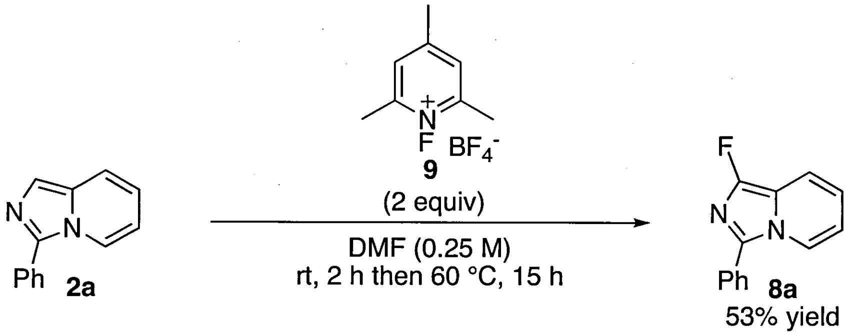


Entry	Ar		X (equiv)	Time (h)	Yield (%)[a]	
1	Ph-	**2a**	1.3	1.5	**7a**	80
2	4-MeOC$_6$H$_4$-	**2b**	3	1.5	**7b**	80
3	4-FC$_6$H$_4$-	**2c**	1.3	1.5	**7c**	84
4	4-CF$_3$C$_6$H$_4$-	**2d**	1.5	2	**7d**	86
5	4-MeC$_6$H$_4$-	**2e**	1.3	1.5	**7e**	90
6	4-BrC$_6$H$_4$-	**2f**	1.5	2	**7f**	84
7	2-pyridyl	**2h**	3	2	**7h**	88

[a] Isolated yields.

2.2.4. Fluorination

Whereas a cross-coupling reaction rarely occurs on a carbon-fluorine bond, heterocycles bearing a fluorine atom often play an important role in pharmaceutical, agrochemical, and material science.[18] Thus, fluorination of imidazopyridine **2a** was also investigated. 1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**9**) was chosen as a fluoronium source for fluorination due to its ready availability. The reaction of **9** in dichloromethane or benzene gave a small amount of the desired product **8a** in 5.6% and 13% yields, respectively. After the optimization of the solvents, DMF was a suitable solvent for this reaction. Concentration of the solution also slightly affected the product yield and the reaction in 0.25 M DMF solution of **2a** gave the best result, with an isolated yield of 53% (eq. 3).



(3)

2.3. Cross-coupling reactions

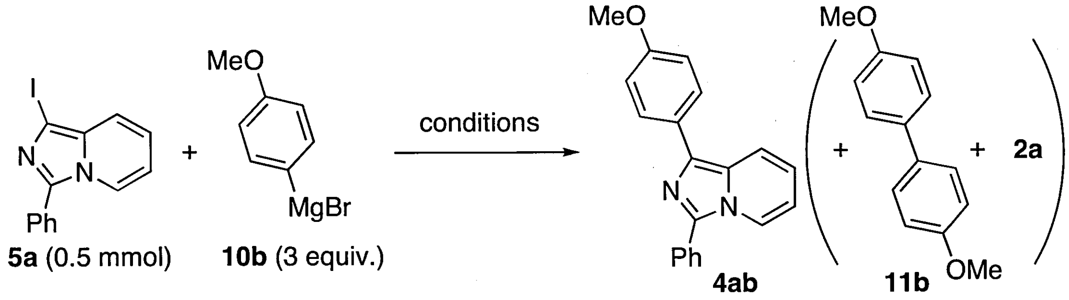
2.3.1. Kumada-Tamao-Corriu Coupling reaction

Kumada-Tamao-Corriu (KTC) cross-coupling was examined as the first choice for a cross-coupling reaction with iodo-imidazopyridines **5** due to the ready availability of Grignard reagents.

2.3.1.1. Optimization of Reaction Conditions

First, KTC cross-coupling of **5a** and 4-methoxyphenylmagnesium bromide (**10b**) under different typical conditions was examined (Table 4).

Table 4. Optimization of KTC cross-coupling of **5a** and 4-methoxyphenylmagnesium bromide



Entry	Conditions	Yield (%)[a]
1	$NiCl_2$(10 mol%), rt, 3 h	44
2	$NiCl_2$(10 mol%), 0 °C then reflux, 2.5 h	40
3	$NiCl_2$(10 mol%), -78 °C then rt, 19 h	complex mixture
4	Ni(acac)$_2$(10 mol%), DIBAL-H(20 mol%) 0 °C then rt, 4 h	13
5	Ni(acac)$_2$(10 mol%), DIBAL-H(20 mol%) dppp(20 mol%), 0 °C then rt, 3 h	40
6	Ni(dppp)Cl_2(10 mol%), 0 °C then rt, 3 h	44
7	Ni(dppp)Cl_2(10 mol%), 0 °C then reflux, 2.5 h	complex mixture
8	Ni(dppp)Cl_2(10 mol%), 0 °C then rt, 1 h	86

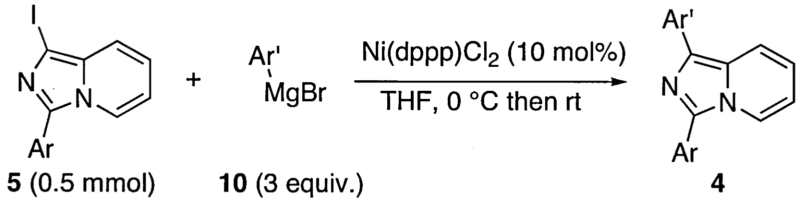
[a] Isolated yields.

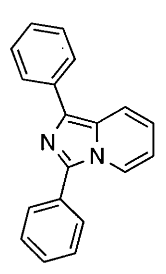
A mixture of **5a** and $NiCl_2$ (10 mol%) was treated with **10b** at room temperature to give the coupling product **4ab** in 44% yield along with significant amounts of homocoupling product **11b** and reduced starting imidazopyridine **2a** (entry 1). A higher temperature did not affect the yield, and the reaction under reflux conditions furnished **4ab** in 40% yield along with similar byproducts (entry 2). Treatment with Grignard reagent at -78 °C followed by stirring at room temperature was not effective for the conversion of **5a** (entry 3). In this case, the reaction gave a complex mixture after 19 h, though **5a** still remained. The use of $Ni(acac)_2$ as a catalyst and diisopropylaluminum hydride (DIBAL-H) as a reductant for catalyst to prepare Ni(0) species *in situ* did not give a good result (entry 4). Meanwhile, the use of diphenylphosphinopropane (dppp) as a ligand slightly improved the yield of **4ab** (entries 4 vs 5). Although the yield of **4ab** did not improve (44%), the use of $Ni(dppp)Cl_2$ suppressed the formation of **11b** (entry 6). Harsh conditions gave a complex mixture (entry 7). Finally, immediate workup after complete conversion of the substrate **5a**, which was monitored by TLC analysis, was effective and the reaction at rt for 1 h gave **4ab** in 86% yield (entry 8). The results suggested that the product **4ab** is unstable under these reaction conditions.

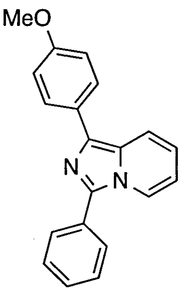
2.3.1.2. Scope of Substrates

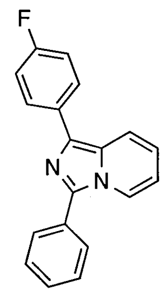
With the optimum conditions in hand, the KTC cross-coupling of **5** and a variety of Grignard reagents **10** were examined with a combinatorial approach. The results are summarized in Table 5. The coupling with substituted aryl Grignard reagents **10** proceeded smoothly to give the products **4** in good to excellent NMR yields and moderate to high isolated yields. The use of tolyl Grignard **10e** tends to decrease the isolated yields of the products **4ae-4de**, maybe due to the instability of the product on silica gel. *p*-Trifluoromethyl imidazopyridine **5d** was a relatively sluggish substrate and the reaction required a slightly longer reaction time (**4da-4df**). Since the crystallization of **4bb** is quite fast and the product crystallized in a column under purification by column chromatography on silica gel, the isolated yield of **4bb** was significantly less than the NMR yield. The heteroaryl Grignard reagent 2-thienylmagnesium bromide (**10g**) also acted as a coupling partner of **5** to give the products **4ag-4dg** in moderate to high yields, though the reactions needed *ca* 36 h for complete conversion. In addition, no reactions were observed in the reaction of pyridyl imidazopyridine **5h** and any of the Grignard reagents tested under these conditions.

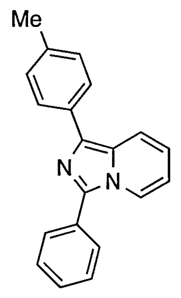
Table 5. Substrate scope of KTC cross-coupling[a]

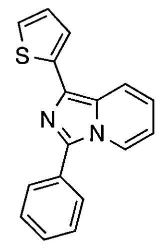


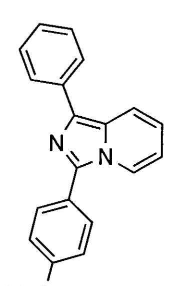

4aa
30 min, 99%(80%)

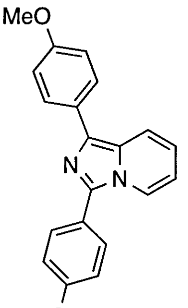

4ab
1 h, 90%(83%)

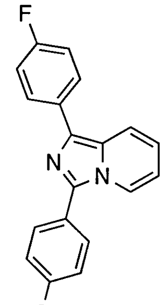

4ac
1 h, 83%(58%)

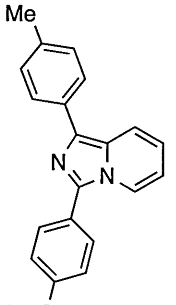

4ae
1 h, 85%(52%)

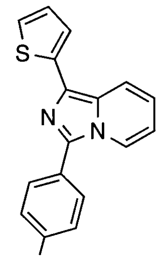

4ag
36 h, nd[b](52%)

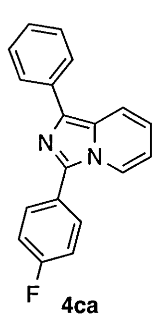

4ba
1 h, 93%(81%)

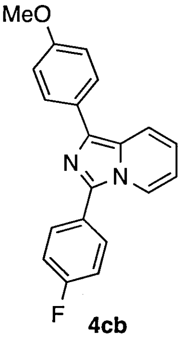

4bb
1 h, 83%(62%)

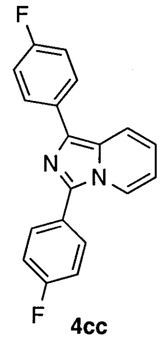

4bc
1 h, 98%(96%)

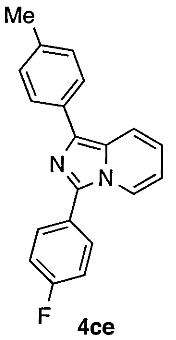

4be
1 h, 90%(58%)

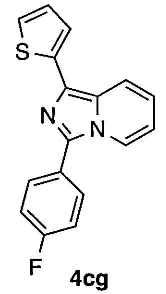

4bg
37 h, nd[b](68%)

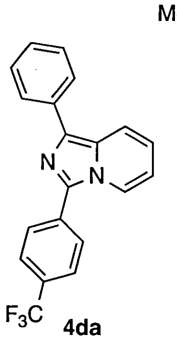

4ca
1 h, 95%(89%)

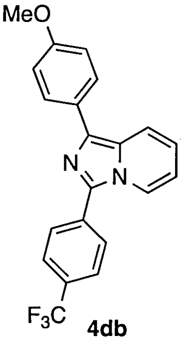

4cb
1 h, 88%(83%)

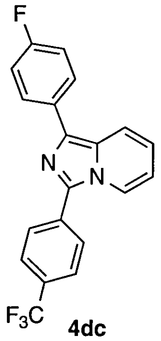

4cc
1 h, 83%(83%)

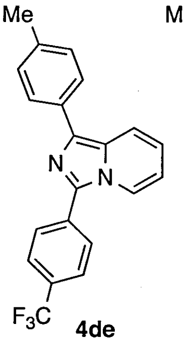

4ce
1 h, 80%(52%)

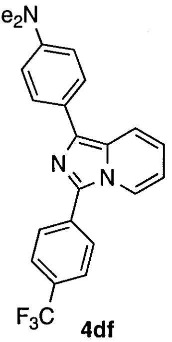

4cg
36 h, nd[b](81%)

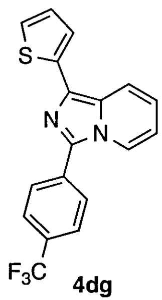

4da
1.5 h, 68%(37%)


4db
1 h, 68%(66%)


4dc
2 h, 83%(55%)


4de
1.5 h, 70%(58%)


4df
2 h, 98%(48%)


4dg
36 h, nd[b](93%)

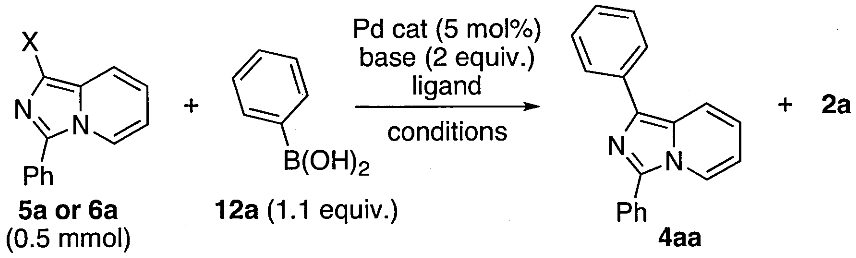
[a] NMR yields are shown. Isolated yields are shown in parentheses. [b] Not determined.

2.3.2. Suzuki-Miyaura cross-coupling reaction

Although KTC cross-coupling of **5** and aryl Grignard reagents **10** was succeeded, the compatibility of the substituents (e.g. the use of ester, nitrile and nitro groups) was still problematic under these conditions. Therefore, Suzuki-Miyaura cross-coupling was investigated next.

In the first unsuccessful attempts at Suzuki-Miyaura cross-coupling, iodinated imidazopyridines **5a** or **5d** were used in the reaction as a coupling partner. For example, the treatment of **5a** with a catalytic amount of $Pd(OAc)_2$ and a stoichiometric amount of Cs_2CO_3 and phenylboronic acid (**12a**) did not give the coupling product, and starting **5a** was recovered in 54% yield (Table 6, entry 1). The use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ in the reaction with **5d** led to the reduced product **2d** in quantitative yield (entry 2). On the other hand, the use of brominated imidazopyridine **6a** in the presence of $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$ gave the coupling product **4aa** in respective yields of 38% and 59%, (entries 3 and 4). After several optimizations, we found that the treatment of **6a** with $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as a catalyst and KOH as a base for 3 h gave the product in 84% yield (entry 5).

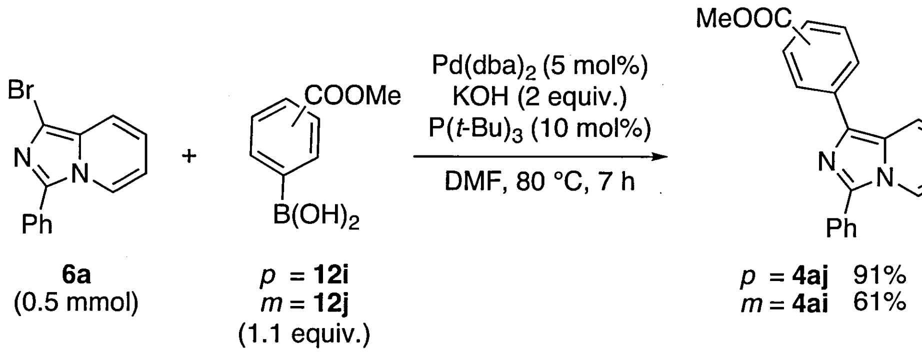
Table 6. Optimization of Suzuki-Miyaura Cross-coupling of **5** and Phenylboronic Acid (**12a**)



Entry	X	Pd cat	Base	ligand	Conditions	Yield (%)[a]
1	I	$Pd(OAc)_2$	Cs_2CO_3	——	50 °C, 30 h	—[b]
2[c]	I	$Pd(PPh_3)_4$	Cs_2CO_3	——	90 °C, 27 h	—[d]
3	Br	$Pd(OAc)_2$	Cs_2CO_3	——	80 °C, 90 h	38
4	Br	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	——	80 °C, 90 h	59
5	Br	$Pd(dba)_2$	KOH	$P(t\text{-}Bu)_3$[e]	80 °C, 3 h	84

[a] Isolated yield. [b] Starting **5a** was recovered in 54% yield. [c] **5d** was used as a substrate.
[d] **2d** was obtained as a reduced product in 97% yield. [e] 10 mol%.

Subsequently, the reactions of *p*- or *m*-methoxycarbonylphenylboronic acid **12i-j** were carried out under these conditions (eq 4). The reaction of **12i** afforded the product **4ai** in high yield. Although the yield was slightly decreased, the reaction of **12j** also gave the product **4aj** in 61% yield. In both cases, no hydrolysis of ester was observed.



(4)

2.4. Photophysical properties of imidazo[1,5-*a*]pyridines

The obtained products emitted a variety of fluorescence, as shown in Fig. 2. To better understand the details of the photophysical properties, UV/Vis and fluorescent spectra of the products are summarized in Table 7. As a result, trends in absorption, emission, and quantum yield are still unclear due to the complicated dual influences of two aryl groups, whereas the introduction of an aryl group into imidazo[1,5-*a*]pyridines obviously affected emission color and improved the quantum yield compared with those of parent **2a-h** (entries 1-8 vs 9-29). Nonetheless, the emissions of *p*-fluorophenyl substituted at C3 **4ca-4cg** were significantly influenced by the substituents at the C1 positions compared to other substrates (entries 19-23). Similarly, the emissions of a *p*-tolyl or 2-thienyl group at C1 **4ae-4de** (entries 12, 17, 22, and 27) and **4ag-4dg** (entries 13, 18, 23, and 28) were quite sensitive to the substituents on C3. The emission efficiencies for a strong electron-withdrawing carboxymethyl group-substituted **4ai** and **4aj** were significantly decreased as in the case of 3-(4-nitro-1,1'-biphen-4'-yl)imidazo[1,5-*a*]pyridine.[19]

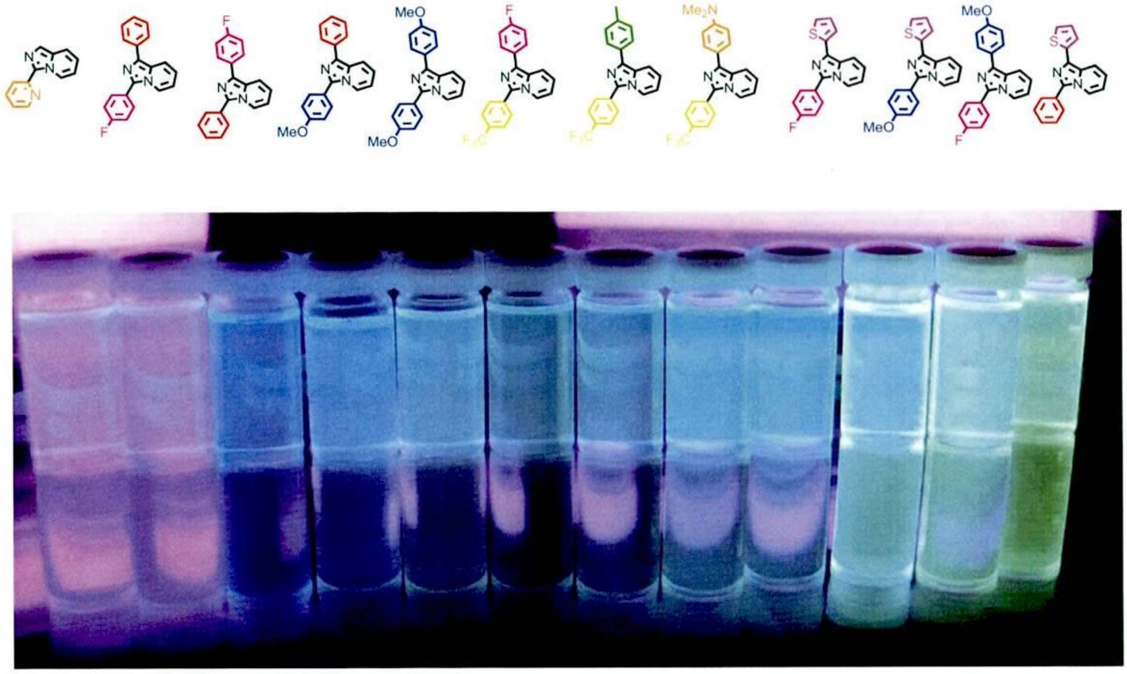
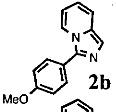
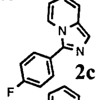
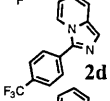
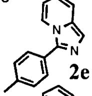
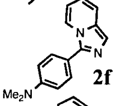
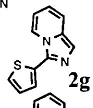
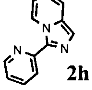
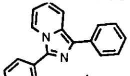
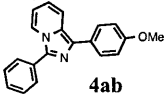
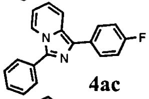
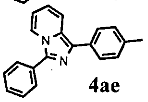
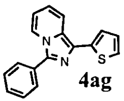
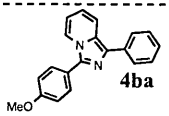
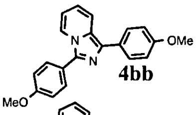
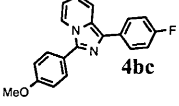
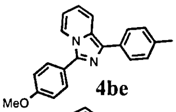
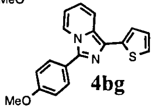
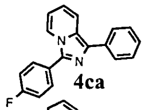
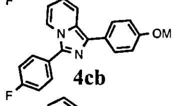
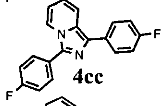
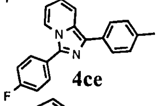
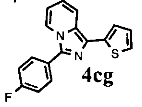
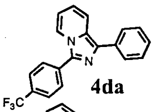
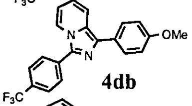
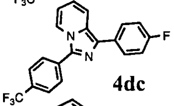
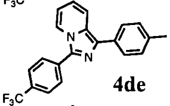
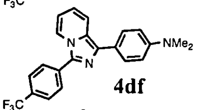
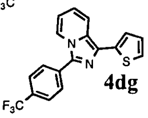
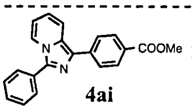
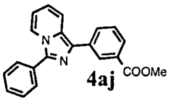


Figure 2. Selected emissions of obtained imidazo[1,5-*a*]pyridines in $CHCl_3$ under 365 nm irradiation

Table 7. Photophysical studies on obtained imidazo[1,5-*a*]pyridines

entry	compound	UV/Vis[a]		fluorescence[a]	
		λmax (nm)	log ε	λmax (nm)	Φ_F[b]
1	 **2a**	317	4.25	461	0.072
2	 **2b**	306	4.05	469	0.052
3	 **2c**	312	4.11	465	0.060
4	 **2d**	340	4.12	459	0.039
5	 **2e**	314	4.11	458	0.064
6	 **2f**	269 322	4.14 4.33	482	0.076
7	 **2g**	340	4.12	475	0.025
8	 **2h**	348	4.04	425	0.022
9	 **4aa**	308	4.18	454	0.14
10	 **4ab**	308	4.35	471	0.17
11	 **4ac**	308	4.30	461	0.14
12	 **4ae**	293	3.92	457	0.20
13	 **4ag**	322	4.16	533	0.087
14	 **4ba**	301	4.25	465	0.18
15	 **4bb**	303	4.31	479	0.22
16	 **4bc**	317	4.25	461	0.063
17	 **4be**	303	4.25	521	0.13
18	 **4bg**	316	4.05	483	0.14
19	 **4ca**	304	4.11	449	0.19
20	 **4cb**	268	4.12	526	0.17
21	 **4cc**	297	4.11	486	0.20
22	 **4ce**	293	4.10	523	0.16
23	 **4cg**	319	4.12	511	0.12
24	 **4da**	301 343	3.85 3.87	479	0.11
25	 **4db**	301 353	4.02 3.94	467	0.16
26	 **4dc**	291 353	3.95 3.90	478	0.15
27	 **4de**	296 359	4.16 4.08	487	0.11
28	 **4df**	313	4.12	508	0.12
29	 **4dg**	269 309	4.00 3.77	474	0.11
30	 **4ai**	339	4.38	477	0.080
31	 **4aj**	339	4.92	474	<0.01

[a] Measured in $CHCl_3$. [b] Quantum yields (Φ_F) were determined with reference to quinine sulfate in 0.1 M aqueous sulfuric acid (excited at 350 nm).[20]

2.5. Summary

In conclusion, a set of halogenations for imidazo[1,5-*a*]pyridines have been investigated. The iodinated and brominated imidazopyridines obtained could be used in KTC or Suzuki-Miyaura cross-coupling. Although the trend in emission is still unclear, a series of imidazopyridines showed a wide variety of fluorescent emissions.

2.6. Experimental

2.6.1 General Information

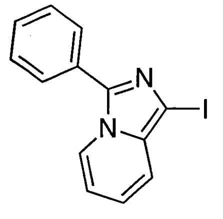
General Remarks: The IR spectra were obtained on a JASCO FT-IR spectrophotometer. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a JEOL α-400 (400, 100, 376 MHz) in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C are reported in d values referred to tetramethylsilane and $CDCl_3$ as an internal standard, respectively. The ^{19}F chemical shifts are expressed in d value deshielded with respect to CF_3COOH as an external standard. The mass spectra (MS) and high resolution mass spectra (HRMS) were taken on a JEOL JNM 700 mass spectrometer. Elemental analyses were carried out by Elemental Analysis Center of Kyoto University. Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. UV/Vis spectra were measured on a JAI Ubest-55 spectrophotometer. Fluorescence spectra were measured on a Hitachi F-4500 spectrophotometer. Preparative recycling gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-908 recycling preparative HPLC equipped with JAIGEL-1H and -2H columns (chloroform as an eluent).

Materials: Unless otherwise noted, reagents were commercially available and were used without purification. Imidazo[1,5-*a*]pyridines **2** were prepared according to previously reported method.[5] Tetrahydrofuran (dehydrated) was purchased from Kanto Chemical Co., and used without further purification. DMF was distilled over calcium hydride under reduced pressure. Silica gel used for column chromatography was Silica gel 60 N (Spherical, Neutral, 100–210 mm) from Kanto Chemical Co., Inc.

2.6.2. General procedure for the iodination of 3-arylimidazo[1,5-*a*]pyridines 2

To a solution of 3-arylimidazo[1,5-*a*]pyridine **2** (2 mmol) in THF (4 mL) was added iodine (1.53 g, 6 mmol, 3 equiv) at room temperature under an Ar atmosphere. The resulting mixture was stirred at reflux temperature. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq., neutralized with $NaHCO_3$ aq., and extracted with CH_2Cl_2 (30 mL x3). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 1-iodo-3-arylimidazo[1,5-*a*]pyridine **5**.

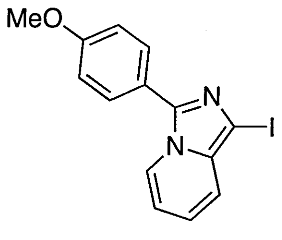
1-Iodo-3-phenylimidazo[1,5-a]pyridine (**5a**)



Chemical Formula: $C_{13}H_9IN_2$
Exact Mass: 319.9810
Molecular Weight: 320.1284

87% yield, brownish solid, mp 118-119 °C, Rf = 0.52 (hexane : AcOEt = 4 : 1). IR (KBr) 1629.6, 1511.0, 1453.1, 1356.7, 1257.4, 1005.7, 942.1, 773.3, 740.5, 698.1, 682.7 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.52 (t, *J* = 7.3 Hz, 1H), 6.72 (dd, *J* = 7.3, 9.3 Hz, 1H), 7.27 (d, *J* = 9.3 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.68 (d, *J* = 7.3 Hz, 2H), 8.13 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (CDCl$_3$) δ 74.1, 113.9, 119.0, 120.2, 121.8, 128.0, 129.0, 129.1, 129.3, 133.4, 140.5 (Ar). HRMS (EI) *m/z*: Calcd for $C_{13}H_9IN_2$ (M^+), 319.9810; Found 319.9820.

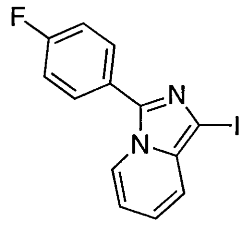
1-Iodo-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**5b**)



Chemical Formula: $C_{14}H_{11}IN_2O$
Exact Mass: 349.9916
Molecular Weight: 350.1544

99% yield, green solid, mp 114.0-114.5 °C, Rf = 0.23 (hexane : AcOEt = 4 : 1). IR (KBr) 3009, 2935, 2835, 1606, 1525, 1505, 1455 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.80 (s, 3H, OMe), 6.51 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.70 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 6.93 (d, *J* = 8.8 Hz, 2H, Ar), 7.27 (d, *J* = 9.3 Hz, 1H, Ar), 7.61 (d, *J* = 8.8 Hz, 2H, Ar), 8.07 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 55.4 (OMe), 113.7, 114.4, 114.7, 118.9, 119.9, 121.7, 129.5, 129.8, 133.0, 140.0, 160.1 (Ar). HRMS (EI) *m/z*: Calcd for $C_{14}H_{11}IN_2O$ (M^+) 349.9916; Found: 349.9911.

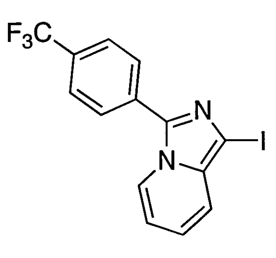
1-Iodo-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**5c**)



Chemical Formula: $C_{13}H_8FIN_2$
Exact Mass: 337.9716
Molecular Weight: 338.1189

96% yield, colorless solid, mp 125.0-125.5 °C, Rf = 0.51 (hexane : AcOEt = 4 : 1) IR (KBr) 3055, 3020, 1520, 1503, 1230 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.63 (t, *J* = 6.8 Hz, 1H, Ar), 6.82 (dd, *J* = 6.8, 9.1 Hz, 1H, Ar), 7.22 (t, *J* = 8.8 Hz, 2H, Ar), 7.37 (d, *J* = 9.1 Hz, 1H, Ar), 7.75 (q, *J* = 8.8 Hz, 2H, Ar), 8.14 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 114.1 (Ar), 116.2 (d, *J* = 21.9 Hz, F-C-$\underline{C}$), 119.1, 120.2, 121.5, 125.5, 126.0 (Ar), 130.0 (d, *J* = 8.8 Hz, F-C-C=$\underline{C}$), 133.4, 139.5, 162.2 (d, *J* = 272 Hz, F-C). ^{19}F NMR (CDCl$_3$) δ -111.8 (F). HRMS (EI) *m/z*: Calcd for $C_{13}H_8FIN_2$ (M^+) 337.9716; Found: 337.9719.

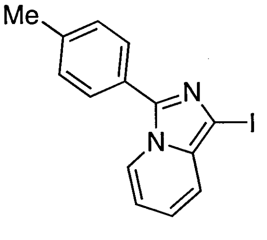
***1-Iodo-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine* (5d)**



Chemical Formula: $C_{14}H_8F_3IN_2$
Exact Mass: 387.9684
Molecular Weight: 388.1264

98% yield, off-white solid, mp 91.0-91.5 ℃, Rf = 0.47 (hexane : AcOEt = 4 : 1) IR (KBr) 3109, 3078, 1586, 1523, 1503, 1321 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.57 (dd, *J* = 6.4, 5.6 Hz, 1H, Ar), 6.76 (dd, *J* = 5.6, 8.6 Hz, 1H, Ar), 7.28 (d, *J* = 8.6 Hz, 1H, Ar), 7.65 (d, *J* = 7.6 Hz, 2H, Ar), 7.80 (d, *J* = 7.6 Hz, 2H, Ar), 8.13 (d, *J* = 6.4 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 114.7, 119.3, 120.8, 121.6, 123.9 (q, *J* = 272.1 Hz, F$_3$<u>C</u>), 126.0 (q, *J* = 4.1 Hz, F$_3$C-C=<u>C</u>), 128.0 (two carbon peaks were overlaped) (Ar), 130.7 (q, *J* = 33.1 Hz, F$_3$C-<u>C</u>), 132.8, 134.0, 138.9 (Ar). ^{19}F NMR (CDCl$_3$) δ -63.4 (CF$_3$). HRMS (EI) *m/z*: Calcd for $C_{14}H_{18}$ F_3IN_2 (M$^+$) 387.9684; Found: 387.9687.

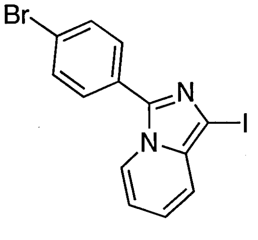
***1-Iodo-3-(4-methylphenyl)imidazo[1,5-a]pyridine* (5e)**



Chemical Formula: $C_{14}H_{11}IN_2$
Exact Mass: 333.9967
Molecular Weight: 334.1550

82% yield, green solid, mp 80.5-82 °C, Rf = 0.50 (hexane : AcOEt = 4 : 1). IR (KBr) 2918, 2361, 1712, 1630, 1523, 1504, 1455, 1361, 1260, 1113, 1005, 741 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.34 (s, 3H, Me), 6.49 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.68 (dd, *J* = 6.8, 8.7 Hz, 1H, Ar), 7.18-7.27 (m, 3H, Ar), 7.56 (d, *J* = 7.8 Hz, 2H, Ar), 8.10 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 21.3 (Me), 113.6, 118.8, 119.9, 121.8, 126.4, 127.8 (two carbon atoms were overlapped.), 129.6, 133.1, 139.0, 140.5 (Ar). HRMS (EI) *m/z*: Calcd for $C_{14}H_{11}IN_2$ (M$^+$) 333.9967; Found: 333.9936.

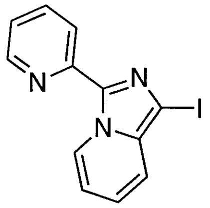
***1-Iodo-3-(4-bromophenyl)imidazo[1,5-a]pyridine* (5f)**



Chemical Formula: $C_{13}H_8BrIN_2$
Exact Mass: 397.8916
Molecular Weight: 399.0245

81% yield, pale green solid, mp 134-135 ℃, Rf = 0.63 (hexane : AcOEt = 4 : 1). IR (KBr) 2931, 1627, 1497, 1359, 1260, 1003, 833, 740 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.56 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.74 (dd, *J* = 6.3, 8.2 Hz, 1H, Ar), 7.29 (d, *J* = 9.3 Hz, 2H, Ar), 7.55-7.58 (m, 4H, Ar), 8.09 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 114.3, 119.1, 120.4, 121.6, 123.1, 128.2, 129.3, 132.2, 133.6, 139.3 (Ar). HRMS (EI) *m/z*: Calcd for $C_{13}H_8{}^{79}BrIN2$ (M$^+$) 397.8916; Found: 397.8905.

1-Iodo-3-(2-pyridyl)imidazo[1,5-a]pyridine (**5h**)



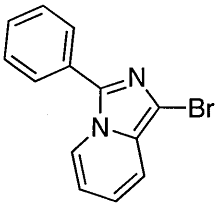
Chemical Formula: $C_{12}H_8IN_3$
Exact Mass: 320.9763
Molecular Weight: 321.1165

86% yield, pale yellow solid, mp 157-158 °C; Rf = 0.45 (hexane : AcOEt = 4 : 1). IR (KBr) 2358, 1586, 1495, 1353, 1013, 754, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.72 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.90 (dd, *J* = 6.3, 8.7 Hz, 1H, Ar), 7.17 (ddd, *J* = 1.5, 4.8, 6.3 Hz, 1H, Ar), 7.37 (d, *J* = 8.3 Hz, 1H, Ar), 7.73 (ddd, *J* = 1.5, 6.3, 8.3 Hz, 1H, Ar), 8.30 (d, *J* = 8.7 Hz, 1H, Ar), 8.58 (d, *J* = 4.8 Hz, 1H, Ar), 9.90 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 114.2, 118.2, 121.4, 121.8, 121.9, 126.5 (two carbon atoms were overlapped), 134.5, 136.5, 137.7, 148.0, 150.2 (Ar). HRMS (EI) *m/z*: Calcd for $C_{12}H_8IN_3$ (M^+) 320.9763; Found: 320.9780.

2.6.3. General procedure for the bromination of 3-arylimidazo[1,5-*a*]pyridines 2

To a solution of 3-arylimidazo[1,5-*a*]pyridine **2** (5.0 mmol) in dioxane (10 mL) was added a solution of bromine (0.27 mL, 5.5 mmol, 1.1 equiv) in dioxane (10 mL) at 0 °C under an air atmosphere. The resulting solution was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq., neutralized with NaOH aq., and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 1-bromo-3-arylimidazo[1,5-*a*]pyridine **6**.

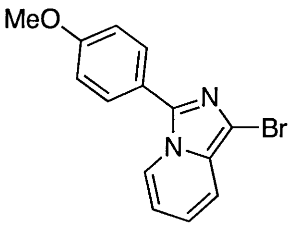
1-Bromo-3-phenylimidazo[1,5-a]pyridine (**6a**)



Chemical Formula: $C_{13}H_9BrN_2$
Exact Mass: 271.9949
Molecular Weight: 273.1280

82% yield, brownish solid, mp 127-129 °C, Rf = 0.53 (hexane : AcOEt = 4 : 1). IR (KBr) 3390. 1632, 1513, 1264, 1010, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.54 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.72 (dd, *J* = 6.3, 8.8 Hz, 1H, Ar), 7.35-7.48 (m, 4H, Ar), 7.72 (d, *J* = 8.3 Hz, 2H, Ar), 8.15 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 106.5, 113.2, 113.9, 118.0, 119.6, 121.5, 127.9, 128.9, 129.1, 129.3, 137.6 (Ar). HRMS (EI) *m/z*: Calcd for $C_{13}H_9{}^{79}BrN_2$ (M^+) 271.9949; Found: 271.9952.

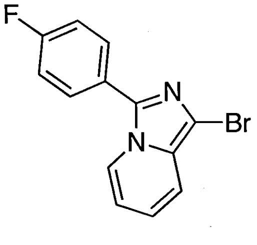
1-Bromo-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**6b**)



Chemical Formula: $C_{14}H_{11}BrN_2O$
Exact Mass: 302.0055
Molecular Weight: 303.1539

97% yield, yellow solid, mp 89-89.5 °C, Rf = 0.34 (hexane : AcOEt = 4 : 1). IR (KBr) 2935, 1523, 1247 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H, OMe), 6.51 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.70 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 6.93 (d, *J* = 8.8 Hz, 2H, Ar), 7.27 (d, *J* = 9.3 Hz, 1H, Ar), 7.61 (d, *J* = 8.8 Hz, 2H, Ar), 8.07 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe), 113.7, 114.4, 114.7, 118.9, 119.9, 121.7, 129.5, 129.8, 133.0, 140.0, 160.1 (Ar). HRMS (EI) *m/z*: Calcd for $C_{14}H_{11}{}^{79}BrN_2O$ (M^+) 302.0055; Found: 302.0059.

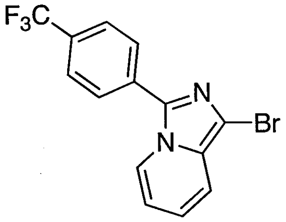
1-Bromo-3-(4-fluorophenyl)imidazo[1,5-a]pyridine **(6c)**



Chemical Formula: $C_{13}H_8BrFN_2$
Exact Mass: 289.9855
Molecular Weight: 291.1184

93% yield, pale yellow solid, mp 82-83 °C, Rf = 0.68 (hexane : AcOEt = 2 : 1). IR (KBr) 3083, 1520, 1231, 1009 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.53 (dd, *J* = 6.8, 7.4 Hz, 1H, Ar), 6.72 (dd, *J* = 7.4, 9.2 Hz, 1H, Ar), 7.10-7.16 (m, 2H, Ar), 7.34 (d, *J* = 9.2 Hz, 1H, Ar), 7.62-7.71 (m, 2H, Ar), 8.06 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 106.2, 114.0 (Ar), 115.1 (d, *J* = 21.8 Hz, F-C-$\underline{C}$), 117.8, 119.6, 121.1, 125.3, 128.7 (Ar), 129.6 (d, *J* = 8.3 Hz, F-C-C=$\underline{C}$), 136.4 (Ar), 162.7 (d, *J* = 250 Hz, F-C). ^{19}F NMR ($CDCl_3$) δ –111.8 (F). HRMS (EI) *m/z*: Calcd for $C_{13}H_8F^{79}BrN_2$ (M^+) 289.9855; Found: 289.9850.

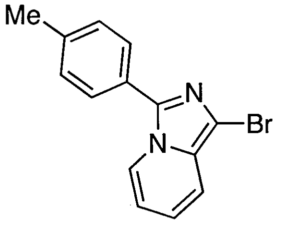
1-Bromo-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine **(6d)**



Chemical Formula: $C_{14}H_8BrF_3N_2$
Exact Mass: 339.9823
Molecular Weight: 341.1259

99% yield, brownish solid, mp 111-113 °C, Rf = 0.23 (hexane : AcOEt = 4 : 1). IR (KBr) 2923, 1714, 1617, 1362, 1324, 1221, 1119, 1066, 1012 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.62 (dd, *J* = 6.5, 7.3Hz, 1H, Ar), 6.78 (dd, *J* = 6.5, 9.3 Hz, 1H, Ar), 7.39 (d, *J* = 9.3 Hz, 1H, Ar), 7.69 (d, *J* = 8.3 Hz, 2H, Ar), 7.84 (d, *J* = 8.3 Hz, 2H, Ar), 8.18 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 107.2, 114.6, 118.1, 120.2, 121.2, (Ar), 123.9 (q, *J* = 272 Hz, $F_3\underline{C}$), 125.9 (q, *J* = 3.3 Hz, F_3C-C=$\underline{C}$), 127.7, 129.5 (Ar), 130.4 (q, *J* = 32.2 Hz, F_3C-$\underline{C}$), 132.6, 135.8 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.4 (CF_3). HRMS (EI) *m/z*: Calcd for $C_{14}H_8{}^{79}BrF_3N_2$ (M^+) 339.9823; Found: 339.9818.

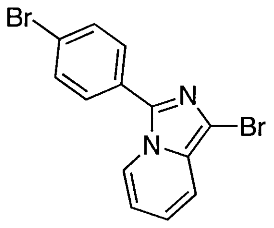
1-Bromo-3-(4-methylphenyl)imidazo[1,5-a]pyridine **(6e)**



Chemical Formula:
$C_{14}H_{11}BrN_2$
Exact Mass: 286.0106
Molecular Weight: 287.1545

56% yield, pale green solid, mp 107-109 °C, Rf = 0.68 (hexane : AcOEt = 2 : 1). IR (KBr) 3064, 1502, 1366 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H, Me), 6.49 (dd, *J* = 7.3, 8.3 Hz, 1H, Ar), 6.68 (dd, *J* = 8.3, 9.3 Hz, 1H, Ar), 7.22 (d, *J* = 8.3 Hz, 2H, Ar), 7.32 (d, *J* = 9.3 Hz, 1H, Ar), 7.56 (d, *J* = 8.3 Hz, 2H, Ar), 8.10 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.45(Me), 113.7, 118.0, 119.4, 121.5, 126.4, 127.8, 128.7, 129.6, 129.7, 131.7, 139.0 (Ar). HRMS (EI) *m/z*: Calcd for $C_{14}H_{11}{}^{79}BrN_2$ (M^+) 286.0106; Found: 286.0099.

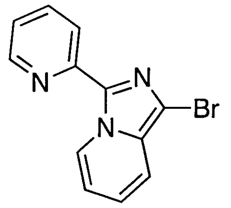
1-Bromo-3-(4-bromophenyl)imidazo[1,5-a]pyridine (**6f**)



Chemical Formula: $C_{13}H_8Br_2N_2$
Exact Mass: 349.9054
Molecular Weight: 352.0240

92% yield, yellow solid, mp 132-133 °C, Rf = 0.69 (hexane : AcOEt = 3 : 1). IR (KBr) 3083, 1500, 1368 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.56 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.74 (dd, *J* = 6.8, 9.1 Hz, 1H, Ar), 7.35 (dd, *J* = 4.9, 7.6 Hz, 1H, Ar), 7.54-7.59 (m, 4H, Ar), 8.09 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 106.7, 114.4, 118.2, 119.9, 121.3, 123.1, 128.2, 129.1, 129.2, 132.2, 136.4 (Ar). HRMS (EI) *m/z*: Calcd for $C_{13}H_8{}^{79}Br_2N_2$ (M^+) 349.9054; Found: 349.9050.

1-Bromo-3-(2-pyridyl)imidazo[1,5-a]pyridine (**6h**)



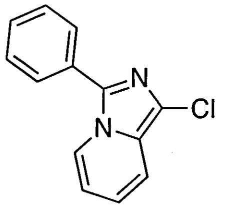
Chemical Formula: $C_{12}H_8BrN_3$
Exact Mass: 272.9902
Molecular Weight: 274.1160

89% yield, yellow solid, mp 126-127 °C, Rf = 0.65 (hexane : AcOEt = 3 : 1). IR (KBr) 3116, 1587, 1495, 1369 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.68 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.84 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), d 7.11 (dd, *J* = 4.9, 7.6 Hz, 1H, Ar), 7.38 (d, *J* = 9.3 Hz, 1H, Ar), 7.77 (dd, *J* = 7.6, 8.2 Hz, 1H, Ar), 8.22 (d, *J* = 7.3 Hz, 1H, Ar), 8.53 (d, *J* = 4.9 Hz, 1H, Ar), 9.85 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 106.9, 114.3, 117.2, 121.0, 121.7, 121.8, 126.2, 130.2, 134.7, 136.5, 148.1, 150.2 (Ar). HRMS (EI) *m/z*: Calcd for $C_{12}H_8{}^{81}BrN_3$ (M^+) 274.9881; Found: 274.9852.

2.6.4. General procedure for the chlorination of 3-arylimidazo[1,5-*a*]pyridines 2

To a solution of 3-arylimidazo[1,5-*a*]pyridine **2** (0.50 mmol) in CH_2Cl_2 (1 mL) was added NCS (0.09 g, 0.65 mmol, 1.3 equiv) at room temperature under an Ar atmosphere. The resulting solution was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq., neutralized with $NaHCO_3$ aq., and extracted with CH_2Cl_2 (30 mL x 3). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 1-chloro-3-arylimidazo[1,5-*a*]pyridine **7**.

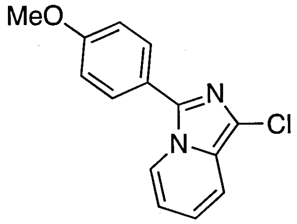
1-Chloro-3-phenylimidazo[1,5-a]pyridine (**7a**)



Chemical Formula: $C_{13}H_9ClN_2$
Exact Mass: 228.0454
Molecular Weight: 228.6770

80% yield, colorless solid, mp 118-120 ℃, Rf = 0.51 (hexane :AcOEt = 4 : 1). IR (KBr) 2963, 1515, 1375 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.51 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.68 (dd, *J* = 6.3, 8.3 Hz, 1H, Ar), 7.31-7.44 (m, 5H, Ar), 7.68 (d, *J* = 8.3 Hz, 1H, Ar), 8.12 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.8, 117.5, 119.2, 119.7, 121.3, 126.3, 127.8, 128.9, 129.0, 129.3, 135.8 (Ar). HRMS (EI) *m/z*: Calcd for $C_{13}H_9{}^{35}ClN_2$ (M^+) 228.0454; Found: 228.0442.

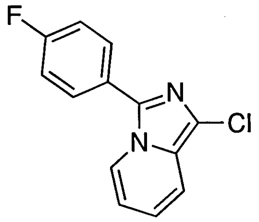
1-Chloro-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine **(7b)**



Chemical Formula: $C_{14}H_{11}ClN_2O$
Exact Mass: 258.0560
Molecular Weight: 258.7029

80% yield, brownish solid, mp 85.5-86.5 °C, Rf = 0.10 (hexane : AcOEt = 10 : 1). IR (KBr) 2963, 1515, 1375 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H, OMe), 6.48 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.68 (dd, *J* = 6.3, 9.1 Hz, 1H, Ar), 6.96 (d, *J* = 8.8 Hz, 2H, Ar), 7.34 (d, *J* = 9.1 Hz, 1H, Ar), 7.61 (d, *J* = 8.8 Hz, 2H, Ar), 8.04 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 1113.6, 114.4, 117.5, 118.8, 119.4, 121.3, 121.7, 125.9, 129.3, 135.9, 160.9 (Ar). HRMS (EI) *m/z*: Calcd for $C_{14}H_{11}{}^{35}ClN_2O$ (M^+) 258.0560; Found: 258.0542.

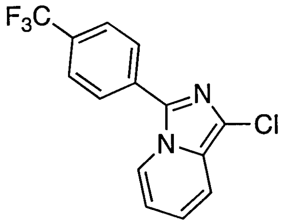
1-Chloro-3-(4-fluorophenyl)imidazo[1,5-a]pyridine **(7c)**



Chemical Formula: $C_{13}H_8ClFN_2$
Exact Mass: 246.0360
Molecular Weight: 246.6674

84% yield, brownish solid, mp 83-85 °C, Rf = 0.55 (hexane : AcOEt = 3 : 1). IR (KBr) 2922, 1524, 1232, 1023 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.65 (dd, *J* = 6.4, 7.3 Hz, 1H, Ar), 6.81 (dd, *J* = 6.4, 9.3 Hz, 1H, Ar), 7.22-7.30 (m, 2H, Ar), 7.49 (d, *J* = 9.3 Hz, 1H, Ar), 7.76-7.80 (m, 2H, Ar), 8.16 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 114.0 (Ar), 116.1 (d, *J* = 21.9 Hz, F-C-$\underline{C}$), 117.6, 119.2, 121.0, 125.4, 125.5, 126.4 (Ar), 129.8 (d, *J* = 7.7 Hz, F-C-C=$\underline{C}$), 134.9 (Ar), 162.9 (d, *J* = 249 Hz, F-C). ^{19}F NMR ($CDCl_3$) δ -111.8 (F). HRMS (EI) *m/z*: Calcd for $C_{13}H_8{}^{35}ClFN_2$ (M^+) 246.0360; Found: 246.0347.

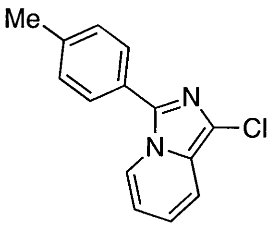
1-Chloro-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine **(7d)**



Chemical Formula: $C_{14}H_8ClF_3N_2$
Exact Mass: 296.0328
Molecular Weight: 296.6749

86% yield, brownish solid, mp 104-105 °C, Rf = 0.43 (hexane : AcOEt = 4 : 1). IR (KBr) 2914, 1743, 1706, 1657, 1617, 1461, 1414, 1325, 1165, 1122, 1067 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.66 (dd, *J* = 6.3, 7.3Hz, 1H, Ar), 6.81 (dd, *J* = 6.3, 9.0 Hz, 1H, Ar), 7.48 (d, *J* = 9.0 Hz, 1H, Ar), 7.74 (d, *J* = 8.2 Hz, 2H, Ar), 7.89 (d, *J* = 8.2 Hz, 2H, Ar), 8.22 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 114.7, 117.8, 119.8, 120.7, 121.2 (Ar), 123.9 (q, *J* = 272 Hz, $F_3\underline{C}$), 126.0 (q, *J* = 3.9 Hz, F_3C-C=$\underline{C}$), 127.2, 127.9 (Ar), 130.5 (q, *J* = 32.7 Hz, F_3C-$\underline{C}$), 132.8, 134.3 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.4 (CF_3). HRMS (EI) *m/z*: Calcd for $C_{14}H_8{}^{35}ClF_3N_2$ (M^+) 296.0328; Found: 296.0337.

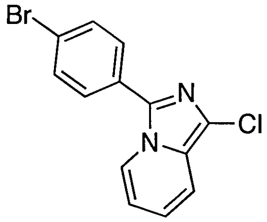
1-Chloro-3-(4-methylphenyl)imidazo[1,5-a]pyridine (**7e**)



Chemical Formula: $C_{14}H_{11}ClN_2$
Exact Mass: 242.0611
Molecular Weight: 242.7035

90% yield, brownish solid, mp 68-69 °C, Rf = 0.48 (hexane : AcOEt = 3 : 1). IR (KBr) 3064, 1507, 1376, 1024 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, Me), 6.49 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.66 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 7.22 (d, *J* = 7.8 Hz, 2H, Ar), 7.35 (d, *J* = 9.3 Hz, 1H, Ar), 7.58 (d, *J* = 7.8 Hz, 2H, Ar), 8.09 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.3 (Me), 113.7, 117.4, 119.0, 119.5, 121.4, 126.1, 126.4, 127.7, 129.6, 136.0, 139.0 (Ar). HRMS (EI) *m/z*: Calcd for $C_{14}H_{11}{}^{35}ClN_2$ (M^+) 242.7035; Found: 242.0610.

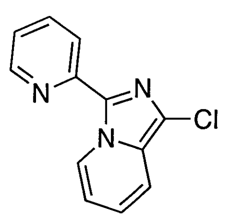
1-Chloro-3-(4-bromophenyl)imidazo[1,5-a]pyridine (**7f**)



Chemical Formula: $C_{13}H_8BrClN_2$
Exact Mass: 305.9559
Molecular Weight: 307.5730

84% yield, brownish solid, mp 124-126 °C, Rf = 0.23 (hexane : AcOEt = 10 : 1). IR (KBr) 2935, 1526, 1249, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.54 (dd, *J* = 6.3, 6.8 Hz, 1H, Ar), 6.70 (dd, *J* = 6.8, 9.3 Hz, 1H, Ar), 7.36 (d, *J* = 9.3 Hz, 1H, Ar), 7.52-7.57 (m, 4H, Ar), 8.06 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 114.3, 117.6, 119.4, 120.0, 121.1, 122.9, 126.6, 128.1, 129.1, 132.2, 134.6 (Ar). HRMS (EI) *m/z*: Calcd for $C_{13}H_8{}^{81}Br^{37}ClFN_2$ (M^+) 309.9530; Found: 309.9516.

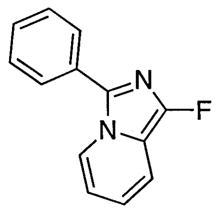
1-Chloro-3-(2-pyridyl)imidazo[1,5-a]pyridine (**7h**)



Chemical Formula: $C_{12}H_8ClN_3$
Exact Mass: 229.0407
Molecular Weight: 229.6650

88% yield, colorless solid, mp 104-105 °C, Rf = 0.50 (hexane : AcOEt = 3 : 1). IR (KBr) 3118, 1590, 1495, 1377, 1031 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.68 (dd, *J* = 6.3, 7.8 Hz, 1H, Ar), 6.84 (dd, *J* = 6.3, 9.1 Hz, 1H, Ar), d 7.12 (dd, *J* = 4.4, 7.3 Hz, 1H, Ar), 7.43 (d, *J* = 9.1 Hz, 1H, Ar), 7.69 (dd, *J* = 7.3, 7.5 Hz, 1H, Ar), 8.21 (d, *J* = 7.8 Hz, 1H, Ar), 8.54 (d, *J* = 4.4 Hz, 1H, Ar), 9.86 (d, *J* = 7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 106.7, 114.2, 117.1, 120.9, 121.6, 121.7, 126.1, 130.1, 134.5, 136.4, 148.0, 150.1 (Ar). HRMS (EI) *m/z*: Calcd for $C_{12}H_8{}^{35}ClN_3$ (M^+) 229.0407; Found: 229.0405.

2.6.5. Synthesis of 1-fluoro-3-phenylimidazo[1,5-*a*]pyridine (8a)



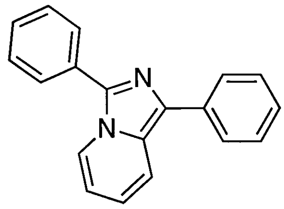
Chemical Formula: $C_{13}H_9FN_2$
Exact Mass: 212.0750
Molecular Weight: 212.2224

To a solution of 3-phenylimidazo[1,5-*a*]pyridine (**2a**) (0.10 g, 0.50 mmol) in DMF (2 mL) was added 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**9**) (0.23 g, 1.0 mmol, 2 equiv) at room temperature under an Ar atmosphere. The resulting solution was stirred at 60 °C for 2 h. The reaction mixture was quenched with 1 N NaOH aq. and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 3 : 1) to give 1-fluoro-3-phenyl-imidazo[1,5-*a*]pyridine (**8a**, 0.05 g, 0.27 mmol, 53%, Rf = 0.47) as a pale yellow solid, mp 103-104 °C. IR (KBr) 2080, 3049, 2922, 1643, 1558, 1521, 1443, 1358, 1258, 1076 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.43-6.46 (m, 1H, Ar), 6.54 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 7.31-7.36 (m, 2H, Ar), 7.40-7.45 (m, 2H, Ar), 7.69 (d, *J* = 8.3 Hz, 2H, Ar), 8.07 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 112.2 (*J* = 38.5 Hz, F-C=$\underline{\text{C}}$), 113.7 (Ar), 116.9 (*J* = 5.9 Hz, F-C-N=$\underline{\text{C}}$), 117.1 (*J* = 2.9 Hz, F-C=C-$\underline{\text{C}}$), 120.4, 127.7, 128.7, 129.0 (three carbon atoms were overlapped), 129.6 (Ar), 147.9 (*J* = 233 Hz, F-$\underline{\text{C}}$). ^{19}F NMR ($CDCl_3$) δ –140.1 (F). HRMS (EI) *m/z*: Calcd for $C_{13}H_9FN_2$ (M^+) 212.0750; Found: 212.0706.

2.6.6. General procedure for KTC cross-coupling of 3-arylimidazo[1,5-*a*]pyridines 5 and aryl Grignard reagents 10

To a solution of 1-iodo-3-arylimidazopyridine **5** (0.5 mmol) and Ni(dppp)Cl_2 (10 mol%, 27 mg) in THF (1 mL) in a flame-dried two-necked round-bottom flask was added dropwise aryl Grignard reagent **10** (1.5 mmol, 3 equiv) at 0 °C under an Ar atmosphere. After addition of Grignard reagent, the reaction mixture was stirred at room temperature. When the reaction was complete, the mixture was immediately quenched with sat. NH_4Claq (1 mL), and extracted with CH_2Cl_2 (20 mL x3). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Unless otherwise noted, the residue was purified by column chromatography on silica gel to give 1,3-diarylimidazo[1,5-*a*]pyridine **4**.

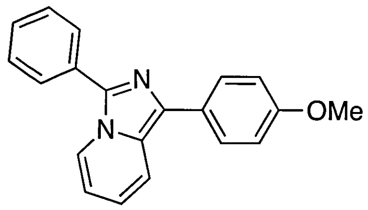
1-Phenyl-3-phenylimidazo[1,5-a]pyridine (4aa)



Chemical Formula: $C_{19}H_{14}N_2$
Exact Mass: 270.1157
Molecular Weight: 270.3279

80% isolated yield (99% NMR yield), yellow solid, mp 111-112 °C, Rf = 0.38 (hexane : AcOEt = 5 : 1). IR (KBr) 1598, 1516, 1457 cm^{-1}.^1H NMR ($CDCl_3$) δ 6.50 (t, *J* = 6.5 Hz, 1H, Ar), 6.73 (dd, *J* = 6.5, 7.3 Hz, 1H, Ar), 7.23 (t, *J* = 7.3 Hz, 1H, Ar), 7.37-7.50 (m, 5H, Ar), 7.78 (dd, *J* = 1.7, 7.3 Hz, 3H, Ar), 7.87 (dd, *J* = 1.0, 7.3 Hz, 2H, Ar), 8.18 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.3, 119.1, 119.7, 121.7, 126.5, 126.8, 127.6, 128.3, 128.7, 128.8, 129.0, 130.1, 131.9, 134.9, 138.1 (Ar). HRMS (EI) *m/z*: Calcd for $C_{19}H_{14}N_2$ (M^+) 270.1157; Found: 270.1149.

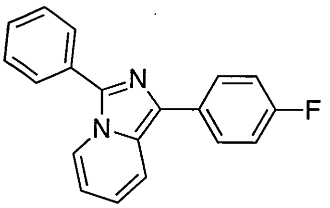
1-(4-Methoxyphenyl)-3-phenylimidazo[1,5-a]pyridine (**4ab**)



Chemical Formula: $C_{20}H_{16}N_2O$
Exact Mass: 300.1263
Molecular Weight: 300.3538

83% isolated yield (90% NMR yield), yellow solid, mp 111.5-113.0 °C, Rf = 0.33 (hexane : AcOEt = 4 : 1). IR (KBr):3063, 2990, 2959, 1600, 1573, 1541, 1502, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H, OMe), 6.37 (t, *J* = 6.7 Hz, 1H, Ar), 6.57 (dd, *J* = 6.7, 9.1 Hz, 1H, Ar), 6.90 (d, *J* = 7.7 Hz, 2H, Ar), 7.30 (t, *J* = 6.8 Hz, 1H, Ar), 7.39 (d, *J* = 7.2 Hz, 2H, Ar), 7.62 (d, *J* = 9.1 Hz, 1H, Ar), 7.69-7.80 (m, 4H, Ar), 8.05 (d, *J* = 6.7 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.2 (OMe), 113.0, 113.3, 114.1, 119.1, 121.4, 123.6, 126.8, 127.5, 127.9, 128.1, 128.8, 130.0, 131.8, 137.5, 158.4 (Ar). HRMS (EI) *m/z*: Calcd for $C_{20}H_{16}N_2O$ (M^+) 300.1262; Found: 300.1264.

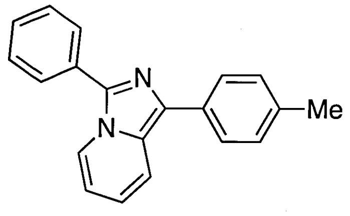
1-(4-Fluorophenyl)-1-phenylimidazo[1,5-a]pyridine (**4ac**)



Chemical Formula: $C_{19}H_{13}FN_2$
Exact Mass: 288.1063
Molecular Weight: 288.3183

58% isolated yield (83% NMR yield), yellow solid, mp 134.5-135.0 °C, Rf = 0.32 (hexane : AcOEt : Et_3N = 4 : 1 : 1 vol%). IR (KBr) 1601, 1542, 1518, 1500, 1461, 1221cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 6.51 (t, *J* = 7.0 Hz, 1H, Ar), 6.72 (dd, *J* = 7.0, 9.2 Hz, 1H, Ar), 7.06-7.11 (m, 2H, Ar), 7.37-7.49 (m, 3H, Ar), 7.69-7.83 (m, 5H, Ar), 8.16 (d, *J* = 7.0 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.3 (Ar), 119.3 (d, *J* = 21.0Hz, $\text{F-C=}\underline{\text{C}}$), 121.7, 126.8, 127.3, 128.3, 128.8, 129.0, 129.4 (Ar), 129.9 (d, *J* = 8.3 Hz, $\text{F-C=C-}\underline{\text{C}}$), 131.7, 131.9, 136.3, 137.8 (Ar), 161.5 (d, *J* = 248.0 Hz, $\text{F-}\underline{\text{C}}$). ^{19}F NMR ($CDCl_3$) δ -116.6 (F). HRMS (EI) *m/z*: Calcd for $C_{29}H_{13}N_2F$ (M^+) 288.1063; Found: 288.1058.

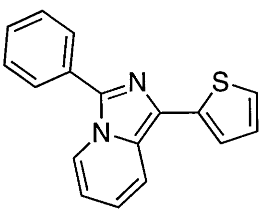
1-(4-Methylphenyl)-3-phenylimidazo[1,5-a]pyridine (**4ae**)



Chemical Formula: $C_{20}H_{16}N_2$
Exact Mass: 284.1313
Molecular Weight: 284.3544

52% isolated yield (85% NMR yield), Yellow solid, mp 134.0-134.5 °C, Rf = 0.41 (hexane : AcOEt = 4 : 1). IR (KBr) 3054, 2915, 1601, 1542, 1518, 1500, 1459cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, Me), 6.37 (t, *J* = 6.5 Hz, 1H, Ar), 6.57 (t, *J* = 7.6 Hz, 1H, Ar), 6.90 (d, *J* = 7.8 Hz, 2H, Ar), 7.30 (t, *J* = 6.8 Hz, 1H, Ar), 7.39 (t, *J* = 7.1 Hz, 2H, Ar), 7.62 (d, *J* = 9.2 Hz, 1H, Ar), 7.72 (dd, *J* = 8.3, 17 Hz, 4H, Ar), 8.05 (d, *J* = 6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.3 (Me), 113.2, 113.4, 118.8, 118.9, 121.8, 126.8, 127.5, 128.4, 128.8, 129.1, 129.5, 130.3, 132.2, 136.6, 138.0 (Ar). HRMS (EI) *m/z*: Calcd for $C_{20}H_{16}N_2$ (M^+) 284.1313; Found: 288.1313.

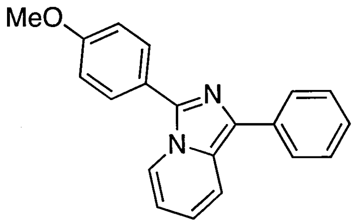
1-(2-Thienyl)-3-phenylimidazo[1,5-a]pyridine (**4ag**)



Chemical Formula: $C_{17}H_{12}N_2S$
Exact Mass: 276.0721
Molecular Weight: 276.3556

The product was isolated by GPC. 52% isolated yield, yellow solid, mp 115-116 °C. IR (KBr) 3060, 1600, 1559, 1522, 1442, 928 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.54 (t, *J* = 6.3 Hz, 1H, Ar), 6.79 (dd, *J* = 6.3, 9.2 Hz, 1H, Ar), 7.12 (dd, *J* = 3.7, 5.6, 1H, Ar), 7.25 (dd, *J* = 5.9, 8.0 Hz, 1H, Ar), 7. 41-7.53 (m, 4H, Ar), 7.78-7.81 (m, 3H, Ar), 8.18 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 113.4, 119.0, 119.9, 121.8, 122.2, 123.3, 124.3, 127.0, 127.6, 128.4, 128.9, 129.0, 129.8, 131.5, 137.9 (Ar). HRMS (EI) *m/z*: Calcd for $C_{17}H_{12}N_2S(M^+)$ 276.0721; Found: 276.0719.

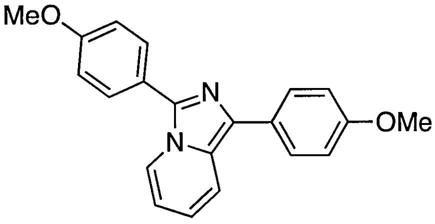
1-Phenyl-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**4ba**)[21]



Chemical Formula: $C_{20}H_{16}N_2O$
Exact Mass: 300.1263
Molecular Weight: 300.3538

81% isolated yield (93% NMR yield), ^{1}H NMR (CDCl$_3$) δ 3.29 (s, 3H, OMe), 6.50 (t, *J*= 6.3 Hz, 1H, Ar), 6.71 (dd, *J* = 6.3, 8.8Hz, 1H, Ar), 7.01 (d, *J* = 8.8 Hz, 2H, Ar), 7.24(dd, *J* = 6.3, 7.8 Hz, 1H, Ar), 7.41 (d, *J* = 7.5 Hz, 2H, Ar), 7.71(d, *J* = 8.8 Hz, 2H, Ar), 7.77 (d, *J* = 8.8 Hz, 1H, Ar), 7.89 (d, *J* = 7.8 Hz, 2H, Ar), 8.11 (d, *J* = 6.3 Hz, 1H, Ar).

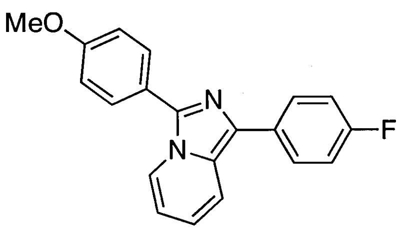
1-(4-Methoxyphenyl)-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**4bb**)



Chemical Formula: $C_{21}H_{18}N_2O_2$
Exact Mass: 330.1368
Molecular Weight: 330.3798

62% isolated yield (83% NMR yield), yellow solid, mp 175-176 °C, Rf = 0.30 (hexane : AcOEt : Et$_3$N = 3 : 1 : 1 vol%). IR (KBr) 2360, 1608, 1503, 1459, 1288, 1241, 1169, 1028 cm^{-1}.^{1}H NMR (CDCl$_3$) δ 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.45 (t, *J* = 6.5 Hz, 1H, Ar), 6.65 (m, 1H, Ar), 6.97 (q, *J* = 9.3 Hz, 4H, Ar), 7.69 (d, *J* = 8.3 Hz, 3H, Ar), 7.78 (d, *J* = 8.3 Hz, 2H, Ar), 8.07 (d, *J* = 6.5 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 55.3, 55.4 (OMe), 114.2, 114.5, 114.5, 119.1, 119.2, 119.5, 121.6, 121.7, 126.5, 126.8, 128.2, 128.7, 129.9, 160.1, 160.2 (Ar). HRMS (EI) *m/z*: Calcd for $C_{21}H_{18}N_2O_2$ (M^+) 330.1367; Found: 330.1367.

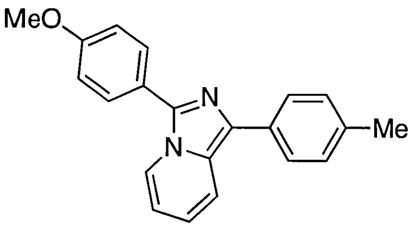
1-(4-Fluorophenyl)-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**4bc**)



Chemical Formula: $C_{20}H_{15}FN_2O$
Exact Mass: 318.1168
Molecular Weight: 318.3443

96% isolated yield (98% NMR yield), yellow solid, mp 171.5-171.2 °C, Rf = 0.25 (hexane : AcOEt = 4 : 1). IR (KBr) 1516, 1501, 1465, 1221, 1173 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.81 (s, 3H, OMe), 6.48 (t, *J* = 6.3 Hz, 1H, Ar), 6.69 (dd, *J* = 2.4, 6.3 Hz, 1H, Ar), 6.99 (dd, *J* = 5.1, 8.8 Hz, 2H, Ar), 7.08 (t, *J* = 8.8 Hz, 2H, Ar), 7.63-7.68 (m, 3H, Ar), 7.81 (t, *J* = 8.8 Hz, 2H, Ar), 8.08 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 55.4 (OMe), 113.1, 114.5 (Ar), 115.5 (d, *J* = 21.5 Hz, F-C=$\underline{\text{C}}$), 118.8, 119.6, 121.7, 122.3, 127.0, 128.3, 128.3, 129.7 (Ar), 130.8 (d, *J* = 8.8 Hz, F-C=C-$\underline{\text{C}}$), 138.5, 160.1 (Ar), 162.9 (d, *J* = 248.8 Hz, F-$\underline{\text{C}}$). ^{19}F NMR (CDCl$_3$) δ -116.8 (F). HRMS (EI) *m/z*: Calcd for $C_{20}H_{15}FN_2O$ (M$^+$) 318.1168; Found: 318.1159.

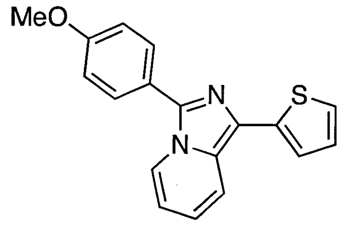
1-(4-Methylphenyl)-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**4be**)



Chemical Formula: $C_{21}H_{18}N_2O$
Exact Mass: 314.1419
Molecular Weight: 314.3804

58% isolated yield (90% NMR yield), yellow solid, mp 151.0-151.5 °C, Rf = 0.26 (hexane : AcOEt = 4 : 1). IR (KBr) 3008, 2911, 1609, 1527, 1514, 1464, 1008 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.31 (s, 3H, Me), 3.82 (s, 3H, OMe), 6.49 (t, *J* = 6.8 Hz, 1H, Ar), 6.69 (dd, *J* = 6.8, 8.8 Hz, 1H, Ar), 7.00 (d, *J* = 8.8 Hz, 2H, Ar), 7.21 (d, *J* = 7.8 Hz, 2H, Ar), 7.69-7.77 (m, 5H, Ar), 8.08 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 21.3 (Me), 55.5 (OMe), 113.0, 114.5, 119.1, 119.3, 121.6, 122.6, 126.7, 127.1, 129.4, 129.8, 131.7, 132.1, 136.1, 137.9, 160.0 (Ar). HRMS (EI) *m/z*: Calcd for $C_{21}H_{18}N_2O$ (M$^+$) 314.1419; Found: 314.1413.

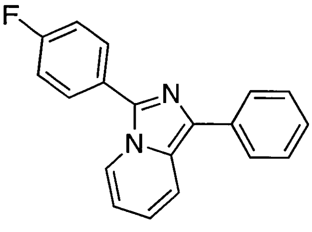
1-(2-Thienyl)-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**4bg**)



Chemical Formula: $C_{18}H_{14}N_2OS$
Exact Mass: 306.0827
Molecular Weight: 306.3816

The product was isolated by GPC. 68% isolated yield, Yellow solid, mp 130.0-130.5 °C. IR (KBr) 1516, 1501, 1465, 1221, 1173cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.86 (s, 3H, OMe), 6.53 (t, *J* = 6.5 Hz, 1H, Ar), 6.76 (dd, *J* = 6.3, 9.2 Hz, 1H, Ar), 7.02 (d, *J* = 7.8 Hz, 2H, Ar), 7.11 (dd, *J* = 2.8, 3.6 Hz, 1H, Ar), 7.25 (t, *J* = 2.8 Hz, 1H, Ar), 7.46 (d, *J* = 3.6 Hz, 1H, Ar), 7.71 (d, *J* = 7.8 Hz, 2H, Ar), 7.78 (d, *J* = 9.2 Hz, 1H, Ar), 8.11 (d, *J*= 6.5 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 55.4 (OMe), 113.1, 114.4, 118.9, 119.6, 121.7, 122.1, 122.2, 123.1, 126.7, 126.8, 127.5, 129.8, 137.9, 138.1, 160.1 (Ar). HRMS (EI) *m/z*: Calcd for $C_{18}H_{14}N_2OS$ (M$^+$) 306.0827; Found: 306.0829.

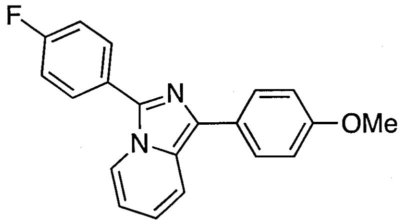
1-Phenyl-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**4ca**)[21]



Chemical Formula: $C_{19}H_{13}FN_2$
Exact Mass: 288.1063
Molecular Weight: 288.3183

89% isolated yield (95% NMR yield), ^{1}H NMR (CDCl$_3$) δ 6.52 (t, *J* = 6.3 Hz, 1H, Ar), 6.73 (dd, *J* = 6.3, 8.8 Hz, 1H, Ar), 7.14-7.25 (m, 3H, Ar), 7.40 (t, *J* = 7.8, 2H, Ar), 7.73-7.79 (m, 3H, Ar), 7.85 (d, *J* = 8.3 Hz, 2H, Ar), 8.08 (d, *J* = 6.5 Hz, 1H, Ar).

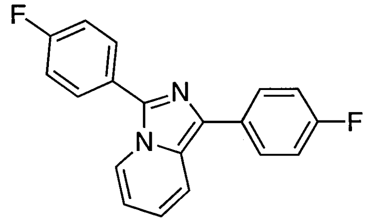
1-(4-Methoxyphenyl)-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**4cb**)



Chemical Formula: $C_{20}H_{15}FN_2O$
Exact Mass: 318.1168
Molecular Weight: 318.3443

83% isolated yield (88% NMR yield), yellow solid, mp 158.5-159.5 ℃, Rf = 0.37 (hexane : AcOEt : Et_3N = 4 : 1 : 1 vol%). IR (KBr) 3076, 2952, 2841, 1609, 1573, 1221 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H, OMe), 6.53 (t, *J* = 6.3 Hz, 1H, Ar), 6.72 (dd, *J* = 6.3, 9.1 Hz, 1H, Ar), 6.95 (d, *J* = 8.5 Hz, 2H, Ar), 7.20 (d, *J* = 8.5 Hz, 2H, Ar), 7.73-7.83 (m, 5H, Ar), 8.10 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe), 113.4, 114.2, 115.9 (Ar), 116.2, (d, *J* = 21.8 Hz, F-C=C), 119.2, 121.3, 126.2, 126.9, 127.3, 128.0 (Ar), 130.2 (d, *J* = 8.3 Hz, F-C=C-C), 131.8, 136.6, 158.5 (Ar), 162.89 (d, *J* = 248.8 Hz, F-C). ^{19}F NMR ($CDCl_3$) δ -112.5 (F). HRMS (EI) *m/z*: Calcd for $C_{20}H_{15}FN_2O$ (M^+) 318.01168; Found: 318.1182.

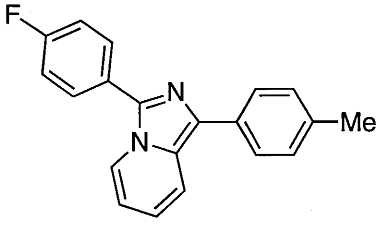
1-(4-Fluorophenyl)-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**4cc**)



Chemical Formula: $C_{19}H_{12}F_2N_2$
Exact Mass: 306.0969
Molecular Weight: 306.3088

83% isolated yield (83% NMR yield), yellow solid, mp 180.0-180.5 ℃, Rf = 0.48 (hexane : AcOEt = 4 :1). IR (KBr) 1604, 1529, 1515, 1499, 1469, 1228, 1154 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.60 (t, *J* = 6.3 Hz, 1H, Ar), 6.80 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 7.13-7.26 (m, 4H, Ar), 7.76-7.90 (m, 5H, Ar), 8.14 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.6 (Ar), 115.7 (d, *J* = 21.4 Hz, F-C=C), 116.2 (d, *J* = 21.5 Hz, F-C=C), 119.0, 119.9, 121.5, 126.1, 127.4 (Ar), 128.4 (d, *J* = 7.7 Hz, F-C=C-C), 130.3 (d, *J* = 8.3 Hz, F-C=C-C), 130.9, 131.0, 137.0 (Ar), 161.9 (d, *J* = 245.5 Hz, F-C), 163.1 (d, *J* = 249.3 Hz, F-C). ^{19}F NMR ($CDCl_3$) δ -112.1, -116.4 (F). HRMS (EI) *m/z*: Calcd for $C_{19}H_{12}F_2N_2$ (M^+) 306.0961; Found: 306.0961.

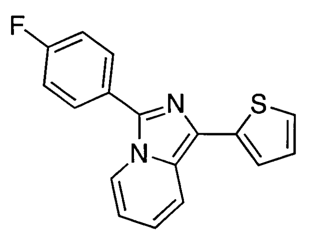
1-(4-Methylphenyl)-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**4ce**)



Chemical Formula: $C_{20}H_{15}FN_2$
Exact Mass: 302.1219
Molecular Weight: 302.3449

52% isolated yield (80% NMR yield), yellow solid, mp 106.0-107.0 °C, Rf = 0.45 (hexane : AcOEt = 4 : 1). IR (KBr) 1524, 1459, 1223 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.59 (dd, *J* = 6.4, 6.8 Hz, 1H, Ar), 6.82 (dd, *J* = 6.4, 8.8 Hz, 1H, Ar), 7.01-7.26 (m, 4H, Ar), 7.50 (d, *J* = 8.8 Hz, 1H, Ar), 8.20-8.39 (m, 4H, Ar), 8.11 (d, *J* = 6.8, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.3 (Me) 113.4 (Ar), 116.1 (d, *J* = 21.8 Hz, F-C=C), 119.3, 119.4, 121.4, 126.7, 126.9, 127.3, 127.4, 128.6 (Ar), 130.2 (d, *J* = 8.2 Hz, F-C=C-C), 131.8, 132.1, 136.3 (Ar), 162.9 (d, *J* = 248.3 Hz, F-C) (Ar). ^{19}F NMR ($CDCl_3$) δ -112.4 (F). HRMS (EI) *m/z*: Calcd for $C_{20}H_{15}FN_2$ (M^+) 302.1219; Found: 302.1222.

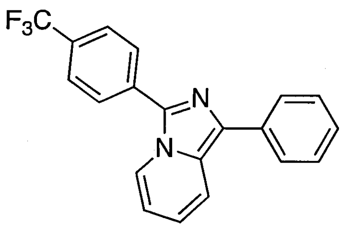
1-(2-Thienyl)-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**4cg**)



Chemical Formula: $C_{17}H_{11}FN_2S$
Exact Mass: 294.0627
Molecular Weight: 294.3460

The product was isolated by GPC. 81% isolated yield, Yellow solid, mp 157.5-158.5 °C. IR (KBr) 1629, 1518, 1311, 1006 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.60 (t, *J* = 6.3 Hz, 1H, Ar), 6.80 (dd, *J* = 6.3, 9.2 Hz, 1H, Ar), 7.13-7.26 (m, 3H, Ar), 7.76-7.90 (m, 5H, Ar), 8.14 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.6 (Ar), 116.1 (d, *J* = 21.5 Hz, F-C=$\underline{C}$), 118.9, 119.9, 120.2, 121.4, 122.2, 123.3, 125.9, 126.8, 127.0 (Ar), 130.2 (d, *J* = 8.8 Hz, F-C=C-$\underline{C}$), 136.9, 137.8 (Ar), 162.9 (d, *J* = 248.8 Hz, F-$\underline{C}$). ^{19}F NMR ($CDCl_3$) δ -112.1. HRMS (EI) *m/z*: Calcd for $C_{17}H_{11}FN_2$ S(M^+) 294.0627; Found: 294.0614.

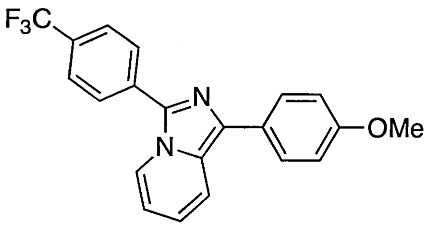
1-Phenyl-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4da**)



Chemical Formula: $C_{20}H_{13}F_3N_2$
Exact Mass: 338.1031
Molecular Weight: 338.3258

37% isolated yield (68% NMR yield), yellow solid, mp 149-151 °C, Rf = 0.42 (hexane : AcOEt = 4 : 1). IR (KBr) 2927, 1617, 1517, 1465, 1323 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.60 (t, *J* = 6.3 Hz, 1H, Ar), 6.78 (dd, *J* = 6.3, 7.8 Hz, 1H, Ar), 7.26 (t, *J* = 7.8 Hz, 1H, Ar), 7.41 (t, *J* = 7.8 Hz, 2H, Ar), 7.72 (d, *J* = 8.3 Hz, 2H, Ar), 7.80-7.94 (m, 5H, Ar), 8.20 (d, *J*= 6.3 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 113.9, 119.2, 120.2, 121.4 (Ar), 123.9 (q, *J* = 272 Hz, $F_3\underline{C}$), 125.9 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 126.8, 128.1, 128.2 (Ar), 130.3 (q, *J* = 33.1 Hz, F_3C-$\underline{C}$), 132.7, 133.6, 134.5, 136.3 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.4 (CF_3). HRMS (EI) *m/z*: Calcd for $C_{20}H_{13}F_3N_2$(M^+) 338.1031; Found: 338.1008.

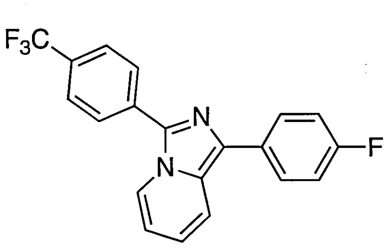
1-(4-Methoxyphenyl)-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4db**)



Chemical Formula: $C_{21}H_{15}F_3N_2O$
Exact Mass: 368.1136
Molecular Weight: 368.3518

66% isolated yield (68% NMR yield), yellow solid, mp 187.5-188.5 °C, Rf = 0.31 (hexane : AcOEt = 4 : 1). IR (KBr) 2951, 1614, 1542, 1518, 1502, 1323, 1066 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H, OMe), 6.61 (t, *J* = 6.5 Hz, 1H, Ar), 6.79 (dd, *J* = 6.5, 7.6 Hz, 1H, Ar), 7.01 (d, *J* = 8.8 Hz, 2H, Ar), 7.75-7.98 (m, 5H, Ar), 7.97 (d, *J* = 7.5 Hz, 2H, Ar), 8.22 (d, *J* = 6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 113.9, 114.3, 119.4, 119.7, 121.3 (Ar), 123.9 (q, *J* = 272 Hz, $F_3\underline{C}$), 126.0 (q, *J* = 3.3 Hz, F_3C-C=$\underline{C}$), 126.9, 127.7, 128.1, 128.2 (Ar), 130.3 (q, *J* = 33.1 Hz, F_3C-$\underline{C}$), 132.6, 133.4, 136.1, 158.7 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.4 (CF_3). HRMS (EI) *m/z*: Calcd for $C_{21}H_{15}F_3N_2O$(M^+) 368.1136; Found: 368.1136.

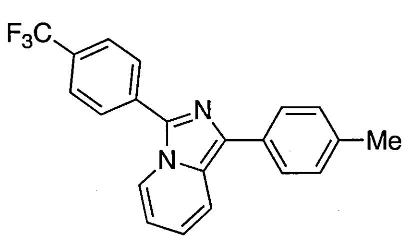
1-(4-Fluorophenyl)-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4dc**)



Chemical Formula: $C_{20}H_{12}F_4N_2$
Exact Mass: 356.0937
Molecular Weight: 356.3163

55% isolated yield (83% NMR yield), yellow solid, mp 209.0-209.5 °C, Rf = 0.48 (hexane : AcOEt = 4 : 1). IR (KBr) 2345, 1614, 1538, 1417, 1108 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.60 (t, *J* = 6.8 Hz, 1H, Ar), 6.80 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 7.10 (d, *J* = 8.3 Hz, 2H, Ar), 7.72-7.83 (m, 5H, Ar), 7.92 (d, *J* = 8.3 Hz, 2H, Ar), 8.20 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 114.0 (Ar), 115.7 (d, *J* = 21.5 Hz, F-C=$\underline{\text{C}}$), 119.1, 120.3, 121.5 (Ar), 123.9 (d, *J* = 272 Hz, F$_3\underline{\text{C}}$), 126.0 (d, *J* = 3.3 Hz, CF$_3$-C=C-$\underline{\text{C}}$), 128.0, 128.2 (Ar), 128.5 (d, *J* = 7.7 Hz, F-C=C-$\underline{\text{C}}$), 130.3 (Ar), 130.8 (q, *J* = 32.3 Hz, F$_3$C-$\underline{\text{C}}$), 131.9, 133.5, 136.4 (Ar), 162.9 (d, *J* = 248.9 Hz, F-$\underline{\text{C}}$) (Ar). ^{19}F NMR (CDCl$_3$) δ -63.3 (CF$_3$), -116.1 (F). HRMS (EI) *m/z*: Calcd for $C_{20}H_{12}F_4N_2$ (M$^+$) 356.0937; Found: 356.0932.

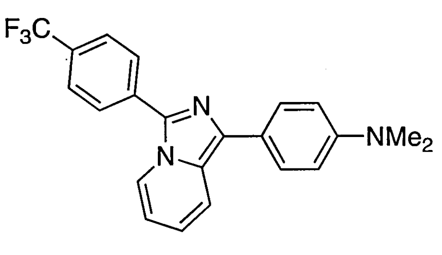
1-(4-Methylphenyl)-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4de**)



Chemical Formula: $C_{21}H_{15}F_3N_2$
Exact Mass: 352.1187
Molecular Weight: 352.3524

58% isolated yield (70% NMR yield), yellow solid, mp 120.0-120.5 ℃, Rf = 0.48 (hexane : AcOEt = 4 : 1). IR (KBr) 2925, 1615, 1541, 1518, 1501, 1321 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.34 (s, 3H, Me), 6.56 (t, *J* = 6.8 Hz, 1H, Ar), 6.75 (dd, *J* = 6.8, 9.1 Hz, 1H, Ar), 7.22 (d, *J* = 8.1 Hz, 2H, Ar), 7.70-7.79 (m, 5H, Ar), 7.92 (d, *J* = 8.1 Hz, 2H, Ar), 8.18 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 21.3 (Me), 113.8, 119.3, 119.8, 121.3 (Ar), 123.9 (q, *J* = 272 Hz, F$_3\underline{\text{C}}$), 125.8 (q, *J* = 3.3 Hz, F$_3$C-C=$\underline{\text{C}}$), 126.6, 128.0, 128.1, 129.4 (Ar), 130.2 (q, *J* = 32.7 Hz, F$_3$C-$\underline{\text{C}}$), 131.7, 132.8, 133.6, 136.1, 136.5 (Ar). ^{19}F NMR (CDCl$_3$) δ -63.3 (CF$_3$). HRMS (EI) *m/z*: Calcd for $C_{21}H_{15}F_3N_2$ (M$^+$) 352.1187; Found: 352.1180.

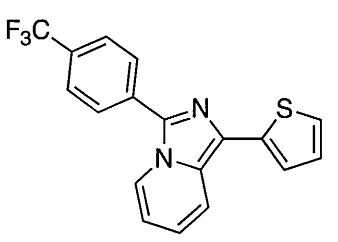
1-[4-(N,N-dimethylamino)phenyl]-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4df**)



Chemical Formula: $C_{22}H_{18}F_3N_3$
Exact Mass: 381.1453
Molecular Weight: 381.3936

48% isolated yield (98% NMR yield), yellow solid, mp 174.0-174.5 °C, Rf = 0.32 (hexane : AcOEt = 4 : 1). IR (KBr) 2922, 1613, 1543, 1520, 1505, 1323 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.00 (s, 6H, NMe$_2$), 6.57 (t, *J* = 6.5 Hz, 1H, Ar), 6.73 (dd, *J* = 6.5, 9.2 Hz, 1H, Ar), 6.86 (d, *J* = 8.8 Hz, 2H, Ar), 7.74-7.80 (m, 5H, Ar), 7.97 (d, *J* = 7.5 Hz, 2H, Ar), 8.20 (d, *J* = 6.5 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 40.7 (NMe$_2$), 112.9, 113.8, 119.0, 119.6, 121.2, 122.3 (Ar), 123.9 (q, *J* = 271 Hz, F$_3\underline{\text{C}}$), 125.8 (q, *J* = 3.3 Hz, F$_3$C-C=$\underline{\text{C}}$), 127.4, 127.8, 128.1, (Ar), 129.8 (q, *J* = 32.6 Hz, F$_3$C-$\underline{\text{C}}$), 133.5, 133.8, 135.8, 149.5 (Ar). ^{19}F NMR (CDCl$_3$) δ -62.9. HRMS (EI) *m/z*: Calcd for $C_{22}H_{18}F_3N_3$ (M$^+$) 381.1453 Found: 381.1452.

1-(2-Thienyl)- 3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4dg**)

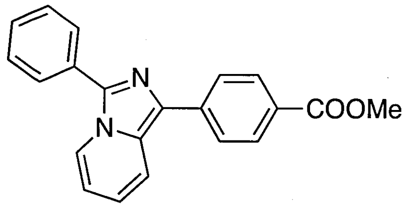


Chemical Formula: $C_{18}H_{11}F_3N_2S$
Exact Mass: 344.0595
Molecular Weight: 344.3535

The product was isolated by GPC. 93% isolated yield, yellow solid, mp 152.0-152.5 °C. IR (KBr) 1614, 1505, 1323, 1123 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.64 (dd, *J* = 6.5, 6.8 Hz, 1H, Ar), 6.86 (dd, *J* = 6.8, 9.1 Hz, 1H, Ar), 7.12 (dd, *J* = 3.1, 4.6 Hz, 1H, Ar), 7.28 (d, *J* = 4.6 Hz, 1H, Ar), 7.48 (d, *J* = 3.1 Hz, 1H, Ar), 7.76 (d, *J* = 7.8 Hz, 2H, Ar), 7.85 (d, *J* = 9.1 Hz, 1H, Ar), 7.96 (d, *J* = 7.8 Hz, 2H, Ar), 8.22 (d, *J* = 6.5 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$ δ 114.1, 119.3, 120.5, 121.5, 122.8, 123.7 (Ar), 123.9 (q, *J* = 272 Hz, $F_3\underline{C}$), 125.9, (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 127.5, 127.7, 127.8, 128.3 (Ar), 130.5 (q, *J* = 32.6 Hz, $F_3C\text{-}\underline{C}$), 133.1, 136.3, 137.5 (Ar). ^{19}F NMR (CDCl$_3$) δ -63.4 (CF$_3$). HRMS (EI) *m/z*: Calcd for $C_{18}H_{11}F_3N_2S(M^+)$ 344.0595; Found: 344.0531.

2.6.7. Suzuki-Miyaura cross-coupling reaction of 1-bromo-3-phenylimidazo[1,5-*a*]pyridine (6a) and methoxycarbonylphenylboronic acids 12

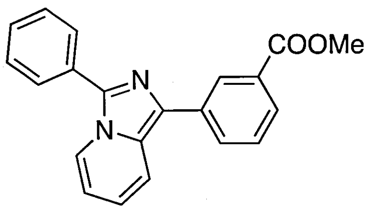
1-(4-Methoxycarbonylphenyl)-3-phenylimidazo[1,5-a]pyridine (**4ai**)



Chemical Formula: $C_{21}H_{16}N_2O_2$
Exact Mass: 328.1212
Molecular Weight: 328.3639

To a solution of 1-bromo-3-phenylimidazo[1,5-*a*]pyridine **6a** (0.08 g, 0.25 mmol) in DMF (2 mL) was added 4-methoxycarbonylphenylboronic acid **12i** (0.05 g, 0.28 mmol, 1.1 equiv), potassium hydroxide (0.03 g, 0.50 mmol, 2 equiv), tris(dibenzylideneacetone)dipalladium(0) (23 mg, 0.025 mmol), and tri-t-butylphosphine (0.048 mL, 0.050 mmol) at room temperature under an Ar atmosphere, and mixture was heated at 80 °C for 7 h with stirring. The reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 4 : 1) to give 1-(4-methoxycarbonylphenyl)-3-phenylimidazo[1,5-*a*]pyridine (**4ai,** 0.075 g, 0.23 mmol, 91%, Rf = 0.29) as a pale yellow solid: mp 118-120 ℃. IR (KBr) 3053, 1716, 1608, 1276 cm^{-1} ^{1}H NMR (CDCl$_3$) δ 3,.86 (s, 3H, OMe), 6.51 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.70 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 6.93 (d, *J* = 8.8 Hz, 2H, Ar), 7.27 (d, *J* = 9.3 Hz, 1H, Ar), 7.61 (d, *J* = 8.8 Hz, 1H, Ar), 8.07 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 51.9 (Me), 113.4, 118.9, 120.8, 122.1, 126.0, 127.5, 128.3 (two carbon atoms are overlapped), 128.5, 129.0, 129.8, 130.0, 130.5, 138.7, 139.5 (Ar), 167.1 (C=O). HRMS (EI) *m/z*: Calcd for $C_{21}H_{16}N_2O_2$ (M^+) 328.1212; Found: 328.1174.

1-(3-Methoxycarbonylphenyl)-3-phenylimidazo[1,5-a]pyridine (**4aj**)



Chemical Formula: $C_{21}H_{16}N_2O_2$
Exact Mass: 328.1212
Molecular Weight: 328.3639

3-Methoxycarbonylphenylboronic acid **12j** was used as a coupling partner. The procedure of the reaction was the same as that of **4ai**. Pale yellow solid, 111-113 °C, Rf = 0.33 (hexane : AcOEt = 4 : 1). IR (KBr) 3066, 1719, 1602, 1263 $\mathrm{cm^{-1}}$. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H, OMe), 6.52 (dd, J = 6.3, 7.3 Hz, 1H, Ar), 6.76 (ddd, J = 1.0, 6.3, 9.3 Hz, 1H, Ar), 7.36-7.48 (m, 4H, Ar), 7.75 (d, J = 7.8 Hz, 2H, Ar), 7.79 (d, J = 9.3 Hz, 1H, Ar), 7.88 (d, J = 7.8 Hz, 1H, Ar), 8.09 (d, J = 7.8 Hz, 1H, Ar), 8.17 (d, J = 7.3 Hz, 1H, Ar), 8.51 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 52.1 (Me), 113.4, 118.9, 120.3, 121.9, 127.4, 127.5, 128.0, 128.3, 128.8, 128.9, 129.0, 129.9, 130.5, 130.7, 131.1, 135.3, 138.6 (Ar) 167.2 (C=O). HRMS (EI) *m/z*: Calcd for $C_{21}H_{16}N_2O_2$ (M^+) 328.1212; Found: 328.1190.

References and notes

(1) (a) Hajos, G.; Riedl, Z. *Sci. Synth.* **2002**, *12*, 613. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry 4th ed.* Blackwell Science, Oxford, **2000**, pp. 489–503.

(1) For recent advances in the synthesis of imidazo[1,5-a]pyridines via an acetic acid-mediated condensation pathway, see: (a) Wang, J.; Mason, R.; VanDerveer, K.; Feng, D.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415. (b) Dyers, J. W. L., Jr.; Mason, R., Jr.; Amoyaw, P.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353. (c) Siddiqui, S. A.; Potewar, T. M.; Lahoti, R. J., Srinivasan, K. V. *Synthesis* **2006**, *17*, 2849 and references cited therein.

(2) For recent advances in the synthesis of imidazo[1,5-a]pyridines via an oxidative pathway, see: (a) Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2962. (b) Bluhm, M. E.; Folli, C.; Pufky, D.; Kröer, M.; Walter, O.; Döring, M. *Organometallics* **2005**, *24*, 4139. (c) Ostermeier, M.; Limberg, C.; Ziemer, B.; Karunakaran, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 5329, (d) Moulin, A.; Garcia, S.; Martinez, J.; Fehrentz, J.-A. *Synthesis* **2007**, *17*, 2667 and references cited therein.

(3) (a) Murai, T.; Niwa, H.; Kimura, T.; Shibahara, F. *Chem. Lett.* **2004**, *33*, 508. (b) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (c) Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, *70*, 8148. (d) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312. (e) Shibahara, F.; Suenami, A.; Yoshida, A.; Murai, T.; *Chem. Commun.* **2007**, 2354. (f) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780. (g) Shibahara, F.; Yoshida, A.; Murai, T.; *Chem. Lett.* **2008**, *37*, 646. (h) Murai, T.; Asai, F. *J. Org. Chem.* **2008**, *73*, 9518.

(4) Shibahara, F.; Kitagawa, A.; Yamaguchi, E. Murai, T. *Org. Lett.* **2006**, *8*, 5621.

(5) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai. T. *J. Org. Chem.* **2009**, *74*, 3566..

(6) For reviews of Kumada-Tamao-Corriu cross-coupling (Mg), see: (a) Tamao, K. In *Comprehensive Organic Synthesis*; Torst, B., Ed.; Permagon: Oxford, 1991; Vol 3, pp. 435-480. (b) Corriu, R. J. P. *J. Organomet. Chem.* **2002**, *653*, 20. (c) Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23.

(7) For a review of Negishi cross-coupling (Zn), see: Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233.

(8) For reviews of Migita-Kosugi-Stille cross-coupling (Sn), see: (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508. (b) Kosugi, M. Fugami, K. *J. Organomet. Chem.* **2002**, *653*, 50.

(9) For reviews of Suzuki-Miyaura cross-coupling (B), see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54.

(10) For reviews of Hiyama-Hatanaka cross-coupling (Si), see: (a) Hiyama, T. Hatanaka, Y. *Pure. Appl. Chem.* **1994**, *66*, 1471. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

(11) For recent general reviews of cross-coupling reactions, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) *Metal–Catalyzed Cross-Coupling Reactions*, 2nd Ed; de Meijere, A.; Diederich, F. Eds.; Wiley-VHC: Weinheim, 2004. (c) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (d) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.

(12) For example, see: (a) Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763. (b) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362. (c) Olsen, C. A.; Parera, N.; Albericio, F.; Álvarez, M. *Tetrahedron Lett.* **2005**, *46*, 2041. (d) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537.

(13) For an example with arylboronic acid, see: Milne, J. E., Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126,* 13028. Also see: ref. 13b.

(14) In the electrophilic substitution of imidazo[1,5-a]pyridines with acetyl chloride, the course of the reaction is entirely different from usual electrophilic substitution. The imidazole nitrogen atom first attacks the electrophile. Next, the intermediate salt is deprotonated at the C1 (or C3) position. Finally, migration of the electrophile to this position gives the product. Therefore, Lewis acid or base additive may inhibit iodination. See: Hlasta, D. J. *Tetrahedron Lett.*, **1990**, *31*, 5833.

(15) The bromination of imidazopyridines has been noted, but no actual example has been reported. See: Paudler, W. W.; Kuder, J. E. *J. Org. Chem.* **1967**, *32*, 2430.

(16) Shaw, H.; Perlmutter, H. D.; Gu, C.; Arco, S. D.; Quibuyen, T. O. *J. Org. Chem.* **1997**, *62*, 236

(17) (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006.

(18) 3-(4-Nitro-1,1'-biphen-4'-yl)imidazo[1,5-a]pyridine did not show fluorescence emission. see ref 5

(19) Demas, J. N.; Crosby, G. A. *J. Phys. Chem.* **1971**, *75*, 991.

(20) Kovtun, P. Y.; Prostota, A. Y. *Chem. Hetero. Compounds.* **2000**, *36*, 557.

Chapter 3

Introduction of Planar π-Conjugated System to Imidazo[1,5-*a*]pyridines by Means of Palladium Catalysis

A variety of alkynyl and alkenyl groups were introduced into imidazo[1,5-*a*]pyridines to expand the π-conjugated system. Sonogashira coupling reaction of 1-iodoimidazo[1,5-*a*]pyridines with a variety of terminal alkynes were investigated to obtain alkynylated imidazopyridines. The reaction gave the desired products in good to high yields. Mizoroki-Heck reaction of 1-iodoimidazo[1,5-*a*]pyridines with styrene derivatives also carried out to give alkenylated imidazopyridines in moderate to good yields. The fluorescence maxima of the alkynylated products and alkenylated products were in the range of 458-560 nm and 479-537 nm, respectively.

3.1. Introduction

In chapter 2, the author described syntheses of a variety of 1,3-diarylated imidazo[1,5-*a*]pyridine derivatives by means of transition-metal-catalyzed cross-coupling reactions and their photo-physical properties. Meanwhile, alkynylated and alkenylated imidazo[1,5-*a*]pyridines are also attractive compounds for functional materials owing to their electronic nature of unsaturated moieties, whereas the straightforward methods to achieve the desired imidazopyridines bearing alkynyl or alkenyl groups have not been established. In this chapter, transition metal-catalyzed cross-coupling reactions of aryl halides and terminal alkynes or alkenes, that are known as Hagihara-Sonogashira coupling[1] and Mizoroki-Heck coupling,[2] are one of the most versatile methods for introducing alkynyl- and alkenyl- moieties into aromatic compounds, respectively. To date, a tremendous amount of reviews regarding those reactions are available. However, there are few examples in which electron-rich nitrogen-containing heteroarenes are used as one or both of substrates in cross-coupling reactions including Hagihara-Sonogashira coupling and Mizoroki-Heck reaction,[3] since electron-rich heteroaryl metal species, even heteroaryl–transition metal intermediates in these processes, are often unstable and readily undergo protonolysis or decomposition under the reaction conditions.[4] Therefore, investigation of the reactions with such substrates is still important. Below, the author describes syntheses of alkynyl or alkenyl group introduced imidazo[1,5-*a*]pyridines towards tunable photofunctional materials by means of Hagihara-Sonogashira and Mizoroki-Heck reactions. Photophysical properties of those imidazo[1,5-*a*]pyridine derivatives obtained are also investigated. During the investigations, the author found a linear relationship between Hammett substituent constants of introduced substituents on arylalkynyl groups and emission wavelength.

3.2. Synthesis of 1-alkynylated imidazo[1,5-a]pyridines by Hagihara-Sonogashira coupling reaction

The author has been interested in substituents effects on photophysical properties of imidazo[1,5-*a*]pyridines and already investigated the properties of the series of 1,3-diaryl imidazopyridines, whereas there were less-ordered tendencies with the nature of their substituents. Meanwhile, most of biaryl moieties have twisted structures due to steric repulsion of their substituents, and result in formation of a distorted π-conjugated system.[5] As a result, electronic properties of substituents sometimes do not influence efficiently their photophysical properties. In common with most of the 1,3-diarylated imidazo[1,5-*a*]pyridines **1** also form distorted π-conjugated systems due to steric repulsion of hydrogen atom at 4- or 7-positions of imidazo[1,5-*a*]pyridines and substituted aromatic rings, that are suggested by X-ray analyses[5] and DFT calculations[6] (Figure 1, left). In order to achieve planar π-conjugated systems with two aryl groups, ethynyl group have frequently been introduced into Ar-Ar moieties as a π-conjugated rod-like spacer. In fact, the motifs are often found in organic functional materials.[7] Thus, to achieve sterically undistorted imidazo[1,5-*a*]pyridines, the author designed arylalkynyl imidazopyridines **2** and investigated the electronic influences of its substituents on photophysical properties (Figure 1).

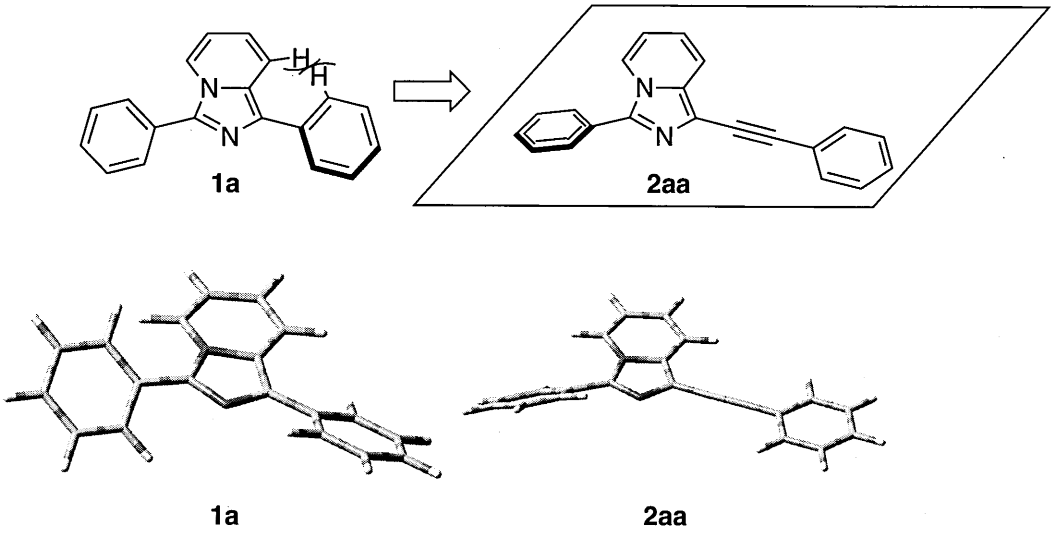
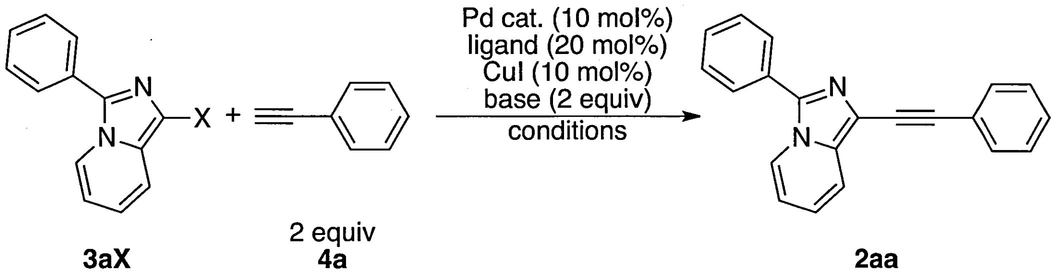


Figure 1. Steric repulsion of **1a** and planar structure of **2aa** and the optimized structures of **1a** and **2aa** calculated by B3LYP/6-31 G level.

For this purpose, introduction of an ethynyl spacer by means of Hagihara-Sonogashira reaction was investigated. The results of initial screening of the reaction conditions for halogenated imidazopyridines **3a** and phenylacetylene **4a** are shown in Table 1. The reaction of 1-bromo-3-phenylimidazo[1,5-*a*]pyridine **3aBr** with phenylacetylene **4a** (2 equiv), HN(*i*-Pr)$_2$ (2 equiv) and a catalytic amount of Pd(PPh$_3$)$_2$Cl$_2$ (10 mol%) and CuI (10 mol%) in dioxane did not give any product at all (entry 1).[8] The use of P(*t*-Bu)$_3$ as a ligand was not effective, although the Suzuki-Miyaura coupling reaction of a series of imidazopyridines was significantly accelerated by using this ligand (entry 2).[5b] The desired alkynylated product **2aa** was obtained when Pd(PPh$_3$)$_4$ was used as a catalyst (entry 3), and the use of acetonitrile as a solvent slightly improved the yield of **2aa** (entry 4). The reaction of **3aI** with Pd(PPh$_3$)Cl$_2$ as a catalyst in Et$_3$N gave **2aa** in the highest yield of their investigations (entry 5), thus the author chose these reaction conditions to use further investigations.

Table 1. Optimization of Hagihara-Sonogashira coupling reaction with 3a and 4a

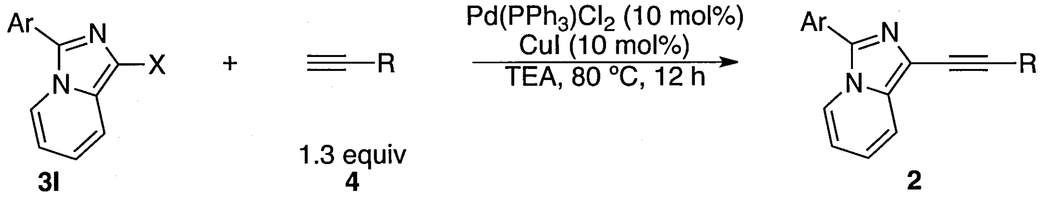


entry	X	cat.	ligand	base	conditions	**4aa** yield (%)[a]
1	Br	$Pd(PPh_3)_2Cl_2$	none	HN(*i*-Pr)$_2$	dioxane, rt, 17 h	no reaction
2	Br	$Pd(MeCN)_2Cl_2$	P(*t*-Bu)$_3$•HBPh$_4$	HN(*i*-Pr)$_2$	dioxane, rt, 24 h	no reaction
3	Br	$Pd(PPh_3)_4$	none	EtN(*i*-Pr)$_2$	dioxane, 60 °C, 20 h	53
4	Br	$Pd(PPh_3)_4$	none	EtN(*i*-Pr)$_2$	MeCN, 60 °C, 20 h	60
5	I	$Pd(PPh_3)_2Cl_2$	none	none	Et_3N, 80 °C, 12 h	65[b]

[a] Isolated yield. [b] The reaction was carried out with 1.3 equiv of **4a**.

Then, scope of substrate in the Hagihara-Sonogashira coupling reaction of **2** was examined. The results are summarized in Table 2. A variety of substituents on the terminal alkynes such as methoxyphenyl (**4b**), 4-trifluoromethylphenyl (**4c**), 2-pyridyl (**4d**), 1-naphthyl (**4e**), silyl (**4f** and **4g**), alkenyl (**4h**) and alkyl (**4i**) groups were tolerated to give the coupling products in moderate to high yields (entries1-9). A prolonged reaction time improved the yield of the products in some of the reactions (*eg*. entry 5). The reaction of an electron-donating 4-methoxyphenyl substituted iodoimidazo[1,5-*a*]pyridines (**3bI**) and terminal alkynes **4a, d-f** gave the corresponding products in good yields (entries 10-14). The reaction also proceeded by using electron-deficient substrates such as trifluoromethylphenyl- (**3cI**) and fluorophenyl- (**3dI**) imidazopyridines as substrates (entries 15-22). The coupling reaction was not disturbed by the use of 2-pyridylimidazopyridine **3eI** as a substrate, which potentially works as a bidentate ligand for the catalyst and could not be applied to Kumada-Tamao-Corriu coupling reactions.[5b] As results, the reaction of **3eI** and various terminal alkynes **4** took place to give **2** in good to high yields (entries 23-34) even with the arylacetylene bearing a formyl group (**4j**). The coupling reaction of Imidazopyridine bearing electron-rich heteroaromatics such as 2-thienylimidazopyridine **3fI** also proceeded to give the corresponding product in good yields (entries 35-39).

Table 2. Reaction of various terminal alkynes **4** and imidazopyridine derivatives



Ar = Ph; **3al**
4-MeOC$_6$H$_4$; **3bl**
4-CF$_3$C$_6$H$_4$; **3cl**
4-FC$_6$H$_4$; **3dl**
2-pyridyl; **3el**
2-thienyl; **3fl**

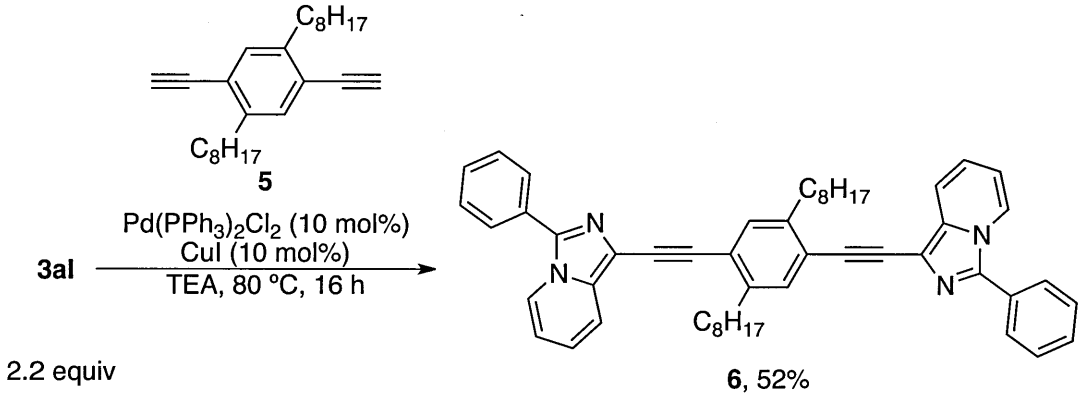
R = Ph; **4a**
4-MeOC$_6$H$_4$; **4b**
4-CF$_3$C$_6$H$_4$; **4c**
2-pyridyl; **4d**
1-naphtyl; **4e**
TMS; **4f**
TES; **4g**
1-cyclohexyenyl; **4h**
1-pentyl; **4i**
4-FC$_6$H$_4$; **4j**
4-ClC$_6$H$_4$; **4k**
4-MeC$_6$H$_4$; **4l**
4-NMe$_2$C$_6$H$_4$; **4m**
2-CHOC$_6$H$_4$; **4n**
2-MeOC$_6$H$_4$; **4o**
2-MeSC$_6$H$_4$; **4p**

Entry	3	R	2	Yield (%)	Entry	3	R	2	Yield (%)
1	**3aI**	Ph	**2aa**	65	21	**3dI**	2-pyridyl	**2dd**	72
2		PMP	**2ab**	64	22		1-Naph	**2de**	90
3		4-CF$_3$C$_6$H$_4$	**2ac**	99	23	**3eI**	Ph	**2ea**	86
4		2-pyridyl	**2ad**	84	24		PMP	**2eb**	84
5		1-Naph	**2ae**	69 (85)[b]	25		4-CF$_3$C$_6$H$_4$	**2ec**	91
6		TMS	**2af**	88	26		2-pyridyl	**2ed**	91
7		TES	**2ag**	80	27		1-naphtyl	**2ef**	59
8		1-cyclohexenyl	**2ah**	73	28		4-FC$_6$H$_4$	**2ej**	99
9		C$_5$H$_{11}$	**2ai**	81	29		4-ClC$_6$H$_4$	**2ek**	99
10	**3bI**	Ph	**2ba**	79	30		4-MeC$_6$H$_4$	**2el**	99[c]
11		PMP	**2bb**	77	31		4-NMe$_2$C$_6$H$_4$	**2em**	87
12		2-pyridyl	**2bd**	69	32		2-CHOC$_6$H$_4$	**2en**	87[d]
13		1-Naph	**2be**	80	33		2-MeOC$_6$H$_4$	**2eo**	63[c]
14		TMS	**2bf**	99	34		2-MeSC$_6$H$_4$	**2ep**	83
15	**3cI**	Ph	**2ca**	82	35	**3fI**	Ph	**2fa**	81
16		PMP	**2cb**	74	36		4-CF$_3$C$_6$H$_4$	**2fc**	76
17		2-pyridyl	**2cd**	71	37		4-FC$_6$H$_4$	**2fj**	77
18		1-Naph	**2ce**	99	38		4-ClC$_6$H$_4$	**2fk**	73
19	**3dI**	Ph	**2da**	99	39		4-MeC$_6$H$_4$	**2fl**	70
20		PMP	**2db**	75					

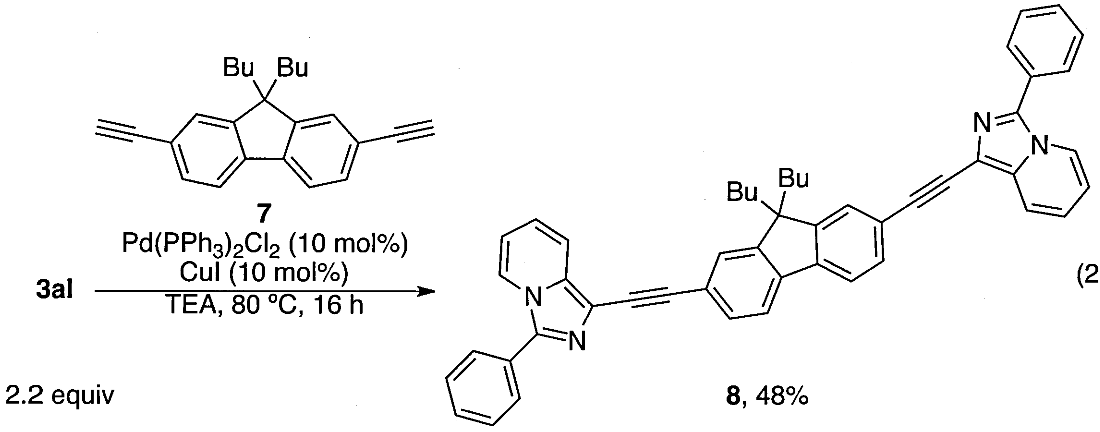
[a] Isolated yield. [b] Reaction was performed for 14 h. [c] Reaction was performed at 60 °C for 5 h.

[d] Reaction was performed at 60 °C for 4 h.

The author then focused on synthesis of bisimidazo[1,5-*a*]pyridine linked by π-conjugated spacer such as benzene and fluorene based bis-ethynylene, which would be expected to increased their absorption and fluorescent strength.[9] Additionally, synthesis of direct ethynylene-bridged bisimidazopyridines were carried out. Under the optimized reaction conditions, the reaction with **3aI** and 1,4-dialkyl-2,5-diethynylbenzene (**5**) gave the corresponding diarylated product **6** in 52% yield (eq 3). Fluorene-based spacer (**7**) could also be introduced to give the product **8** in 48% yield (eq 4).

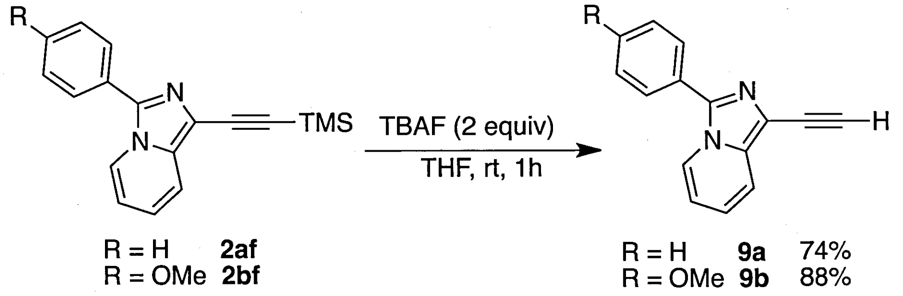


(1)

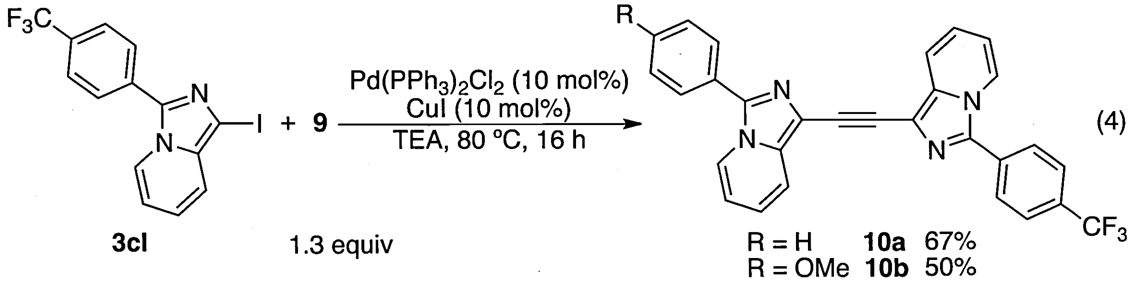


(2)

Ethynylene-bridged bisimidazopyridines were prepared as follows: First, treatment of **2af** and **2bf** with tetrabutylammonium fluoride in THF at room temperature led to desilylated products **9a** and **9b** in 74% and 88% yield, respectively (eq 4). Then **9a** and **9b** were treated with **3cI** in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$ and CuI in Et_3N at 80 °C for 16 h to give the bisimidazopyridines **10a** and **10b** in moderate yields (eq 5).



(3)

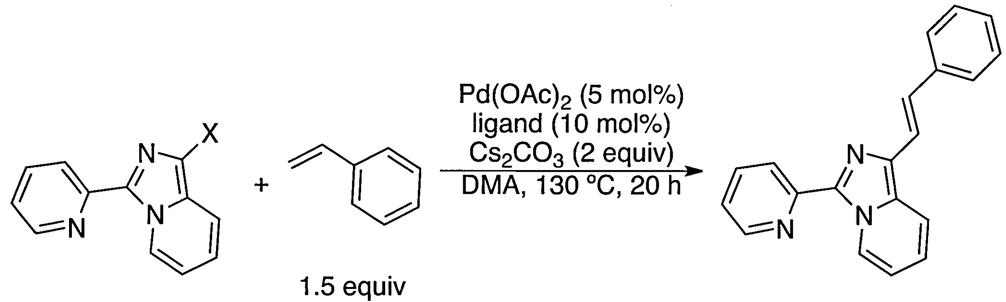


(4)

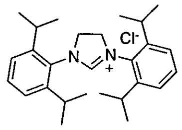
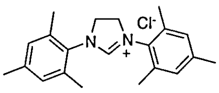
3.3. Synthesis of 1-alkenylated imidazo[1,5-*a*]pyridines by Mizoroki-Heck reaction

The Mizoroki-Heck reaction is one of the versatile methods to develop internal alkene species. In order to introduce arylalkenyl groups into the imidazopyridines, the Mizoroki-Heck reaction of **2** and terminal alkene **12** was examined. The optimization of reaction conditions is displayed in Table 3.

Table 3. Optimization of Mizoroki-Heck coupling reaction with **2** and **12**



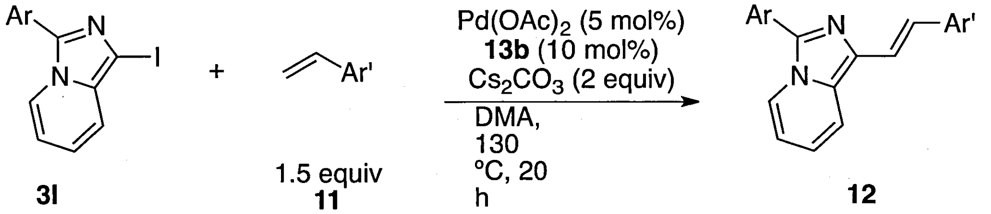
3eX **11a** **12ea**

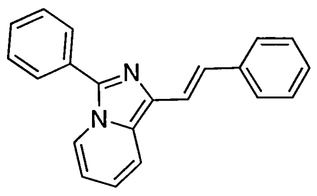
entry	X	ligand	yield (%)[a]
1[b]	Br	none	N. R.
2	I	PPh_3[c]	56
3	I	$P(t\text{-}Bu)_3 \cdot HBPh_4$	76
4	I	 **13a**	58
5	I	 **13b**	85

[a] Isolated yield. [b] The reaction was carried out with 2 equiv of styrene. [c] The reaction was carried out with 20 mol% of PPh_3.

The reaction of **3eBr** with styrene **11a**, Cs_2CO_3 and a catalytic amount of $Pd(OAc)_2$ in DMA at 100 °C for 20 h did not give the product at all.[2] In contrast, the reaction took place by using **3eI** instead of bromide **3eBr** and PPh_3 as a ligand to give the product (**12ea**) in 56% yield. The use of an electron-rich ligand such as $P(t\text{-}Bu)_3$ improved the yield of **12ea**. *N*-Heterocyclic carbene (NHC) ligand **13a** did not participate in this reaction,[10] whereas the NHC ligand bearing mesityl groups (**13b**) worked as the most suitable ligand for the reaction and gave the corresponding product **12ea** in highest yield .

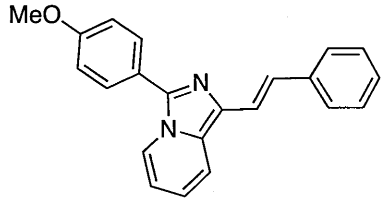
Table 4. Reaction of various styrenes **11** with imidazopyridine derivatives **3** [a]





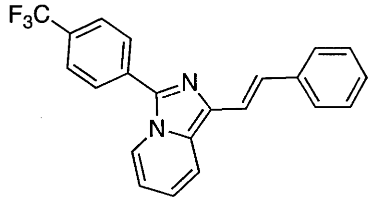
12aa

55%



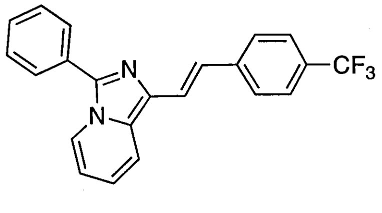
12ba

54%



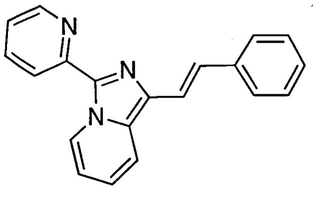
12ca

54%



12ac

90%



12ea

85%

a

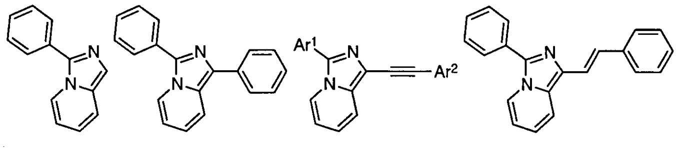
[a] Isolate yield.

3.4. Photophysical properties of imidazo[1,5-*a*]pyridine derivatives

UV/vis and fluorescence spectra of the obtained imidazopyridine derivatives were measured. The selected results are summarized in Table 5. The photophysical properties of the alkynylated imidazo[1,5-*a*]pyridines indicated that the arylalkynyl groups clearly influence absorption and emission maxima (λ_{abs} and λ_{em}), and fluorescence quantum yields (entries 3-21). As expected, in a series of 3-phenylimidazopyridines such as **14a**, **1a** and **2aa**, the λ_{abs} (**14a** 317 nm, **1a** 388 nm vs **2aa** 397 nm) and λ_{em} (**14a** 461 nm, **1a** 477 nm vs **2aa** 478 nm) values of 1-phenylethynyl-3-phenylimidazopyridine **2aa** were red-shifted, since formation of the expanded planar π-conjugated system leads to smaller HOMO-LUMO band gap (entries 1 and 2 vs 3). The absorption and emission of alkenylated imidazopyridine **12aa** were also significantly red-sifted (λ_{abs} 425 nm, λ_{em} 534 nm) compared with those of parent **14a** and **1a** (entry 26). To understand the phenomenon, DFT and TDDFT calculations of series of imidazopyridines at the B3LYP level with a 6-311G**(d,p) basis set were carried out. As a result, the HOMO-LUMO band gaps were narrowing in the order of **14a>1aa>2aa>12aa** and the predicted absorption wavelength increases in the order of **14a<1aa<2aa<12aa** (Figure 2, left, Table 6). Those results are consistent with the experimental observations. In addition, the fluorescence quantum yield of **2aa** was improved from **14a** and **1a**. Aryl groups at C3 position of **2** less affected their absorptions, emissions and quantum yields (entries 3, 6–9 and 17) as is the cases of **14** and **1**. In contrast, the electronic properties of substituents on arylalkynyl group of **2** clearly influence their photophysical properties. For instance, the 2-thienylimidazopyridines **2f** bearing electron-rich alkynes show red-shifted emissions based on **2fa** (entries 9 vs 10, 14 and 15). On the other hand, electron-poor alkynes show blue-shifted emissions (entries 9 vs 11, 12 and 13). Dramatically red-shifted emission was observed with imidazopyridines bearing 2-formyl-phenylethynyl group **2en** (560 nm, entry 16). During the investigation of the electronic influences on the alkynyl substituents on 1-position, the author realized an interesting relationship between the λ_{em} (nm) and the Hammett substituent constants. As shown in Figure 3, the λ_{em} (nm) values of the 3-phenylimidazopyridine derivatives **2a** are found to have a linear dependence on the Hammett substituent constants of the substituents on the arylalkynyl group. The similar dependence is also found with 3-(2-pyridyl)- **2e** and 3-(2-thienyl)imidazopyridine **2f** derivatives. In contrast, 1,3-diarylated imidazopyridines **1** shows no trends on emission wavelength as described in introduction (figure 3, lower right). These observations imply that the electronic influence of substituents on arylalkynyl groups affected directly imidazopyridine ring of **2** via their planar π-conjugated system efficiently resulting in the linear dependence between emission and their electronic properties of the substituents. Also, the photophysical properties such as absorption and emission behavior are consistent with the results of the calculated HOMO-LUMO gaps by DFT calculations and predicted absorption behaviors, that should also be related to emission behaviors, by TDDFT calculations (*e.g.* figure 2, right). Meanwhile, the observed longest UV/vis absorptions of the series of alkynylated imidazopyridines **2** seem to no trend with the substituents on alkynyl group, whereas the peak tops of those absorptions were indistinct to discuss since the peaks are immersed in adjacent larger absorptions.

The imidazopyridine dimers bearing benzene and fluorene-based spacer **6** and **8** indicate similar λ_{em} of **2aa**, while stronger UV absorption and slightly improved Φ_F were observed (entries 3 vs 22 and 23). Both ethynylene-bridged dimer **10a** and **10b** show the similar UV absorption wavelength (329 nm, 330 nm) but red-shifted fluorescent emission wavelength (501 nm and 506 nm) compared with **2aa** (entries 3 vs entries 24 and 25). In the case of a series of alkenylated products **12**, large stokes shift and decreased fluorescence quantum yields were observed (entry 26).

Table 5. Selected photophysical properties on obtained imidazo[1,5-*a*]pyridines



14a **1a** **2Ar^{1}Ar^2** **12ea**

Ar^1 = Ph: **a**, 4-MeOC$_6$H$_4$: **b**, 4-CF$_3$C$_6$H$_4$: **c**, 4-FC$_6$H$_4$: **d**, 2-pyridyl: **e**, 2-thienyl: **f**

Ar^2 = Ph: **a**, 4-MeOC$_6$H$_4$: **b**, 4-CF$_3$C$_6$H$_4$: **c**, 2-pyridyl: **d**, 1-naphtyl: **e**, 4-FC$_6$H$_4$: **j**, 4-ClC$_6$H$_4$: **k**, 4-MeC$_6$H$_4$: **l**, 4-NMe$_2$C$_6$H$_4$: **m**, 2-CHOC$_6$H$_4$: **n**, 2-MeOC$_6$H$_4$: **o**, 2-MeSC$_6$H$_4$: **p**

entry		UV/vis^a λ max (nm)	log ε	fluorescence^a λ max (nm)	Φ_F^{b}
1	**14a**	317	4.25	461	0.07
2	**1a**	388 345 306	3.45 3.88 4.14	477	0.16
3	**2aa**	397 333 320	3.78 4.41 4.40	478	0.23
4	**2ab**	387 331 315	3.91 4.56 4.60	485	0.23
5	**2ac**	416 373 344	3.70 4.26 4.49	465	0.21
6	**2ba**	398 335 321	3.81 4.43 4.45	488	0.20
7	**2ca**	411 355 330 317	3.50 4.32 4.43 4.36	473	0.16
8	**2da**	377 332 318	3.93 4.40 4.41	478	0.25
9	**2ea**	410 368 331	3.93 4.55 4.36	458	0.15
10	**2eb**	410 370 330	3.88 4.44 4.36	464	0.15
11	**2ec**	410 387 369	4.18 4.52 4.60	447	0.19
12	**2ej**	409 367 330	3.90 4.48 4.48	458	0.19
13	**2ek**	410 389 367 336	4.04 4.42 4.53 4.47	455	0.07
14	**2el**	407 370 332	4.01 4.42 4.42	460	0.19
15	**2em**	410 379 339	4.09 4.37 4.43	476	0.07
16	**2en**	420 398 371 287	4.20 4.30 4.40 3.43	560	0.20
17	**2fa**	405 369 337	3.91 4.30 4.50	490	0.06
18	**2fc**	399 363 348	4.16 4.44 4.52	483	0.08
19	**2fj**	399 370 333	3.97 4.29 4.43	489	0.07
20	**2fk**	397 343	3.96 4.41	487	0.07
21	**2fl**	402 371 335	3.74 4.05 4.28	493	0.08
22	**6**	405 342	4.62 4.64	479	0.26
23	**8**	409 379	4.80 4.77	476	0.26
24	**10a**	407 329 318 295	4.21 4.45 4.42 4.34	501	0.15
25	**10b**	405 330 318 298	4.19 4.45 4.45 4.40	506	0.16
26	**12aa**	425 346	3.73 4.42	536	0.03

[a] Measured in CHCl$_3$ (10^{-5} M). [b] Quantum yields (Φ_F) were determined with reference to quinine sulfate in 0.1 M aqueous sulfuric acid (excited at 350 nm).

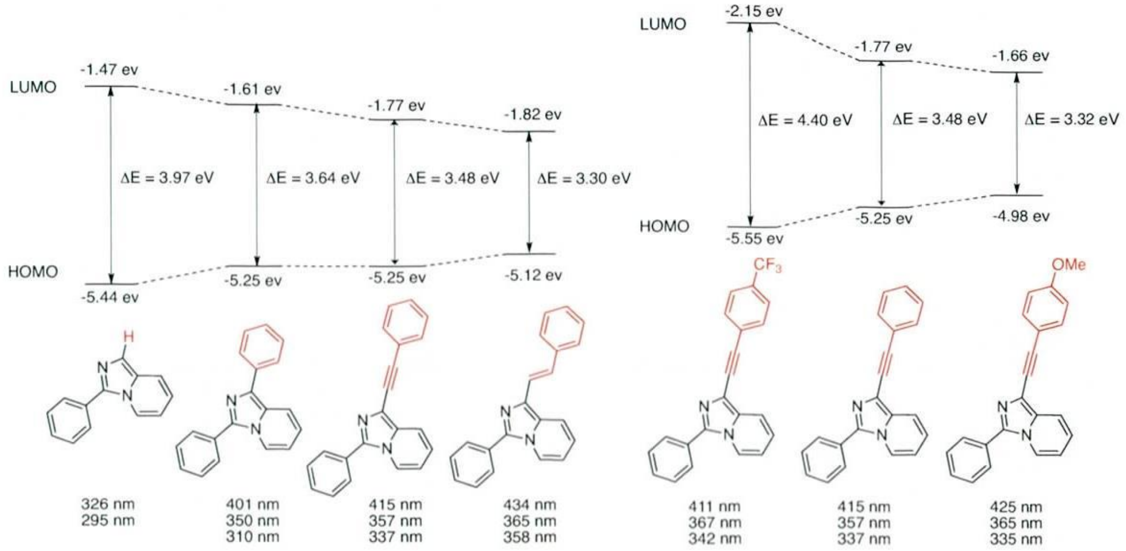


Figure 2. Energy levels of the HOMO and LUMO and predicted absorption wave length by TDDFT calculations of compounds **14a**, **1a**, **2** and **12aa** at the B3LYP/6-311G**(d,p) level.

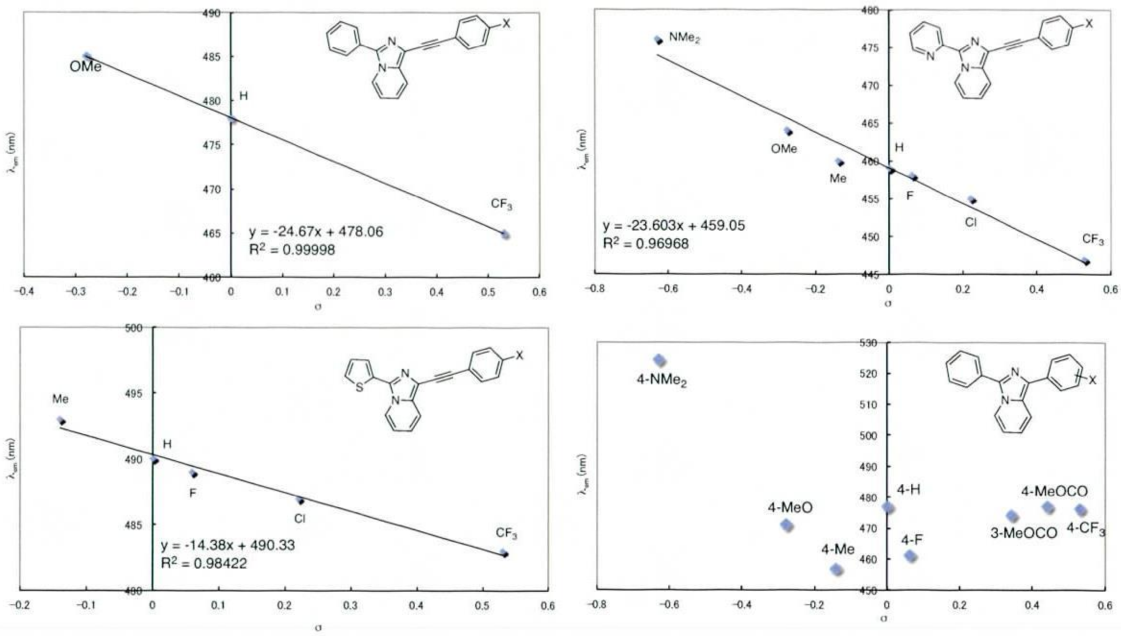


Figure 3. The correlation between the λ_{em} and Hammett's substituent constant[11] of **2a, 2e, 2f and 1a**.

Table 6. Full details of electronic excitation energies (eV) and corresponding oscillator strengths (*f*) and CI coefficients of **14a**, **1a**, **2** and **12aa**[a]

Entry	compound	Wave length (nm)	Energy (eV)	f^b	Compositions[c]	CI[d]
1	**14a**	366	3.38	0.0316	HOMO→LUMO	0.6353
		327	3.80	0.3859	HOMO→LUMO+2	0.6289
		295	4.20	0.0069	HOMO→LUMO+2	0.6801
2	**1a**	401	3.09	0.1075	HOMO→LUMO	0.6386
		350	3.54	0.2997	HOMO→LUMO+1	0.6494
		310	3.99	0.0323	HOMO→LUMO+3	0.5826
3	**2aa**	415	2.98	0.2282	HOMO→LUMO	0.6285
		357	3.47	0.4434	HOMO→LUMO+1	0.6617
		338	3.67	0.4836	HOMO→LUMO+2	0.6264
4	**2ab**	425	2.91	0.2228	HOMO→LUMO	0.6396
		365	3.39	0.3589	HOMO→LUMO+2	0.6636
		335	3.69	0.6896	HOMO→LUMO+3	0.6381
5	**2ac**	412	3.01	0.4646	HOMO→LUMO	0.6046
		367	3.38	0.5010	HOMO→LUMO+1	0.6332
		342	3.62	0.2112	HOMO→LUMO+3	0.3687
6	**12aa**	434	2.85	0.2555	HOMO→LUMO	0.6081
		365	3.32	0.4405	HOMO→LUMO+1	0.6497
		359	3.46	0.3808	HOMO→LUMO+2	0.6000

[a] Calculated by TDDFT//B3LYP/6-311G**(d,p) level based on the DFT//B3LYP/6-31G (d,p) optimized ground state geometries. [b] Oscillator strength. [c] Only the main configurations with configuration interaction (CI) coefficients >0.3 are presented. [d] CI coefficients are in absolute values.

3.6. Summary

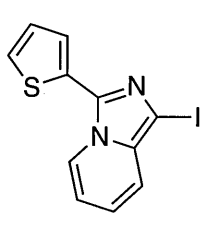
In conclusion, we have synthesized 1-alkynyl- and 1-alkenyl-imidazo[1,5-*a*]pyridines by means of Hagihara-Sonogashira coupling and Mizoroki-Heck reactions and investigated their photophysical properties. All the imidazopyridine derivatives obtained exhibited fluorescence in solution. The fluorescence maxima and fluorescence quantum yields of the alkynylated products were in the range of 458-560 nm and $\Phi_F = 0.08$-0.26 in chloroform solution. Furthermore, the fluorescence maxima and fluorescence quantum yields of the alkenylated imidazopyridines were in the range of 479-537 nm and $\Phi_F = 0.03$-0.13, respectively. The alkynylated imidazopyridines **4** obtained shows linear dependence between the Hammett substituent constants of the substituents on the arylalkynyl group and their fluorescence behavior. With this predictable property, a series of alkynylated imidazopyridines are potentially applicable to tunable fluorescent materials.

3.5. Experimental

Materials: Unless otherwise noted, reagents were commercially available and were used without purification. Terminal alkynes **4k**,[12] **4l**,[13] **7**,[14] and imidazo[1,5-*a*]pyridyne derivatives **3**[5] were prepared according to the literature. **5** was prepared modified procedure of the literature.[15] Silica gel 60N (Spherical, Neutral, 40-50 ⌠m) was from Kanto Chemical Co., Inc.

3.5.1. Synthesis of 1-Iodo-imidazo[1,5-a]pyridine (3)

1-Iodo-3-(2-thienyl)imidazo[1,5-a]pyridine **(3fI)**



Chemical Formula: $C_{11}H_7IN_2S$
Exact Mass: 325.9375
Molecular Weight: 326.1562

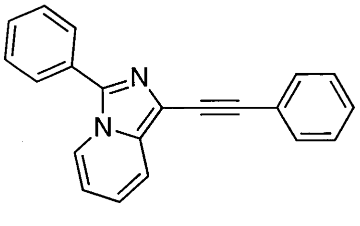
To a solution of 3-(2-thienyl)imidazo[1,5-*a*]pyridine (0.30 g, 1.5 mmol) in THF (3 mL) was added iodine (0.42 g, 1.7 mmol, 1.1 equiv) at room temperature under an Ar atmosphere. The resulting mixture was stirred at 40 °C for 15 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq, neutralized with $NaHCO_3$ aq, and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-Hex : EtOAc = 4 : 1) to give 1-iodo-3-(2-thienyl)imidazo[1,5-*a*]pyridine (0.25 g, 52%) as a yellow solid. mp 104-105 °C, Rf = 0.43 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3096, 2916, 1738, 1628, 1498, 1401, 1359, 1262 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.67 (dd, *J* = 7.3, 6.8 Hz, 1H, Ar), 6.80 (dd, *J* = 8.8, 6.8 Hz, 1H, Ar), 7.16 (dd, *J* = 4.9, 3.4 Hz, 1H, Ar), 7.34 (d, *J* = 9.3 Hz, 1H, Ar), 7.41 (d, *J* = 4.9 Hz, 1H, Ar), 7.48 (d, *J* = 3.4 Hz, 1H, Ar), 8.26 (d, *J*

= 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 74.3, 114.5, 118.9, 120.2, 122.1, 125.3, 126.4, 127.6, 131.1, 133.5, 135.1 (Ar). MS (EI) *m/z* 325 (M^+); HRMS (EI) Calcd for $C_{11}H_7IN_2S$ (M^+); 325.9375. Found: 325.9371.

3.5.2. General procedure for Sonogashira coupling reaction

An oven-dried screw-capped reaction tube was added $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), 3-iodo-1-arylimidazo[1,5-a]pyridine (0.25 mmol), terminal alkyne (1.3 equiv) and triethylamine (1 mL). After flashed Ar, the resulting solution was heated at 80 °C and after the reaction period. The mixture was cooled at room temperature and purified by flash column chromatography on silica gel (*n*-Hex : EtOAc) to give the title compound.

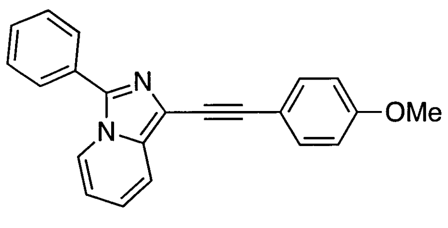
1-Phenylethynyl-3-phenyl-imidazo[1,5-a]pyridine (**2aa**)



Chemical Formula: $C_{21}H_{14}N_2$
Exact Mass: 294.1157
Molecular Weight: 294.3493

yellow solid, mp 156-158 °C, Rf = 0.35 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2203, 1597, 1522, 1487, 1352, 1212, 1126, 756, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.59 (dd, *J* = 6.3, 7.2 Hz, 1H, Ar), 6.83 (dd, *J* = 6.3, 8.8 Hz, 1H, Ar), 7.24-7.30 (m, 3H, Ar), 7.37-7.48 (m, 3H, Ar), 7.53 (d, *J* = 7.1 Hz, 2H, Ar), 7.65 (d, *J* = 8.8 Hz, 1H, Ar), 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 8.21 (d, *J* = 7.1 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 82.7 (CC), 92.7 (CC), 114.1, 115.0, 118.9, 120.8, 122.1, 123.6, 127.9, 128.2, 128.3, 129.1, 129.2, 129.6, 131.4, 134.3, 138.4 (Ar). MS (EI) *m/z* 294 (M^+); HRMS (EI) Calcd for $C_{21}H_{14}N_2$ (M^+); 294.1157. Found: 294.1158.

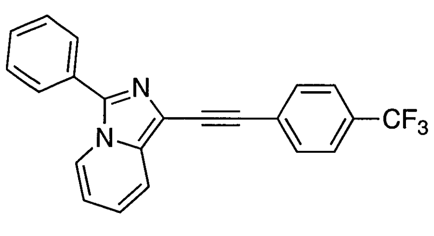
1-(4-Methoxyphenyl)ethynyl-3-phenyl-imidazo[1,5-a]pyridine (**2ab**)



Chemical Formula: $C_{22}H_{16}N_2O$
Exact Mass: 324.1263
Molecular Weight: 324.3752

yellow solid, mp 129-130 °C, Rf = 0.25 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2834, 2359, 2203, 1602, 1521, 1502, 1439, 1245, 1171, 1125, 836, 746, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H, OMe), 6.63 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.86 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 6.89 (d, *J* = 8.8 Hz, 2H, Ar), 7.43-7.55 (m, 5H, Ar), 7.69 (d, *J* = 9.3 Hz, 1H, Ar), 7.82 (d, *J* = 6.8 Hz, 2H, Ar), 8.26 (dd, *J* = 7.3 Hz, 1H, Ar), ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe), 81.4, 92.8 (CC), 114.3, 115.6, 116.0, 119.2, 120.8, 122.3, 128.5, 129.3 (two carbon atoms were overlapped), 129.4, 129.9, 133.2, 134.3, 138.5, 159.8 (Ar). MS (EI) *m/z* 324 (M^+); HRMS (EI) Calcd for $C_{22}H_{16}N_2O$ (M^+); 324.1263. Found: 324.1263.

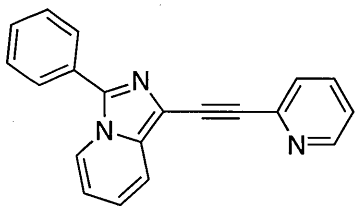
3-Phenyl-1-(4-trifluoromethylphenylethynyl)-imidazo[1,5-a]pyridine (2ac)



Chemical Formula: $C_{22}H_{13}F_3N_2$
Exact Mass: 362.1031
Molecular Weight: 362.3472

yellow solid, mp 187-189 °C, Rf = 0.50 (*n*-Hex : EtOAc = 1 : 1), IR (KBr) 2976, 2960, 2201, 1609, 1562, 1325 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.67 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.92 (dd, *J* = 9.0, 6.3 Hz, 1H, Ar), 7.47 (t, *J* = 7.3 Hz, 1H, Ar), 7.53 (t, *J* = 7.3 Hz, 2H, Ar), 7.60 (d, *J* = 8.3 Hz, 2H, Ar), 7.67-7.71 (m, 3H, Ar), 7.81 (d, *J* = 8.8 Hz, 2H, Ar), 8.28 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 85.5, 91.6 (CC), 114.2, 118.6, 121.4, 122.2 (Ar), 124.0 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.2 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 127.5, 128.2, 129.1, 129.3 (Ar), 129.4 (q, *J* = 33.3 Hz, CF_3-$\underline{C}$), 131.3, 133.6, 133.8, 134.9, 138.7 (Ar). ^{19}F NMR ($CDCl_3$) δ 63.0 (CF_3). MS (EI) *m/z* 362 (100, M$^+$). HRMS (EI): Exact mass calcd for $C_{22}H_{22}F_3N_2$ (M$^+$); 362.1031. Found: 1028.

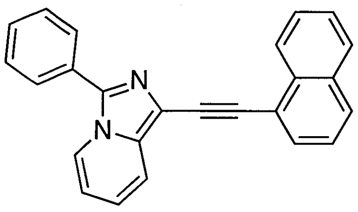
1-(2-Pyridyl)ethynyl-3-phenyl-imidazo[1,5-a]pyridine (2ad)



Chemical Formula: $C_{20}H_{13}N_3$
Exact Mass: 295.1109
Molecular Weight: 295.3373

yellow solid, mp 132-134 °C, Rf = 0.22 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2359, 2341, 2202, 1580, 1558, 1508, 1465, 1428, 1350, 1126, 1068, 775, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.60 (dd, *J* = 7.3, 7.8 Hz, 1H, Ar), 6.93 (dd, *J* = 7.3, 9.3 Hz, 1H, Ar), 7.21 (dd, *J* = 4.9, 7.8 Hz, 1H, Ar), 7.44-7.69 (m, 5H, Ar), 7.80-7.83 (m, 3H, Ar), 8.29 (d, *J* = 7.3 Hz, 1H, Ar), 8.60 (d, *J* = 4.9 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 83.2, 92.3 (CC), 113.5, 113.9, 118.6, 121.2, 121.8, 121.9, 126.7, 127.9, 128.1, 128.7, 128.9, 135.0, 135.8, 136.4, 143.5, 149.5 (Ar). MS (EI) *m/z* 295 (M$^+$); HRMS (EI) Calcd for $C_{20}H_{13}N_3$ (M$^+$); 295.1109. Found: 295.1104.

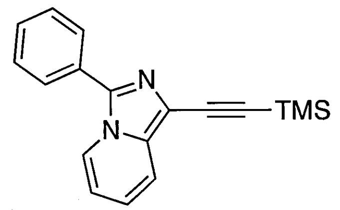
1-(1-Naphthyl)ethynyl-3-phenyl-imidazo[1,5-a]pyridine (2ae)



Chemical Formula: $C_{25}H_{16}N_2$
Exact Mass: 344.1313
Molecular Weight: 344.4079

yellow solid, mp 129-130.5 °C, Rf = 0.30 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2359, 2341, 1558, 1506, 1457, 1247, 1029, 803, 743, 689 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.65 (dd, *J* = 6.8, 7.2 Hz, 1H, Ar), 6.92 (dd, *J* = 6.8, 8.8 Hz, 1H, Ar), 7.44-7.62 (m, 6 H, Ar), 7.77-7.87 (m, 6H, Ar), 8.26 (d, *J* = 7.3 Hz, 1H, Ar), 8.58 (dd, *J* = 8.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 87.6, 90.9 (CC), 114.1, 115.1, 118.8, 121.0, 121.3, 122.1, 125.4, 126.4, 126.5, 126.7, 128.3, 128.3, 129.1, 129.2, 129.5, 130.1, 132.1, 133.0, 133.2, 134.5, 138.5 (Ar). MS (EI) *m/z* 344 (M$^+$); HRMS (EI) Calcd for $C_{25}H_{16}N_2$ (M$^+$); 344.1313. Found: 344.1321.

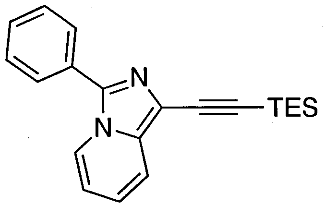
1-Trimethylsilylethynyl-3-phenyl-imidazo[1,5-a]pyridine **(2af)**



Chemical Formula: $C_{18}H_{18}N_2Si$
Exact Mass: 290.1239
Molecular Weight: 290.4344

brown oil, Rf = 0.50 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 2943, 2863, 2145, 1604, 1510, 1461, 1407, 1353, 1317, 1129, 1075, 997, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.29 (s, 9H, $SiMe_3$), 6.63 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.67 (dd, *J* = 6.8, 9.3 Hz, 1H, Ar), 7.44-7.53 (m, 3H, Ar), 7.63 (d, *J* = 9.3 Hz, 1H, Ar), 7.79 (d, *J* = 7.3 Hz, 1H, Ar), 8.24 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ -0.03 ($\mathrm{Si\underline{Me}_3}$), 97.8, 97.9 (CC), 114.0, 114.9, 118.8, 120.9, 122.0, 128.2, 129.0, 129.1, 129.5, 134.8, 138.0 (Ar). MS (EI) *m/z* 290 (M^+); HRMS (EI) Calcd for $C_{28}H_{18}N_2Si$ (M^+); 290.1239. Found: 290.1246.

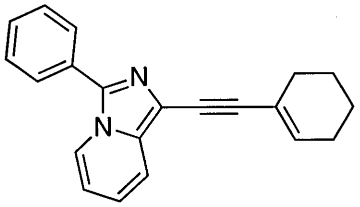
1-Triethylsilylethynyl-3-phenyl-imidazo[1,5-a]pyridine **(2ag)**



Chemical Formula: $C_{21}H_{24}N_2Si$
Exact Mass: 332.1709
Molecular Weight: 332.5142

brown oil, Rf = 0.50 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 2957, 2360, 2145, 1629, 1518, 1350, 1246, 1126, 1073, 843, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 15H, $SiEt_3$), 6.63 (dd, *J* = 6.3, 7.8 Hz, 1H, Ar), 6.87 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 7.45-7.53 (m, 3H, Ar), 7.61 (d, *J* = 9.3 Hz, 1H, Ar), 7.78 (d, *J* = 7.3 Hz, 1H, Ar), 8.23 (d, *J* = 7.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 11.3 (CH_2), 18.7 (CH_3), 94.1, 99.6 (CC), 113.9, 115.3, 118.8, 120.8, 121.9, 128.3, 128.9, 129.1, 129.5, 135.2, 137.8 (Ar). MS (EI) *m/z* 332 (M^+); HRMS (EI) Calcd for $C_{21}H_{24}N_2Si$ (M^+); 332.1709. Found: 332.1716.

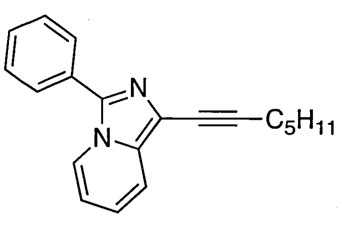
1-(1-Hexyenylethynyl)-3-phenyl-imidazo[1,5-a]pyridine **(2ah)**



Chemical Formula: $C_{21}H_{18}N_2$
Exact Mass: 298.1470
Molecular Weight: 298.3810

brown oil, Rf = 0.55 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 2927, 2362, 2169, 1633, 1509, 1445, 1354, 1301, 1172, 1124, 1075, 951, 916, 771, 728, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.60-1.72 (m, 4H, CH_2), 2.13-2.19 (m, 2H, CH_2), 2.27-2.32 (m, 2H, CH_2), 6.26 (sept, *J* = 2.0 Hz, C=CH), 6.60 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.82 (dd, *J* = 6.3, 9.0 Hz, 1H, Ar), 7.4-7.53 (m, 3H, Ar), 7.61 (d, *J* = 9.0 Hz, 1H, Ar), 7.79 (d, *J* = 7.1 Hz, 2H, Ar), 8.23 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.5, 22.3, 25.7, 29.2 (CH_2), 79.6, 94.4 (CC), 113.8 (Ar), 115.4 (C=C), 118.8, 120.2, 120.8, 121.8, 128.1, 128.9, 128,9, 129.5, 133.7, 134.4 (Ar), 138.0 (C=C). MS (EI) *m/z* 298 (M^+); HRMS (EI) Calcd for $C_{21}H_{18}N_2$ (M^+); 298.1470. Found: 298.1483.

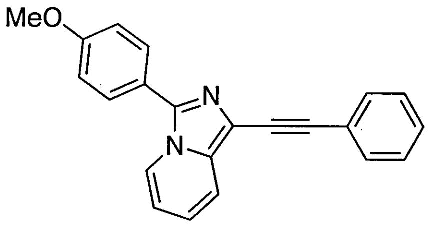
1-(1-Heptynyl)-3-phenylimidazo[1,5-a]pyridine (2ai)



Chemical Formula: $C_{20}H_{20}N_2$
Exact Mass: 288.1626
Molecular Weight: 288.3862

brown oil, Rf = 0.90 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 3065, 2932, 2858, 2361, 2329, 1602, 1461, 1358, 1300, 1189, 957, 773, 745, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H, CH_3), 1.36 (pent, *J* = 6.8 Hz, 2H, CH_2), 1.48 (tq, *J* = 6.8, 7.3 Hz, 2H, CH_2), 1.66 (pent, *J* = 6.8 Hz, 2H, CH_2), 2.51 (t, *J* = 6.8 Hz, 2H, CH_2), 6.59 (d, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.80 (d, *J* = 6.3, 8.3 Hz, 1H, Ar), 7.1-7.52 (m, 3H, Ar), 7.59 (d, *J* = 8.3 Hz, 1H, Ar), 7.78 (d, *J* = 8.3 Hz, 2H, Ar), 8.23 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 19.7, 22.2, 28.5, 31.1 (CH_2), 73.1, 93.6 (CC), 113.7, 115.7, 118.8, 119.9, 121.7, 128.1, 128.8, 128.9, 129.6, 133.5, 137.5 (Ar). MS (EI) *m/z* 288 (M^+); HRMS (EI) Calcd for $C_{20}H_{20}N_2$ (M^+); 288.1626. Found: 288.1622.

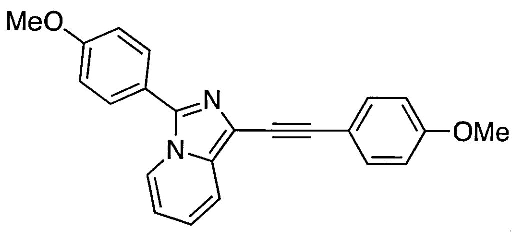
1-Phenylethynyl-3-(4-methoxyphenyl)-imidazo[1,5-a]pyridine (2ba)



Chemical Formula: $C_{22}H_{16}N_2O$
Exact Mass: 324.1263
Molecular Weight: 324.3752

yellow solid, mp 181-182 °C, Rf = 0.40 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2360, 2199, 1607, 1528, 1510, 1486, 1464, 1257, 1182, 1020, 835, 744, 688 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, OMe), 6.60 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.84 (($CDCl_3$) dd, *J* = 6.3, 8.3 Hz, 1H, Ar), 7.04 (d, *J* = 8.8 Hz, 2H, Ar), 7.30-7.37 (m, 3H, Ar), 7.59 (d, *J* = 7.8 Hz, 2H, Ar), 7.67 (d, *J* = 8.3 Hz, 1H, Ar), 7.73 (d, *J* = 8.8 Hz, 2H, Ar), 8.18 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 82.8, 92.6 (CC), 113.8, 114.4, 114.5, 118.7, 120.5, 121.9, 122.0, 123.6, 127.8, 128.3, 129.6, 131.3, 134.1, 138.4, 160.0 (Ar). MS (EI) *m/z* 324 (M^+); HRMS (EI) Calcd for $C_{22}H_{16}N_2O$ (M^+); 324.1263. Found: 324.1264.

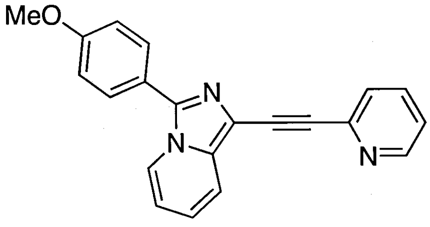
1-(4-Methoxyphenyl)ethynyl-3-(4-methoxyphenyl)-imidazo[1,5-a]pyridine (2bb)



Chemical Formula: $C_{23}H_{18}N_2O_2$
Exact Mass: 354.1368
Molecular Weight: 354.4012

yellow solid, mp 177-178 °C, Rf = 0.15 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2833, 2360, 2201, 1603, 1528, 1503, 1461, 1351, 1288, 1245, 1181, 1105, 835 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.59 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.81 (dd, *J* = 6.8, 9.3 Hz, 1H, Ar), 6.88 (d, *J* = 8.8 Hz, 2H. Ar), 7.04 (d, *J* = 8.8 Hz, 2H, Ar), 7.53 (d, *J* = 8.8 Hz, 2H, Ar), 7.65 (d, *J* = 9.3 Hz, 1H, Ar), 7.73 (d, *J* = 8.8 Hz, 2H, Ar), 8.18 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.2, 55.3 (OMe), 81.3, 92.4 (CC), 113.7, 113.9, 114.4, 114.8, 115.8, 118.8, 120.2, 121.9, 122.0, 129.6, 132.8, 133.7, 138.2, 159.4, 160.2 (Ar). MS (EI) *m/z* 354 (M^+); HRMS (EI) Calcd for $C_{23}H_{18}N_2O_2$ (M^+); 354.1368. Found: 354.1366.

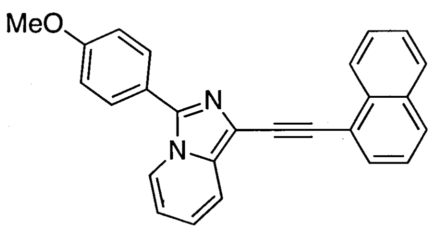
1-(2-Pyridyl)ethynyl-3-(4-methoxyphenyl)-imidazo[1,5-a]pyridine (**2bd**)



Chemical Formula: $C_{21}H_{15}N_3O$
Exact Mass: 325.1215
Molecular Weight: 325.3633

yellow solid, mp 166-167 °C, Rf = 0.10 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2975, 2360, 2199, 1608, 1580, 1529, 1509, 1462, 1255, 1182, 1143, 1021, 839, 778, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, OMe), 6.61 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.86 (dd, *J* = 6.3, 9.0 Hz, 1H, Ar), 7.01 (d, *J* = 8.8 Hz, 2H, Ar), 7.17 (d, *J* = 4.9, 7.8 Hz, 1H, Ar), 7.55 (d, *J* = 7.3 Hz, 1H, Ar), 7.63 (dd, *J* = 7.0, 7.8 Hz, 1H, Ar), 7.69 (d, *J* = 8.8 Hz, 2H, Ar), 7.75 (d, *J* 9.0 Hz, 1H, Ar), 8.17 (d, *J* = 7.0 Hz, 1H, Ar), 8.60 (d, *J* 4.9 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 83.3, 92.3 (CC), 113.4, 113.9, 114.3, 118.8, 121.2, 121.6, 122.0, 122.1, 126.8, 129.6, 135.0, 136.0, 138.6, 143.8, 149.7, 160.2 (Ar). MS (EI) *m/z* 325 (M$^+$); HRMS (EI) Calcd for $C_{21}H_{15}N_3O$ (M$^+$); 325.1215. Found: 325.1222.

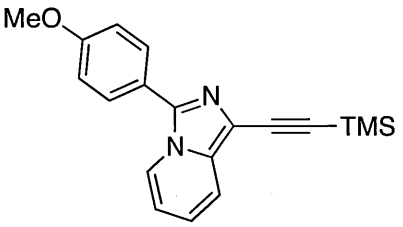
1-(1-Naphthyl)ethynyl-3-(4-methoxyphenyl)-imidazo[1,5-a]pyridine (**2be**)



Chemical Formula: $C_{26}H_{18}N_2O$
Exact Mass: 374.1419
Molecular Weight: 374.4339

yellow solid, mp 163-164 °C, Rf = 0.35 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2360, 2199, 1608, 1576, 1558, 1539, 1458, 1353, 1311, 1244, 1171, 1033, 797, 774, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H, OMe), 6.64 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.89 (dd, *J* = 6.3, 9.0 Hz, 1H, Ar), 7.06 (d, *J* = 8.8 Hz, 2H, Ar), 7.47 (dd, *J* = 7.1, 8.3 Hz, 1H, Ar), 7.54 (dd, *J* = 6.8, 8.1 Hz, 1H, Ar), 7.60 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 7.75-7.78 (m, 3H, Ar), 7.81-7.85 (m, 2H, Ar), 7.87 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 8.20 (d, *J* = 7.3 Hz, 1H, Ar), 8.59 (d, *J* = 8.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 87.8, 90.8 (CC), 113.9, 114.4, 114.7 (two carbon atoms were overlapped), 118.8, 120.8, 121.3, 121.9, 122.1, 125.4, 126.4, 126.5, 126.7, 128.2, 129.7, 130.0, 133.0, 133.2, 134.3, 138.6, 160.3 (Ar). MS (EI) *m/z* 374 (M$^+$); HRMS (EI) Calcd for $C_{26}H_{18}N_2O$ (M$^+$); 374.1419. Found: 374.1416.

1-Ethynyl-3-phenylimidazo[1,5-a]pyridine (**2bf**)

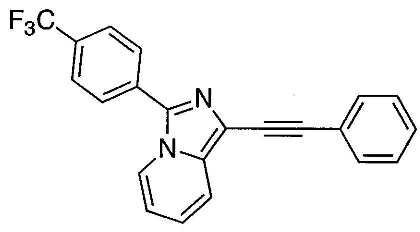


Chemical Formula: $C_{19}H_{20}N_2OSi$
Exact Mass: 320.1345
Molecular Weight: 320.4604

brown oil, Rf = 0.30 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 2957, 2898, 2836, 3243, 1611, 1249, 839 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ -0.27 (s, 9H, $SiMe_3$), 3.87 (s, 3H, OMe), 6.62 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.85 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 7.02 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 9.3 Hz, 1H, Ar), 7.70 (d, *J* = 8.3 Hz, 1H, Ar), 8.17 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ -0.01 ($Si\underline{Me_3}$), 55.3 (OMe), 97.7 (CC), 97.8 (CC), 113.8, 114.4, 114.5, 118.8, 120.6, 121.9, 122.0, 129.7, 134.6, 138.1, 160.3 (Ar). MS (EI) *m/z* 248 (M$^+$); HRMS (EI) Calcd for

$C_{16}H_{12}N_2O$ (M^+); 320.1345. Found: .320.1342.

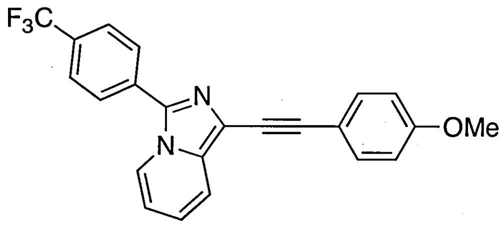
***1-Phenylethynyl-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine* (2ca)**



Chemical Formula: $C_{22}H_{13}F_3N_2$
Exact Mass: 362.1031
Molecular Weight: 362.3472

yellow solid, mp 157-159 °C, Rf = 0.40 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3087, 2925, 2360, 2206, 1616, 1517, 1486, 1410, 1330, 1172, 1126, 1107, 1070, 856, 758, 745, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.72 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.93 (dd, *J* = 6.8, 9.3 Hz, 1H, Ar), 7.33-7.39 (m, 3H, Ar), 7.59 (d, *J* = 8.3 Hz, 2H, Ar), 7.73 (d, *J* = 9.3 Hz, 1H, Ar), 7.77 (d, *J* = 8.3 Hz, 2H, Ar), 7.97 (d, *J* = 8.3 Hz, 2H, Ar), 8.29 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 82.1, 92.8 (CC), 114.7, 119.0, 121.3, 121.7, 123.3 (Ar), 123.5 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 126.0 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 128.2, 128.4, 128.6 (Ar), 130.7 (q, *J* = 33.1 Hz, CF_3-$\underline{C}$), 130.8, 131.4, 133.0, 134.8, 136.7 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.1 (CF_3). MS (EI) *m/z* 362 (M^+); HRMS (EI) Calcd for $C_{22}H_{13}F_3N_2$ (M^+); 362.1031. Found: 362.1035.

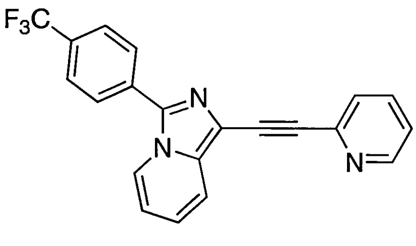
1-(4-Methoxyphenyl)ethynyl-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine (2cb)



Chemical Formula: $C_{23}H_{15}F_3N_2O$
Exact Mass: 392.1136
Molecular Weight: 392.3732

yellow solid, mp 163-164 °C, Rf = 0.20 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2360, 1604, 1519, 1504, 1464, 1411, 1326, 1288, 1250, 1172, 1131, 1106, 1066, 1029, 854 835 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OMe), 6.69 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.89 (d, *J* = 8.8 Hz, 2H, Ar), 6.90- 6.92 (m, 1H, Ar), 7.53 (d, *J* = 8.8 Hz, 2H, Ar), 7.69 (d, *J* = 9.3 Hz, 1H, Ar), 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 7.96 (d, *J* = 8.3 Hz, 2H, Ar), 8.27 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.2 (OMe), 80.7, 92.8 (CC), 114.0, 114.7, 115.4, 118.1, 119.0, 121.0, 121.7 (Ar), 123.8 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.9 (q, *J* = 4.4 Hz, CF_3-C=$\underline{C}$), 128.1 (Ar), 130.5 (q, *J* = 32.6 Hz, CF_3-$\underline{C}$), 132.9, 133.0, 134.4, 136.4, 159.6 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m/z* 392 (M^+); HRMS (EI) Calcd for $C_{23}H_{15}F_3N_2O$ (M^+); 392.1136. Found: 392.1130.

1-(2-Pyridyl)ethynyl-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine (2cd)

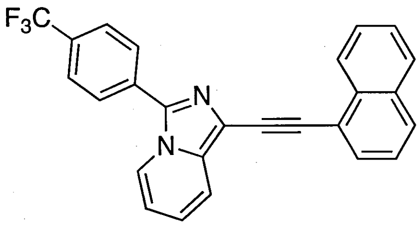


Chemical Formula: $C_{21}H_{12}F_3N_3$
Exact Mass: 363.0983
Molecular Weight: 363.3353

yellow solid, mp 129-130 °C, Rf = 0.35 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2360, 2341, 2199, 1616, 1582, 1514, 1411, 1324, 1159, 1123, 1066, 924, 851 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.76 (dd, *J* = 6.8, 7.8 Hz, 1H, Ar), 6.97 (dd, *J* = 6.8, 9.3 Hz, 1H, Ar), 7.23 (dd, *J* = 4.8, 7.8 Hz, 1H, Ar), 7.60 (d, *J* = 7.8 Hz, 1H, Ar), 7.69 (dd, *J* 7.3, 7.8 Hz, 1H, Ar), 7.79 (d, *J* = 8.3 Hz, 2H, Ar), 7.83 (d, *J* = 9.3 Hz, 1H, Ar), 7.97 (d, *J* = 8.3 Hz, 2H, Ar), 8.31 (d, *J* = 7.3 Hz, 1H, Ar), 8.64 (d, *J* = 4.8 Hz, 1H, Ar). ^{13}C NMR

($CDCl_3$) δ 82.5, 92.5 (CC), 114.7, 114.9, 119.0, 121.9, 121.9, 122.4 (Ar), 123.6 (q, *J* = 272.1 Hz, C̲F$_3$), 126.0 (q, *J* = 4.4 Hz, CF$_3$-C=C̲), 127.0, 128.2 (Ar), 130.8 (q, *J* = 33.0 Hz, CF$_3$-C̲), 132.8, 135.7, 136.1, 143.6, 150.0 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.1 (CF_3). MS (EI) *m/z* 63 (M^+); HRMS (EI) Calcd for $C_{21}H_{12}F_3N_3$ (M^+); 363.0983. Found: 368.0968.

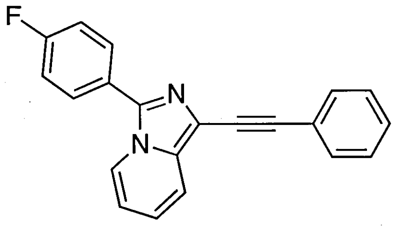
1-(1-Naphthyl)ethynyl-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine **(2ce)**



Chemical Formula: $C_{26}H_{15}F_3N_2$
Exact Mass: 412.1187
Molecular Weight: 412.4059

yellow solid, mp 177-178 °C, Rf = 0.22 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2359, 2202, 1615, 1505, 1460, 1410, 1386, 1326, 1166, 1124, 1068, 957, 852, 799, 744 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.69 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.94 (dd, *J* = 6.8, 8.8 Hz, 1H, Ar), 7.45 (dd, *J* = 7.3, 7.8 Hz, 1H, Ar), 7.52 (dd, *J* = 7.8, 8.3 Hz, 1H, Ar), 7.60 (dd, *J* = 6.8, 7.8 Hz, 1H, Ar), 7.76-7.78 (m, 2H, Ar), 7.77 (d, *J* = 8.3 Hz, 1H, Ar), 7.83 (d, *J* = 7.8 Hz, 2H, Ar), 7.85 (d, *J* = 7.3 Hz, 1H, Ar), 7.96 (d, *J* = 7.8 Hz, 2H, Ar), 8.26 (d, *J* = 7.3 Hz, 1H, Ar), 8.53 (d, *J* = 8.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 87.2, 91.2 (CC), 114.8, 115.9, 118.9, 121.0, 121.5, 121.8 (Ar), 123.8 (q, *J* = 271.1 Hz, C̲F$_3$), 125.3 (Ar), 126.0 (q, *J* = 3.3 Hz, CF$_3$-C=C̲), 126.4, 126.4, 126.7, 128.2, 128.3, 128.5, 130.2 (Ar), 130.7 (q, *J* = 33.1 Hz, CF$_3$-C̲), 132.9, 133.0, 133.2, 134.9, 136.8 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0(CF_3). MS (EI) *m/z* 412 (M^+); HRMS (EI) Calcd for $C_{26}H_{15}F_3N_2$ (M^+); 412.1187. Found: 412.1197.

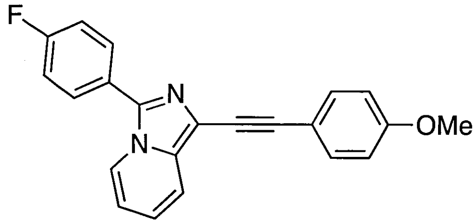
1-Phenylethynyl-3-(4-fluorophenyl)-imidazo[1,5-a]pyridine **(2da)**



Chemical Formula: $C_{21}H_{13}FN_2$
Exact Mass: 312.1063
Molecular Weight: 312.3397

yellow solid, mp 157-159 °C, Rf = 0.40 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3560, 2359, 2204, 1633, 1529, 1514, 1351, 1313, 1224, 1126, 1065, 1006, 958, 845, 755, 691 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.65 (dd, *J* = 6.3, 7.3 Hz, 1H, Ar), 6.88 (dd, *J* = 6.3, 8.8 Hz, 1H, Ar), 7.21 (t, *J* = 8.8 Hz, 2H, Ar), 7.31-7.37 (m, 3H, Ar), 7.60 (d, *J* = 7.3 Hz, 1H, Ar), 7.69 (d, *J* = 8.8 Hz, 1H, Ar), 7.77-7.80 (m, 2H, Ar), 8.27 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 82.5, 92.7 (CC), 114.2, 114.9 (Ar), 116.1 (d, *J* = 22.3 Hz, F-C=C̲), 118.8, 120.8, 121.8, 123.5 (Ar), 125.7 (d, *J* = 4.1 Hz, F-C=C-C̲), 127.9, 128.3 (Ar), 130.1 (d, *J* = 8.3 Hz, F-C=C-C̲), 131.3, 134.3, 137.8 (Ar), 163.1 (d, *J* = 249.8 Hz, F-C̲). ^{19}F NMR ($CDCl_3$) δ -111.4 (F). MS (EI) *m/z* 312 (M^+); HRMS (EI) Calcd for $C_{21}H_{13}FN_2$ (M^+); 312.1063. Found: 312.1059.

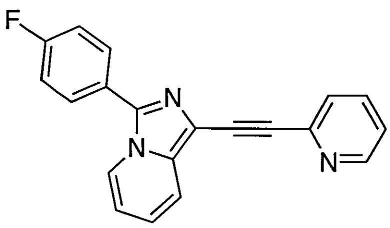
1-(4-Methoxyphenyl)ethynyl-3-(4-fluorophenyl)-imidazo[1,5-a]pyridine (**2db**)



Chemical Formula: $C_{22}H_{15}FN_2O$
Exact Mass: 342.1168
Molecular Weight: 342.3657

yellow solid, mp 144-145 °C, Rf = 0.30 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 3090, 2360, 2202, 1603, 1529, 1283, 1248, 1223, 838, 745 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.82 (s, 3H, OMe), 6.64 (dd, *J* = 6.3, 7.8 Hz, 1H, Ar), 6.66 (dd, *J* = 6.3, 8.8 Hz, 1H, Ar), 6.89 (d, *J* = 8.8 Hz, 2H, Ar), 7.21 (t, *J* = 8.8 Hz, 2H, Ar), 7.53 (d, *J* = 8.8 Hz, 2H, Ar), 7.69 (d, *J* = 7.8 Hz, 1H, Ar), 7.77-7.80 (m, 2H, Ar), 8.18 (d, *J* = 8.8 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 55.2 (OMe), 81.0, 92.5 (CC), 114.0, 114.1, 115.3, 115.6 (Ar), 116.1 (d, *J* = 21.5 Hz, F-C=C), 118.9, 120.5, 121.7 (Ar), 125.8 (d, *J* = 3.3 Hz, F-C=C-C=C), 130.5 (d, *J* = 8.3 Hz, F-C=C-C), 132.9, 133.9, 137.2, 159.5 (Ar), 163.0 (d, *J* = 249.8 Hz, F-C). ^{19}F NMR δ -111.5 (F)· MS (EI) *m/z* 342 (M$^+$); HRMS (EI) Calcd for $C_{22}H_{15}FN_2O$ (M$^+$); 342.1168. Found: 342.1164.

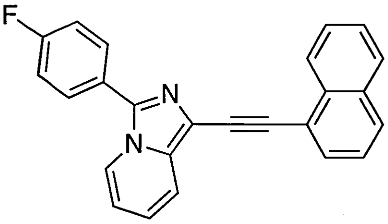
1-(2-Pyridyl)ethynyl-3-(4-fluorophenyl)-imidazo[1,5-a]pyridine (**2dd**)



Chemical Formula: $C_{20}H_{12}FN_3$
Exact Mass: 313.1015
Molecular Weight: 313.3278

yellow solid, mp 132-133 °C, Rf = 0.30 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2359, 2342, 2200, 1579, 1524, 1510, 1224, 851, 777, 745 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.70 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.93 (dd, *J* 7.3, 9.3 Hz, 1H, Ar), 7.20-7.25 (m, 3H, Ar), 7.59 (d, *J* = 6.8 Hz, 1H, Ar), 7.67 (dd, *J* = 7.8, 9.3 Hz, 1H, Ar), 7.78-7.82 (m, 3H, Ar), 8.21 (d, *J* = 6.3 Hz, 1H, Ar), 8.63 (d, *J* = 4.9 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 82.9, 92.4 (CC), 113.9, 114.4 (Ar), 116.2 (d, *J* = 21.5 Hz, F-C=C), 119.0, 121.5, 121.9, 122.3 (Ar), 125.5 (d, *J* = 3.3 Hz, F-C=C-C=C), 126.9 (Ar), 130.2 (d, *J* = 8.3 Hz, F-C=C-C), 135.3, 136.1, 137.7, 143.8, 149.9 (Ar), 163.2 (d, *J* = 250.6 Hz, F-C). ^{19}F NMR (CDCl$_3$) δ -111.2 (F). MS (EI) *m/z* 313 (M$^+$); HRMS (EI) Calcd for $C_{20}H_{12}FN_3$ (M$^+$); 313.1015. Found: 313.1014.

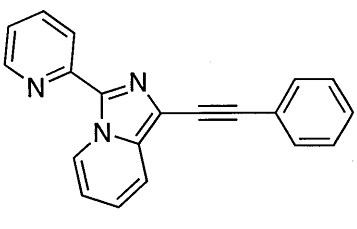
1-(1-Naphthyl)ethynyl-3-(4-fluorophenyl)-imidazo[1,5-a]pyridine (**2de**)



Chemical Formula: $C_{25}H_{15}FN_2$
Exact Mass: 362.1219
Molecular Weight: 362.3984

yellow solid, mp 196-197 °C, Rf = 0.40 (*n*-Hex : EtOAc = 4 : 1) IR (KBr) 2359, 2197, 1531, 1515, 1505, 1351, 1311, 1220, 1157, 1009, 956, 846, 813, 776 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.65 (dd, *J* = 6.3, 7.8 HZ, 1H, Ar), 6.90 (dd, *J* = 6.3, 9.3 Hz, 1H, Ar), 7.20-7.26 (m, 2H, Ar), 7.46 (dd, *J* = 7.1, 8.3 Hz, 1H, Ar), 7.52 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 7.60 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 7.77 (d, *J* = 9.3 Hz, 1H, Ar), 7.80-7.83 (m, 4H, Ar), 7.86 (d, *J* = 7.8 Hz, 1H, Ar), 8.17 (d, *J* = 7.1 Hz, 1H, Ar), 8.56 (d, *J* = 8.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 87.5, 90.9 (CC), 114.3, 115.1 (Ar), 116.2 (d, *J* = 21.5 Hz, F-C=C), 118.8, 121.0, 121.2, 125.3 (Ar), 125.7 (d, *J* = 3.3 Hz, F-C=C-C=C), 126.4 (Ar), 126.4, 126.7, 128.3, 128.4, 128.6, 130.2 (d, *J* = 8.3 Hz, F-C=C-C), 130.3, 133.0, 133.2, 134.5, 137.5 (Ar), 163.2 (d, *J* = 249.8 Hz, F-C). ^{19}F NMR (CDCl$_3$) δ -111.3 (F). MS (EI) *m/z* 362 (M$^+$); HRMS (EI) Calcd for $C_{25}H_{15}FN_2$ (M$^+$); 362.1219. Found: 362.1221.

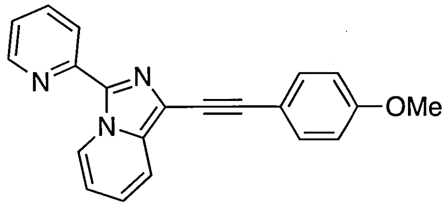
1-Phenylethynyl-3-(2-pyridyl)-imidazo[1,5-a]pyridine (2ea)



Chemical Formula: $C_{20}H_{13}N_3$
Exact Mass: 295.1109
Molecular Weight: 295.3373

yellow solid, mp 109-110 °C, Rf = 0.40 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3040, 2360, 2207, 1586, 1562, 1487, 1428, 1356, 1328, 1312, 1275, 1066, 1002, 781, 746, 689 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.78 (dd, *J* = 7.3, 6.8 Hz, 1H, Ar), 7.00 (dd, *J* = 9.8, 6.8 Hz, 1H, Ar), 7.21 (dd, *J* = 7.3, 4.9 Hz, 1H, Ar), 7.32-7.39 (m, 3H, Ar), 7.63 (d, *J* = 7.8 Hz, 2H, Ar), 7.74 (d, *J* = 9.3 Hz, 1H, Ar), 7.77 (d, *J* = 8.1, 7.3 Hz, 1H, Ar), 8.46 (d, *J* = 8.1 Hz, 1H, Ar), 8.61 (d, *J* = 4.9 Hz, 1H, Ar), 9.99 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 82.5, 92.6 (CC), 114.3, 115.0, 117.8, 122.0, 122.0, 122.1, 123.4, 126.7, 127.9, 128.2, 13.3, 135.1, 135.5, 136.5, 148.0, 150.3 (Ar). MS (EI) *m/z* 295 (M$^+$); HRMS (EI) Calcd for $C_{20}H_{13}N_3$ (M$^+$); 295.1109. Found: 295.1110.

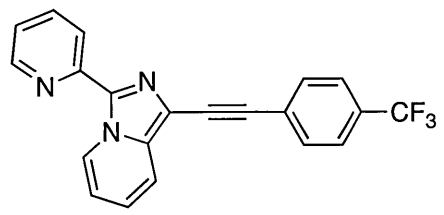
1-(4-Methoxyphenyl)ethynyl-3-(2-pyridyl)-imidazo[1,5-a]pyridine (2eb)



Chemical Formula: $C_{21}H_{15}N_3O$
Exact Mass: 325.1215
Molecular Weight: 325.3633

yellow solid, mp 161-163 °C, Rf = 0.25 (*n*-Hex : EtOAc = 2 : 1), IR (KBr) 2359, 2341, 1607, 1587, 1517, 1504, 1427, 1294, 1254, 1169, 1067, 1022, 757 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.83 (s, 3H, OMe), 6.79 (dd, *J* = 8.3, 7.3 Hz, 1H, Ar), 6.89 (d, *J* = 8.8 Hz, 2H, Ar), 6.98 (dd, *J* = 8.8, 7.3 Hz, 1H, Ar), 7.20 (dd, *J* = 7.8, 5.3 Hz, 1H, Ar), 7.56 (d, *J* = 8.8 Hz, 2H, Ar), 7.73 (d, *J* = 8.8 Hz, 1H, Ar), 7.77 (dd, *J* = 7.8, 7.3 Hz, 1H, Ar), 8.42 (d, *J* = 8.3 Hz, 1H, Ar), 8.63 (d, *J* = 5.3 Hz, 1H, Ar), 10.00 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 55.2 (OMe), 81.0, 92.5 (CC), 114.0, 114.3, 115.4, 115.5, 118.0, 121.8, 122.0, 122.2, 126.7, 133.0, 135.0, 135.3, 136.6, 148.1, 150.5, 159.5 (Ar). MS (EI) *m/z* 325 (M$^+$); HRMS (EI) Calcd for $C_{21}H_{15}N_3O$ (M$^+$); 325.1215. Found: 325.1221.

1-(4-Trifluoromethylphenylethynyl)-3-(2-pyridyl)imidazo[1,5-a]pyridine (2ec)

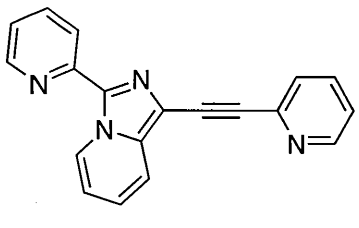


Chemical Formula: $C_{21}H_{12}F_3N_3$
Exact Mass: 363.0983
Molecular Weight: 363.3353

yellow solid, mp 132-134 °C, Rf = 0.26 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2050, 2918, 2200, 1611, 1588, 1502, 1315 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.84 (dd, *J* = 7.8, 6.8 Hz, 1H, Ar), 7.06 (dd, *J* = 9.3, 6.8 Hz, 1H, Ar), 7.24 (dd, *J* = 7.8, 5.8 Hz, 1H, Ar), 7.62 (d, *J* = 7.8 Hz, 2H, Ar), 7.70 (d, *J* = 7.8 Hz, 2H, Ar), 7.74 (d, *J* = 9.3 Hz, 1H, Ar), 7.80 (dd, *J* = 8.3, 7.8 Hz, 1H, Ar), 8.42 (d, *J* = 8.3 Hz, 1H, Ar), 8.65 (d, *J* = 5.8 Hz, 1H, Ar), 10.04 (d, *J* = 7.8 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 85.3, 91.6

(CC), 114.3, 114.5, 117.8, 122.3, 122.4, 122.6 (Ar), 125.3 (q, $J = 4.1$ Hz, $\underline{C}$=C-CF_3), 126.8 (q, $J = 272.1$ Hz, $\underline{C}F_3$), 127.0, 127.3 (Ar), 129.3 (q, $J = 32.3$ Hz, $\underline{C}$-CF_3), 131.5, 135.6, 136.1, 136.7, 148.2, 150.3 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.1 (CF_3). MS (EI) *m/z* 363 (M^+); HRMS (EI) Calcd for $C_{21}H_{12}F_3N_3$ (M^+); 363.0983. Found: 363.0971.

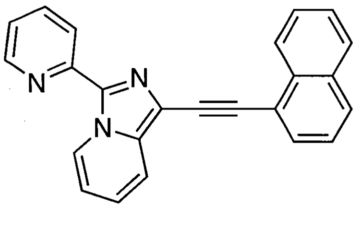
1-(2-Pyridyl)ethynyl-3-(2-pyridyl)-imidazo[1,5-a]pyridine **(2ed)**



Chemical Formula: $C_{19}H_{12}N_4$
Exact Mass: 296.1062
Molecular Weight: 296.3254

yellow solid, mp 155-157 °C, Rf = 0.30 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3047, 2360, 2209, 1581, 1560, 1513, 1467, 1426, 1324, 1314, 1277, 1247, 1187, 1145, 1124, 1005, 960, 781, 689 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.84 (dd, $J = 7.8, 6.8$ Hz, 1H, Ar), 7.05 (dd, $J = 9.3, 6.8$ Hz, 1H, Ar), 7.21-7.24 (m, 2H, Ar), 7.62 (d, $J = 7.8$ Hz, 1H, Ar), 7.69 (dd, $J = 7.8, 7.3$ Hz, 1H, Ar), 7.79 (dd, $J = 9.0, 8.3$ Hz, 1H, Ar), 7.86 (d, $J = 9.3$ Hz, 1H, Ar), 8.41 (d, $J = 7.3$ Hz, 1H, Ar), 8.62-8.64 (m, 2H, Ar), 10.01 (d, $J = 7.3$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 83.0, 92.3 (CC), 114.5, 118.0, 122.2, 122.3, 122.7, 126.9, 126.9, 132.0, 132.1, 135.3, 136.1, 136.5, 136.6, 143.7, 148.1, 139.9, 150.3 (Ar). MS (EI) *m/z* 296 (M^+); HRMS (EI) Calcd for $C_{19}H_{12}N_4$ (M^+); 294.1062. Found: 296.1060.

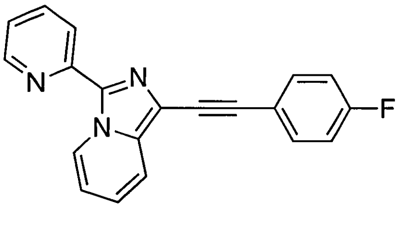
1-(1-Naphthyl)ethynyl-3-(2-pyridyl)-imidazo[1,5-a]pyridine **(2ee)**



Chemical Formula: $C_{24}H_{15}N_3$
Exact Mass: 345.1266
Molecular Weight: 345.3960

yellow solid, mp 157-159 °C, Rf = 0.30 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3116, 2359, 2342, 2192, 1584, 1560, 1502, 1427, 1313, 1276, 1187, 1145, 1098, 795, 766 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.78 (dd, $J = 7.3, 6.8$ Hz, 1H, Ar), 7.01 (dd, $J = 9.3, 6.8$ Hz, 1H, Ar), 7.19 (dd, $J = 7.8, 4.9$ Hz, 1H, Ar), 7.46 (dd, $J = 7.8, 7.6$ Hz, 1H, Ar), 7.52 (dd, $J = 7.6, 6.8$ Hz, 1H, Ar), 7.61 (dd, $J = 8.3, 6.8$ Hz, 1H, Ar), 7.76 (d, $J = 7.8$ Hz, 1H, Ar), 7.79-7.86 (m, 4H, Ar), 8.43 (d, $J = 8.3$ Hz, 1H, Ar), 8.57 (d, $J = 8.3$ Hz, 1H, Ar), 8.62 (d, $J = 4.9$ Hz, 1H, Ar), 10.00 (d, $J = 7.6$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 87.51, 90.9 (CC), 114.4, 115.2, 117.9, 121.1, 1122.2, 122.3, 125.3, 126.3, 126.4, 126.7, 126.8, 128.3, 128.4, 130.2, 133.0, 133.2, 135.3, 135.7, 136.6, 148.2, 150.4 (Ar). MS (EI) *m/z* 345 (M^+); HRMS (EI) Calcd for $C_{24}H_{15}N_3$ (M^+); 345.1266. Found: 345.1263.

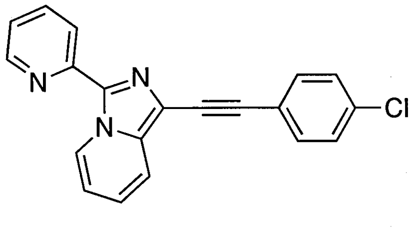
1-(4-Fluorophenylethynyl)-3-(2-pyridyl)-imidazo[1,5-a]pyridine **(2ej)**



Chemical Formula: $C_{20}H_{12}FN_3$
Exact Mass: 313.1015
Molecular Weight: 313.3278

yellow solid, mp 168-170 °C, Rf = 0.27 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3056, 2208, 1589, 1498, 1428, 1227, 1149 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.81 (dd, $J = 7.3, 6.8$ Hz, 1H, Ar), 6.99-7.08 (m, 3H, Ar), 7.22 (dd, $J = 8.8, 4.9$ Hz, 1H, Ar), 7.60 (dd, $J = 8.8, 5.8$ Hz, 2H, Ar), 7.73 (d, $J = 9.3$ Hz, 1H, Ar), 7.79 (dd, $J = 8.3, 7.3$ Hz, 1H, Ar), 8.42 (d, $J = 8.3$ Hz, 1H, Ar), 8.64 (d, $J = 4.9$ Hz, 1H, Ar), 10.01 (d, $J = 7.3$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 82.6, 91.9 (CC), 114.4, 114.9 (Ar), 115.6 (d, $J =$ 22.3 Hz, F-C=$\underline{\text{C}}$), 117.9, 119.5, 122.1, 122.2, 122.2, 126.8 (Ar), 133.3 (d, $J = 8.3$ Hz, F-C=C-$\underline{\text{C}}$), 135.3, 135.6, 136.6, 148.2, 150.4 (Ar), 163.2 (d, $J = 250.6$ Hz, F-$\underline{\text{C}}$). ^{19}F NMR ($CDCl_3$) δ -112.5 (F). MS (EI) *m/z* 313 (M^+); HRMS (EI) Calcd for $C_{20}H_{12}FN_3$ (M^+); 313.1015. Found: 313.1013.

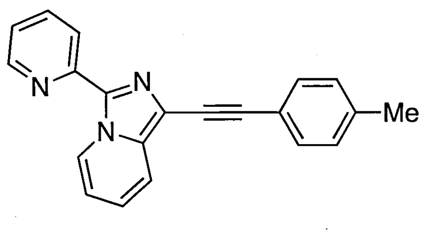
1-(4-Chrolophenylethynyl)-3-(2-pyridyl)-imidazo[1,5-a]pyridine **(2ek)**



Chemical Formula: $C_{20}H_{12}ClN_3$
Exact Mass: 329.0720
Molecular Weight: 329.7824

yellow solid, mp 162-164 °C, Rf = 0.38 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3059, 2205, 1588, 1513, 1428, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.81 (dd, $J = 7.3$, 6.3 Hz, 1H, Ar), 7.02 (dd, $J = 9.0$, 6.3 Hz, 1H, Ar), 7.22 (dd, $J = 7.6$, 4.9 Hz, 1H, Ar), 7.33 (d, $J =$ 8.5 Hz, 2H, Ar), 7.53 (d, $J = 8.5$ Hz, 2H, Ar), 7.72 (d, $J = 9.0$ Hz, 1H, Ar), 7.79 (dd, $J = 7.6$, 7.3 Hz, 1H, Ar), 8.41 (d, $J = 7.3$ Hz, 1H, Ar), 8.53 (d, $J = 4.9$ Hz, 1H, Ar), 10.01 (d, $J = 7.3$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 83.6, 91.6 (CC), 114.5, 114.7, 117.8, 122.0, 122.2, 122.3, 126.9, 128.7, 132.6, 133.9, 135.4, 135.7, 136.6, 136.7, 148.1, 150.4 (Ar). MS (EI) *m/z* 329 (M^+); HRMS (EI) Calcd for $C_{20}H_{12}ClN_3$ (M^+); 329.0720. Found: 329.0719.

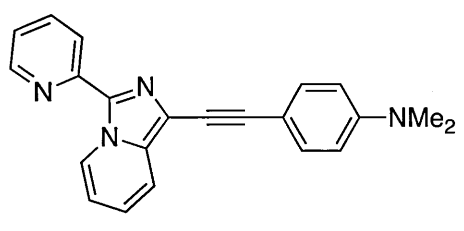
1-(4-Methylphenylethynyl)-3-(2-pyridyl)-imidazo[1,5-a]pyridine **(2el)**



Chemical Formula: $C_{21}H_{15}N_3$
Exact Mass: 309.1266
Molecular Weight: 309.3639

yellow solid, mp 173-174 °C, Rf = 0.30 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2812, 1586, 1516, 1503, 1428, 1249, 1189 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, Me), 6.80 (dd, $J = 7.8$, 6.8 Hz, 1H, Ar), 7.00 (dd, $J = 9.3$, 6.8 Hz, 1H, Ar), 7.17 (d, $J = 8.8$ Hz, 2H, Ar), 7.23 (dd, $J = 7.3$, 6.3 Hz, 1H, Ar), 7.52 (d, $J = 8.3$ Hz, 2H, Ar), 7.73-7.80 (m, 2H, Ar), 8.43 (d, $J = 7.8$ Hz, 1H, Ar), 8.63 (d, $J = 4.9$ Hz, 1H, Ar), 10.01 (d, $J = 7.3$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.7 (Me), 82.1, 93.1 (CC), 114.7, 115.7, 118.4, 120.7, 122.2, 122.4, 122.6, 127.1, 129.4, 131.7, 135.5, 135.8, 136.9, 138.5, 148.5, 150.8 (Ar). MS (EI) *m/z* 309 (M^+); HRMS (EI) Calcd for $C_{21}H_{15}N_3$ (M^+); 309.1266. Found: 309.1243.

1-(4-N,N'-Dimethylphenylethynyl)-3-(2-pyridyl)-imidazo[1,5-a]pyridine **(2em)**

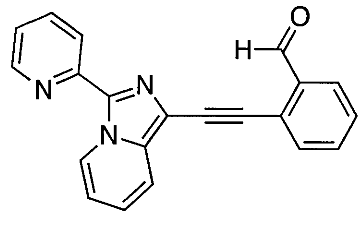


Chemical Formula: $C_{22}H_{18}N_4$
Exact Mass: 338.1531
Molecular Weight: 338.4051

yellow solid, mp 185-186 °C, Rf = 0.12 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2909, 2200, 1605, 1585, 1536, 1372, 1189 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.98 (s, 6H, NMe_2), 6.68 (d, $J =$ 8.8 Hz, 2H, Ar), 6.77 (dd, $J = 7.3$, 6.8 Hz, 1H, Ar), 6.95 (dd, $J = 9.8$, 6.8 Hz, 1H, Ar), 7.20 (dd, $J = 7.8$, 4.9 Hz, 1H, Ar), 7.51 (d, $J = 8.8$ Hz, 2H, Ar), 7.73-7.79 (m, 2H, Ar), 8.43 (d,

J = 8.3 Hz, 1H, Ar), 8.61 (d, J = 4.9 Hz, 1H, Ar), 9.98 (d, J = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 40.1 (NMe_2), 80.0, 93.6 (CC), 110.2, 111.8, 114.3, 116.1, 118.1, 121.4, 121.9, 122.1, 126.5, 130.6, 132.7, 134.9, 136.5, 148.1, 150.0, 150.5 (Ar). MS (EI) *m/z* 338 (M^+); HRMS (EI) Calcd for $C_{22}H_{18}N_4$ (M^+); 338.1531. Found: 338.1518.

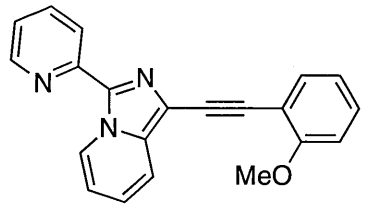
1-(2-Pyridyl)-3-(2-formyl-phenyl)-imidazo[1,5-a]pyridine (**2en**)



Chemical Formula: $C_{21}H_{13}N_3O$
Exact Mass: 323.1059
Molecular Weight: 323.3474

yellow solid, mp 153-154 °C, Rf = 0.20 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2195, 1687, 1590, 1517, 1505, 1268, 1189, 752, 689 cm^{-1}. ^{1}NMR ($CDCl_3$) δ 6.89 (dd, J = 7.4, 6.8 Hz, 1H, Ar), 7.12 (dd, J = 9.3, 6.8 Hz, 1H, Ar), 7.27-7.30 (m, 1H, Ar), 7.46 (dd, J = 7.8, 7.3 Hz, 1H, Ar), 7.62 (dd, J = 7.8, 7.3 Hz, 1H, Ar), 7.76 (d, J = 7.8 Hz, 1H, Ar), 7.78-7.84 (m, 2H, Ar), 8.45 (d, J = 8.3 Hz, 1H, Ar), 8.68 (d, J = 4.8 Hz, 1H, Ar), 10.09 (d, J = 7.4 Hz, 1H, Ar), 10.77 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 88.9, 90.1 (CC), 114.7, 117.9, 122.4, 122.5, 123.0, 127.1, 127.8, 128.2, 130.6, 133.2, 133.9, 134.2, 135.4, 136.5, 136.8, 141.5, 148.3, 150.3 (Ar), 191.2 (CHO). MS (EI) *m/z* 323 (100, M^+). HRMS (EI): Exact mass calcd for $C_{21}H_{13}N_3O$ (M^+); 323.1059 Found: 323.1056.

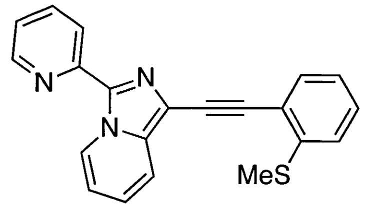
1-[2-(Methoxy)phenyl]ethynyl]-3-(2-pyridyl)-imidazo[1,5-a]pyridine (**2eo**)



Chemical Formula: $C_{21}H_{15}N_3O$
Exact Mass: 325.1215
Molecular Weight: 325.3633

yellow solid, mp 169-171 °C, Rf = 0.23 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3113, 3040, 3002, 2969, 2935, 2207, 1531, 1515, 1250, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H, Ar), 6.83 (dd, J = 7.3, 6.3 Hz, 1H, Ar), 6.92-6.98 (m, 2H, Ar), 7.04 (dd, J = 8.8, 6.3 Hz, 1H, Ar), 7.22-7.27 (m, 2H, Ar), 7.32 (dd, J = 8.3, 7.3 Hz, 1H, Ar), 7.60 (J = 7.3 Hz, 1H, Ar), 7.78-7.82 (m, 2H, Ar), 8.44 (d, J = 8.8 Hz, 1H, Ar), 8.65 (d, J = 4.8 Hz, 1H, Ar), 10.00 (d, J = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.8 (OMe), 88.5 (CC), 89.2 (CC), 110.6, 112.7, 114.5, 115.6, 118.2, 120.5, 121.9, 122.1, 122.2, 126.6, 129.5, 133.2, 135.1, 135.6, 136.6, 148.2, 150.4, 159.9 (Ar). MS (EI) *m/z* 325 (100, M^+). HRMS (EI): Exact mass calcd for $C_{21}H_{15}N_3O$ (M^+); 325.3633. Found: 325.1218.

1-[2-(Methylthio)phenyl]ethynyl]-3-(2-pyridyl)-imidazo[1,5-a]pyridine (**2ep**)

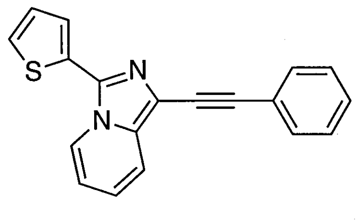


Chemical Formula: $C_{21}H_{15}N_3S$
Exact Mass: 341.0987
Molecular Weight: 341.4289

yellow solid. mp 161-162 °C, Rf = 0.03 (*n*Hex : EtOAc = 10 : 1), IR (KBr) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H, SMe), 6.79 (t, J = 6.8 Hz, 1H, Ar), 7.01 (dd, J = 8.3, 6.8 Hz, 1H, Ar), 7.11 (dd, J = 7.8, 7.3 Hz, 1H, Ar), 7.17-7.21 (m, 2H, Ar), 7.23-7.29 (m, 1H, Ar), 7.56 (d, J =7.3 Hz, 1H, Ar), 7.76 (dd, J = 9.3, 7.8 Hz, 1H, Ar), 7.89 (d, J = 9.3 Hz, 1H, Ar), 8.40 (d, J = 8.3 Hz, 1H, Ar), 8.61 (d, J = 4.4 Hz, 1H, Ar), 9.99 (d, J = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 15.2

(SMe), 89.3, 90.2 (CC), 114.5, 115.0, 118.3, 121.6, 122.1, 122.2, 122.3, 124.1, 124.3, 126.7, 128.3, 131.9, 135.2, 136.0, 136.5, 140.8, 148.0, 150.3 (Ar). MS (EI) *m/z* 341. HRMS (EI): Exact mass calcd for $C_{21}H_{15}N_3S$ (M^+); 341.0987. Found: 341.0977.

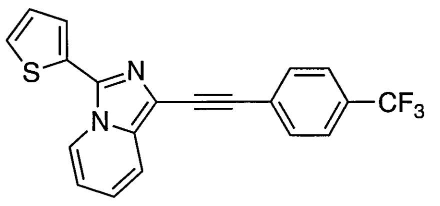
1-Phenylethynyl-3-(2-thienyl)imidazo[1,5-a]pyridine **(2fa)**



Chemical Formula: $C_{19}H_{12}N_2S$
Exact Mass: 300.0721
Molecular Weight: 300.3770

yellow solid, mp 174-175 °C, Rf = 0.38 (*n*-Hex : EtOAc = 3 : 1), IR (KBr) 2931, 1652, 1558, 1509, 1487, 1249, 1047 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.75 (dd, *J* = 6.8, 6.3 Hz, 1H, Ar), 6.91 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar), 7.19 (dd, *J* = 4.9, 3.4 Hz, 1H, Ar), 7.32-7.38 (m, 3H, Ar), 7.45 (d, *J* = 4.9 Hz, 1H, Ar), 7.57-7.61 (m, 3H, Ar), 7.72 (d, *J* = 8.8 Hz, 1H, Ar), 8.36 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 82.3, 92.9 (CC), 114.6, 115.2, 118.9, 120.8, 122.3, 123.4, 125.4, 126.5, 127.6, 127.9, 128.3, 131.3, 131.4, 133.0, 134.3 (Ar). MS (EI) *m/z* 300 (M^+); HRMS (EI) Calcd for $C_{19}H_{12}N_2S$ (M^+); 300.0721. Found: 300.0721.

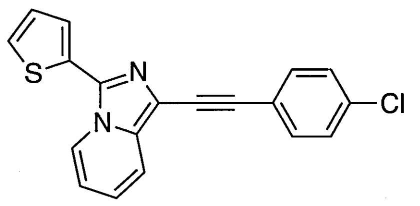
1-(4-Trifluoromethylphenylethynyl)-3-(2-thienyl)imidazo[1,5-a]pyridine **(2fc)**



Chemical Formula: $C_{20}H_{11}F_3N_2S$
Exact Mass: 368.0595
Molecular Weight: 368.3749

yellow solid, mp 144-146 °C, Rf = 0.25 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3076, 2201, 1635, 1560, 1537, 1227, 1210 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.78 (dd, *J* = 6.8, 6.3 Hz, 1H, Ar), 6.97 (dd, *J* = 8.8, 6.8 Hz, 1H, Ar), 7.21 (t, *J* = 4.4 Hz, 1H, Ar), 7.48 (d, *J* = 4.4 Hz, 1H, Ar), 7.60-7.74 (m, 6H, Ar), 8.40 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.5 (Me), 85.4, 92.1 (CC), (Ar). 114.8, 115.1, 119.1, 121.7, 122.8 (Ar), 124.4 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.6 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 126.0, 127.2, 127.7, 128.0 (Ar), 129.8 (q, *J* = 32.6 Hz, CF_3-$\underline{C}$), 131.6, 131.7, 133.8, 135.2 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m/z* 368 (M^+); HRMS (EI) Calcd for $C_{20}H_{11}F_3N_2S$ (M^+); 368.0595. Found: 368.0605.

1-(4-Chlorophenylethynyl)-3-(2-thienyl)imidazo[1,5-a]pyridine **(2fk)**

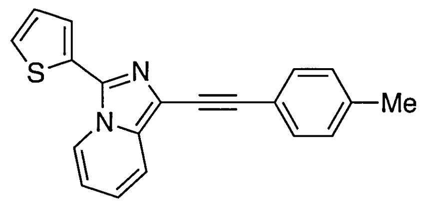


Chemical Formula: $C_{19}H_{11}ClN_2S$
Exact Mass: 334.0331
Molecular Weight: 334.8220

yellow solid, mp 107-109 °C, Rf = 0.40 (*n*-Hex : EtOAc = 3 : 1), IR (KBr) 2925, 2201, 1652, 1512m 1487, 1309, 1253, 1089 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.77 (dd, *J* = 6.8, 6.3 Hz, 1H, Ar), 6.94 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar), 7.20 (dd, *J* = 4.8, 3.4 Hz, 1H, Ar), 7.33 (d, *J* = 8.8 Hz, 2H, Ar), 7.47 (d, *J* = 4.8 Hz, 1H, Ar), 7.52 (d, *J* = 8.8 Hz, 2H, Ar), 7.59 (d, *J* = 3.4 Hz, 1H, Ar), 7.21 (d, *J* = 8.8 Hz, 1H, Ar), 8.40 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 83.4, 91.8 (CC), 114.7, 114.8, 118.8, 121.0, 121.9, 122.4, 125.5, 126.6, 127.6, 128.6, 131.4, 132.5, 133.9, 134.5, 135.7 (Ar). MS (EI) *m/z* 334 (M^+); HRMS (EI) Calcd for $C_{19}H_{11}ClN_2S$ (M^+); 334.0331. Found:

334.0337.

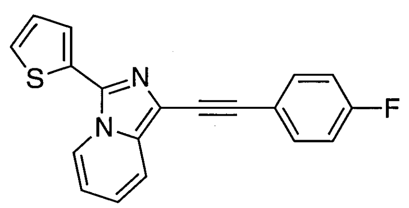
1-(4-Methylphenylethynyl)-3-(2-thienyl)imidazo[1,5-a]pyridine (**2fl**)



Chemical Formula: $C_{20}H_{14}N_2S$
Exact Mass: 314.0878
Molecular Weight: 314.4036

yellow solid, mp 161-162 °C, Rf = 0.45 (*n*-Hex : EtOAc = 3 : 1), IR (KBr) 2945, 2203, 1652, 1558, 1497, 1306, 1256 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H, Me), 6.70 (dd, *J* = 6.8, 6.3 Hz, 1H, Ar), 6.86 (dd, *J* = 8.8, 6.8 Hz, 1H, Ar), 7.14-7.16 (m, 3H, Ar), 7.42 (d, *J* = 4.9 Hz, 1H, Ar), 7.49 (d, *J* = 7.8 Hz, 2H, Ar), 7.54 (d, *J* = 2.4 Hz, 1H, Ar), 7.67 (d, *J* = 8.8 HZ, 1H, Ar), 8.31 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.5 (Me), 81.7, 92.8 (CC), 114.5, 115.4, 118.7, 120.3, 120.6, 122.2, 125.2, 126.4, 127.6, 129.0, 131.2, 131.5, 132.9, 134.2, 138.1 (Ar). MS (EI) *m/z* 314 (M$^+$); HRMS (EI) Calcd for $C_{20}H_{14}N_2S$ (M$^+$); 314.0878. Found: 314.0882.

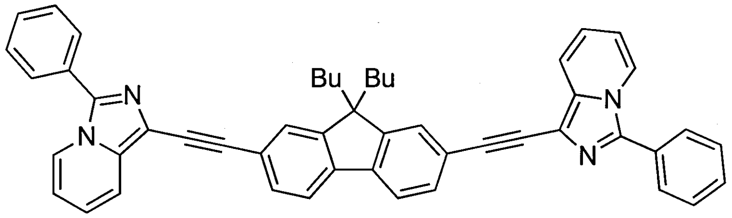
1-(4-Fluorophenylethynyl)-3-(2-thienyl)imidazo[1,5-a]pyridine (**2fj**)



Chemical Formula: $C_{19}H_{11}FN_2S$
Exact Mass: 318.0627
Molecular Weight: 318.3674

yellow solid, mp 144-146 °C, Rf = 0.25 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 3071, 2210, 1595, 1498, 1402, 1311, 1249, 1229 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.65 (dd, *J* = 7.4, 6.3 Hz, 1H, Ar), 6.82 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar), 6.92 (t, *J* = 8.8 Hz, 2H, Ar), 7.10 (dd, *J* = 5.0, 3.6 Hz, 1H, Ar), 7.36 (d, *J* = 5.0 Hz, 1H, Ar), 7.46-7.49 (m, 3H, Ar), 7.60 (d, *J* = 8.8 Hz, 1H, Ar), 8.26 (d, *J* = 7.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 82.0, 91.7 (CC), 114.5, 114.9 (Ar), 115.6 (d, *J* = 21.5 Hz, F-C=$\underline{C}$), 118.7 (Ar), 119.5 (d, *J* = 3.3 Hz, F-C=C-C=$\underline{C}$), 120.8, 122.3, 125.4, 126.5, 127.6, 131.4, 133.1 (Ar), 133.1 (d, *J* = 8.3 Hz, F-C=C-$\underline{C}$), 134.3 (Ar), 162.3 (d, *J* = 249.8 Hz, F-$\underline{C}$). ^{19}F NMR ($CDCl_3$) δ -111.6 (F). MS (EI) *m/z* 318 (M$^+$); HRMS (EI) Calcd for $C_{19}H_{11}FN_2S$ (M$^+$); 318.0627. Found: 318.0621.

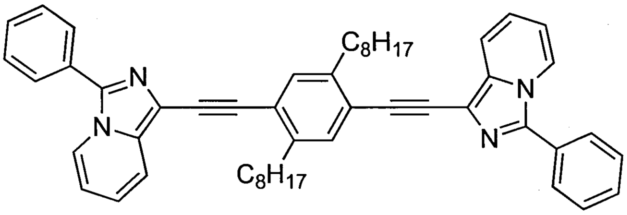
9,9-Dibutyl-2,7-bis(3-phenyl-imidazo[1,5-a]pyridin-1-yl)-ethynyl-9H-fluoren (**6**)



Chemical Formula: $C_{51}H_{42}N_4$
Exact Mass: 710.3409
Molecular Weight: 710.9060

brown solid, mp 126-127.5 °C, Rf = 0.15 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 1601, 1509, 1467, 1352, 1300, 1126 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.61-0.67 (m, 4H, CH_2), 0.70 (t, *J* = 7.3 Hz, 6H, CH_3), 1.11 (pent, *J* = 7.3 Hz, 4H, CH_2), 1.99-2.03 (m, 4H, CH_2), 6.65 (dd, *J* = 7.3, 6.3 Hz, 2H, Ar), 6.90 (dd, *J* = 9.3, 6.3 Hz, 2H, Ar), 7.46 (t, *J* = 7.3 Hz, 2H, Ar), 7.53 (t, *J* = 7.3 Hz, 4H, Ar), 7.61 (d, *J* = 7.3 Hz, 2H, Ar), 7.62 (s, 2H, Ar), 7.68 (d, *J* = 7.3 Hz, 2H, Ar), 7.77 (d, *J* = 9.3 Hz, 2H, Ar), 7.84 (d, *J* = 7.3 Hz, 4H, Ar), 8.28 (d, *J* = 7.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 22.9, 25.8, 40.1 (CH_2), 55.0 ($\underline{C}Bu_2$), 83.1, 93.8 (CC), 114.0, 115.1, 118.9, 119.8, 120.8, 122.0, 122.1, 125.9, 128.2, 129.0, 129.1, 129.5, 130.3, 134.2, 138.4, 140.4, 151.1 (Ar). MS (EI) *m/z* 710 (M^+); HRMS (EI) Calcd for $C_{51}H_{42}N_4$ (M^+); 710.3409. Found: 710.3409.

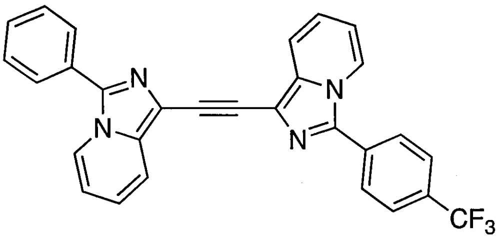
1,4-Dioctyl-2,5-bis(3-phenyl-imidazo[1,5-a]pyridin-1-yl)-ethynylbenzene (**8**)



Chemical Formula: $C_{52}H_{54}N_4$
Exact Mass: 734.4348
Molecular Weight: 735.0120

brown solid, mp 116-117 °C, Rf = 0.13 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 1911, 1698, 1349, 1124, 1064 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.8 Hz, 6H, CH_3), 1.20-1.48 (m, 20H, CH_2), 1.77 (pent, *J* = 6.8 Hz, 4H, CH_2), 2.91 (t, *J* = 6.8 Hz, 4H, CH_2), 6.66 (dd, *J* = 6.8, 6.3 Hz, 2H, Ar), 6.90 (dd, *J* = 9.3, 6.3 Hz, 2H, Ar), 7.46 (t, *J* = 7.8 Hz, 2H, Ar), 7.48 (s, 2H, Ar), 7.53 (t, *J* = 7.8 Hz, 4H, Ar), 7.68 (d, *J* = 9.3 Hz, 2H, Ar), 7.83 (d, *J* = 7.8 Hz, 4H, Ar), 8.28 (d, *J* = 6.8 Hz, 2H, Ar). ^{13} C NMR ($CDCl_3$) δ 14.0 (CH_3), 22.5, 29.2, 29.5, 29.5, 30.4, 31.8, 34.1 (CH_2), 87.1, 91.9 (CC), 114.0, 115.3, 118.7, 120.8, 122.1, 122.4, 128.2, 129.0, 129.1, 129.5, 132.1, 134.4, 138.4, 141.4 (Ar). MS (EI) *m/z* 734 (M^+); HRMS (EI) Calcd for $C_{52}H_{54}N_4$ (M^+); 734.4348. Found: 744.4338.

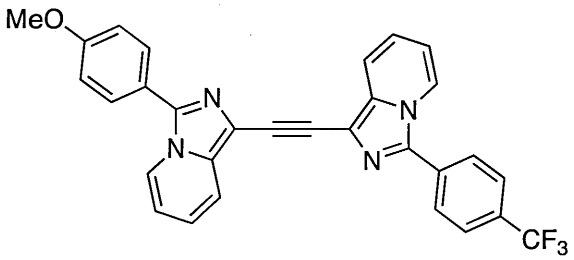
1-(3-phenyl-imidazo[1,5-a]pyridin-1-yl)-ethynyl-3-phenylimidazo[1,5-a]pyridine (**10a**)



Chemical Formula: $C_{29}H_{17}F_3N_4$
Exact Mass: 478.1405
Molecular Weight: 478.4673

brown solid, mp 188-190 °C, Rf = 0.49 (*n*-Hex : EtOAc = 1 : 1), IR (KBr) 2923, 2364, 1614, 1511, 1322, 1133, 1103, 1063, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.63 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.69 (t, *J* = 6.8 Hz, 1H, Ar), 6.83-6.90 (m, 2H, Ar), 7.43 (t, *J* = 7.3 Hz, 1H, Ar), 7.51 (dd, *J* = 7.8, 7.3 Hz, 2H, Ar), 7.74-7.82 (m, 6H, Ar), 7.97 (d, *J* = 8.3 Hz, 2H, Ar), 8.24-8.28 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 85.1, 86.0 (CC), 119.0, 119.2, 120.8, 121.1, 121.6, 121.9 (Ar), 123.7 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.9 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 128.1, 129.0, 129.1, 129.5, 130.0 (Ar), 130.3 (q, *J* = 33.1 Hz, CF_3-$\underline{C}$), 133.1, 134.4, 134.7, 136.4, 138.2 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m/z* 478 (100, M^+). HRMS (EI): Exact mass calcd for $C_{29}H_{17}F_3N_4$ (M^+); 478.1405. Found: 478.1403.

1-{3-(4-Trifluoromethylphenyl-imidazo[1,5-a]pyridin-1-yl)-ethynyl-3-(4-methoxyphenyl)imidazo[1,5-a] pyridine **(10b)**



Chemical Formula: $C_{30}H_{19}F_3N_4O$
Exact Mass: 508.1511
Molecular Weight: 508.4933

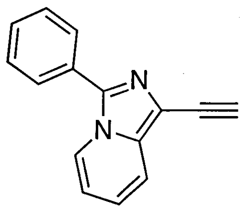
brown solid, mp 198-200 °C, Rf = 0.13 (*n*-Hex : EtOAc = 4 : 1), IR (KBr) 2922, 1631, 1613, 1530, 1514, 1415, 1351, 1324, 1286, 1246, 1163, 1064, 835 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H, OMe), 6.62 (dd, *J* = 7.2, 6.6 Hz, 1H, Ar), 6.71 (dd, *J* = 7.2, 6.6 Hz, 1H, Ar), 6.83 (dd, *J* = 9.1, 6.6 Hz, 1H, Ar), 6.88 (dd, *J* = 9.1, 6.6 Hz, 1H, Ar), 7.05 (d, *J* = 8.8 Hz, 2H, Ar), 7.73-7.82 (m, 6H, Ar), 7.96 (d, *J* = 8.3 Hz, 2H, Ar), 8.19 (d, *J* = 7.2 Hz, 1H, Ar), 8.28 (d, *J* = 7.2 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 85.1, 86.1 (CC), 113.9, 114.4, 114.6, 114.7, 119.0, 119.4, 120.5, 121.1, 121.6, 121.9, 122.0 (Ar), 124.0 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 126.0 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 128.3, 129.7 (Ar), 130.5 (q, *J* = 33.1 Hz, CF_3-$\underline{C}$), 133.1, 134.2, 134.8, 135.2, 136.4, 138.3, 160.2 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m/z* 508 (100, M$^+$). HRMS (EI): Exact mass calcd for $C_{30}H_{19}F_3N_4O$ (M$^+$); 508.1511. Found: 508.1510.

:

3.5.3. General procedure for desilylation

A solution of **2af** (0.5 mmol) in THF was added TBAF in THF (2 equiv) and stirred for 1h at room temperature. The mixture was diluted with water (5 mL) and extracted by DCM (10 mL X 3) and washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hex : EtOAc) to give desilylated product.

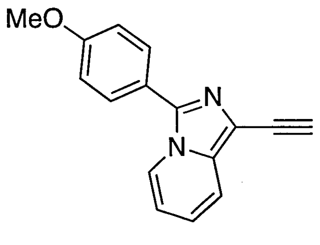
1-Ethynyl-3-phenyl-imidazo[1,5-a]pyridine **(9a)**



Chemical Formula: $C_{15}H_{10}N_2$
Exact Mass: 218.0844
Molecular Weight: 218.2533

brown oil, Rf = 0.35 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 3289, 3062, 2102, 1509, 774 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 1H, CH), 6.54 (dd, *J* = 8.8, 6.6 Hz, 1H, Ar), 6.78 (dd, *J* = 8.3, 6.6 Hz, 1H, Ar), 7.34-7.38 (m, 1H, Ar), 7.44 (t, *J* = 8.1 Hz, 2H, Ar), 7.52 (d, *J* = 8.8 Hz, 1H, Ar), 7.71 (d, *J* = 8.1 Hz, 2H, Ar), 8.15 (d, *J* = 8.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 77.0, 80.4 (CC), 113.5, 113.7, 118.0, 120.9, 121.7, 127.8, 128.7, 128.8, 129.1, 134.7, 137.7 (Ar). MS (EI) *m/z* 218 (M$^+$); HRMS (EI) Calcd for $C_{15}H_{10}N_2$ (M$^+$); 218.0844. Found: 218.0842.

1-Ethynyl-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**9b**)



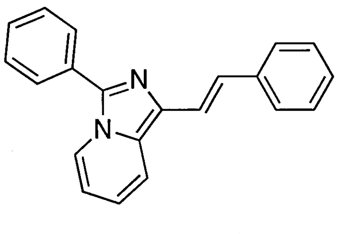
Chemical Formula: $C_{16}H_{12}N_2O$
Exact Mass: 248.0950
Molecular Weight: 248.2793

brown oil, Rf = 0.24 (*n*-Hex : EtOAc = 4 : 1), IR (neat) 3292, 3003, 2097, 1611, 1257, 835, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 1H, CCH), 3.84 (s, 3H, OMe), 6.57 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.82 (dd, *J* = 9.1, 6.3 Hz, 1H, Ar), 7.00 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 1H, Ar), 7.67 (d, *J* = 8.8 Hz, 1H, Ar), 8.15 (d, *J* = 7.3 Hz, 1H, Ar). ^{13} C NMR ($CDCl_3$) δ 55.2 (OMe), 77.2 (CC), 80.4 (CC), 113.3, 113.7, 113.8, 118.3, 120.8, 121.8, 122.0, 129.6, 134.7, 138.1, 160.2 (Ar). MS (EI) *m/z* 248 (100, M$^+$). HRMS (EI): Exact mass calcd for $C_{16}H_{12}N_2O$ (M$^+$); 248.0950. Found: 248.0954..

3.5.4. General procedure for Mizoroki-Heck reaction

In a screw-capped test tube was placed Cs_2CO_3 (1.5 equiv), which was then dried at 150 °C *in vacuo* for 3h. Then $Pd(OAc)_2$ (5 mol%), NHC ligand (10 mol%), 1-Iodo-3-arylimidazo[1,5-a]pyridine (0.25 mmol), freshly distilled styrene (1.1 equiv) and DMA (1 mL) were added to the test tube. The resulting mixture was stirred under Ar atmosphere at 130 °C for 20 h. The residue was purified by flash column chromatography on silica gel to give a title compound.

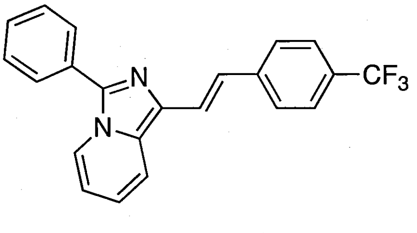
3-Phenyl-1-styrylimidazo[1,5-a]pyridine (**12aa**)



Chemical Formula: $C_{21}H_{16}N_2$
Exact Mass: 296.1313
Molecular Weight: 296.3651

yellow solid, mp 114.5-115.5 °C, Rf = 0.30 (*n*-Hex : EtOAc = 10 : 1), IR (KBr) 3025, 1623, 1595, 1299, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.61 (dd, *J* = 7.3,6.3 Hz, 1H, Ar), 6.83 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 7.27-7.32 (m, 1H, Ar), 7.40-7.45 (m, 3H, Ar), 7.50-7.65 (m, 6H, Ar), 7.71 (d, *J* = 9.3 Hz, 1H, Ar), 7.89 (d, *J* = 7.3 Hz, 2H, Ar), 8.23 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.4, 118.1, 118.4, 119.5, 121.9, 126.2 (Ar), 126.9 (C=C), 128.3, 128.5, 128.6 (Ar), 129.0 (C=C), 129.1, 129.3, 129.9, 130.5, 138.1, 138.7 (Ar). MS (EI) *m/z* 296 (M$^+$); HRMS (EI): Exact mass calcd for $C_{21}H_{16}N_2$ (M$^+$); 296.1313. Found: 296.1312.

3-Phenyl-1-{(4-trifluoromethylphenyl)ethenyl}limidazo[1,5-a]pyridine (**12ab**)

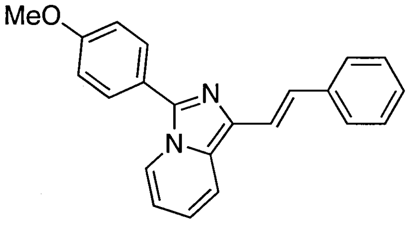


Chemical Formula: $C_{22}H_{15}F_3N_2$
Exact Mass: 364.1187
Molecular Weight: 364.3631

yellow solid, mp 145-147 °C, Rf = 0.28 (*n*-Hex : EtOAc = 10 : 1), IR (KBr) 3028, 2933, 1617, 1596, 1574, 1322 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.61 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.84 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 7.43-7.69 (m, 10H, Ar), 7.84 (d, *J* = 7.3 Hz, 2H, Ar), 8.21 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.4, 117.6, 119.9, 120.3, 121.8, 124.0, (Ar), 124.1 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.3 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 125.8, (Ar), 128.0 (q, *J* = 33.1 Hz, $\underline{C}$-CF_3), 128.1, 128.8, 128.9 (Ar), 129.4 (C=C), 129.6 (Ar), 129.6 (C=C), 138.9, 141.3 (Ar). ^{19}F

NMR ($CDCl_3$) δ -62.8 (CF_3). MS (EI) *m/z* 364 (M^+); HRMS (EI): Exact mass calcd for $C_{22}H_{15}F_3N_2$ (M^+); 364.1187. Found 364.1189.

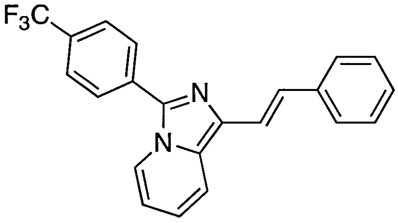
3-(4-Methoxyphenyl)-1-styrylimidazo[1,5-a]pyridine (**12ba**)



Chemical Formula: $C_{22}H_{18}N_2O$
Exact Mass: 326.1419
Molecular Weight: 326.3911

yellow solid, mp 163-164 °C, Rf = 0.20 (*n*-Hex : EtOAc = 10 : 1), IR (KBr) 3028, 1623, 1609, 1593, 1254, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H, OMe), 6.51 (dd, *J* = 7.3, 6.8 Hz, 1H, Ar), 6.74 (dd, *J* = 8.8, 6.8 Hz, 1H, Ar), 7.09 (d, *J* = 8.8 Hz, 2H, Ar), 7.23 (t, *J* = 7.3 Hz, 1H, Ar), 7.34-7.38 (m, 3H, Ar), 7.52 (d, *J* = 16.1 Hz, 1H, C=CH), 7.58 (d, *J* = 7.8 Hz, 2H, Ar), 7.63 (d, *J* = 8.8 Hz, 1H, Ar), 7.75 (d, *J* = 8.8 Hz, 2H, Ar), 8.10 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe), 113.2, 114.5, 118.1, 118.4, 119.3, 121.8, 122.4, 125.9, 126.1, 126.8, 128.6 (Ar), 129.0 (C=C), 129.8 (Ar), 130.1 (C=C), 138.2, 138.8, 160.2 (Ar). MS (EI) *m/z* 326 (M^+); HRMS (EI): Exact mass calcd for $C_{22}H_{18}N_2O$ (M^+); 326.1419. Found: 326.1418.

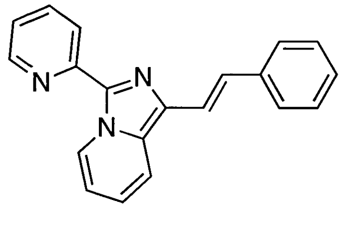
1-Styryl-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**12ca**)



Chemical Formula: $C_{22}H_{15}F_3N_2$
Exact Mass: 364.1187
Molecular Weight: 364.3631

yellow solid, mp 143-145 °C, Rf = 0.28 (*n*-Hex : EtOAc = 10 : 1), IR (KBr) 3029, 2926, 1635, 1625, 1607, 1572, 1325 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.62 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.84 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar), 7.25 (t, *J* = 7.8 Hz, 1H, Ar), 7.34 (dd, *J* = 7.8, 7.3 Hz, 2H, Ar), 7.35 (d, *J* = 16.1 Hz, 1H, C=CH), 7.54 (d, *J* = 16.1 Hz, 1H, C=CH), 7.59 (d, *J* = 7.3 Hz, 2H, Ar), 7.70 (d, *J* = 8.8 Hz, 1H, Ar), 7.80 (d, *J* = 8.3 Hz, 2H, Ar), 7.98 (d, *J* = 8.3 Hz, 2H, Ar), 8.20 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 114.2, 118.1, 118.3, 119.9, 121.6 (Ar), 124.0 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 126.0 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 126.3 (Ar), 126.8 (C=C), 127.1 (C=C), 128.3, 128.3, 128.7, 129.8 (Ar), 130.5 (q, *J* = 33.1 Hz, $\underline{C}$-CF_3), 131.3, 133.5, 137.9 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.8 (CF_3). MS (EI) *m/z* 364 (M^+). HRMS (EI): Exact mass calcd for $C_{22}H_{15}F_3N_2$ (M^+); 364.1187. Found: 364.1180.

3-(2-Pyridyl)-1-styrylimidazo[1,5-a]pyridine (**12ea**)



Chemical Formula: $C_{20}H_{15}N_3$
Exact Mass: 297.1266
Molecular Weight: 297.3532

yellow solid, mp 168-170 °C, Rf = 0.20 (*n*-Hex : EtOAc = 10 : 1), IR (KBr) 3047, 1621, 1585, 1560, 743 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.56 (dd, *J* = 7.3, 6.5 Hz, 1H, Ar), 6.75 (d, *J* = 8.8, 6.5 Hz, 1H, Ar), 7.03 (dd, *J* =7.3, 4.4 Hz, 1H, Ar), 7.09 (t, *J* = 7.3 Hz, 1H, Ar), 7.21 (d, *J* = 16.1 Hz, 1H, CH=C$\underline{H}$), 7.22 (d, *J* = 7.3 Hz, 2H, Ar), 7.39 (d, *J* = 16.1 Hz, 1H, C$\underline{H}$=CH), 7.43 (d, 7.3 Hz, 2H, Ar), 7.53 (d, *J* = 8.8 Hz, 1H, Ar), 7.63 (dd, *J* = 7.8, 7.3 Hz, 1H, Ar), 8.3 (d, *J* = 7.8 Hz, 1H, Ar), 8.47 (d,

J = 4.4 Hz, 1H, Ar), 9.77 (1H, J = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.9, 117.3, 118.5, 120.8, 121.9, 122.3, 126.3, 126.6 (Ar), 126.6 (C=C), 127.0, 128.7, 130.7 (Ar), 130.7 (C=C), 135.5, 136.5, 138.0, 148.2, 150.8 (Ar). MS (EI) *m/z* 297 (M^+); HRMS (EI): Exact mass calcd for $C_{20}H_{15}N_3$ (M^+); 297.1266. Found 297.1266.

References and notes

(1) For recent general review of Hagihara-Sonogashira-coupling reactions, see: Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(2) For recent general review of Heck reactions, see: *The Mizoroki-Heck Reaction*, Oestreich, M., Ed.; John Wiley and Sons, New York, 2009.

(3) For example, see: (a) Berthiol, F.; Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002,** *43*, 5625. (b) Chittiboyina, G. A.; Reddy, R.; Watkins E. B.; Avery, A. M. *Tetrahedron Lett.* **2004**, *45*, 1869. (c) Feuerstein, M.; Doucet, H.; Santelli. M. *Tetrahedron Lett.* **2005**, *46*,1717. (d) Pei, W.; Mo, J.; Xiao, J. *J. Organomet. Chem.* **2005**, *690,* 3546.

(4) For example, see: (a) Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763. (b) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362. (c) Olsen, C. A.; Parera, N.; Albericio, F.; Alvarez, M. *Tetrahedron Lett.* **2005**, *46*, 2041. (d) Handy, S. T.; Sabatini, J. *J. Org. Lett.* 2006, 8, 1537.

(5) (a) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621. (b) Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron*, **2009**, *65*, 5062.

(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr., Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O. , Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Forestman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzales, C., Pople, J. A. *Gaussian 03*; Gaussian Inc.: Wallingford, CT, 2004.

(7) *Functional Organic Materials: Synthesis, Strategies, and Applications*, Müller, T. J. J.; Bunz U. H. F. Eds.; Wiley-VCH, Weinheim, 2007.

(8) Suffert, J. Ziessel, R. *Tetrahedron Lett.* **1991**, *32*, 757.

(9) Andrade, D. C.; Yanez, O. C.; Rodriguez, L.; Belfield, D. K. *J. Org. Chem.* **2010**, *75*, 3975.

(10) Herrmann, A. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.

(11) *Kagakubinran*, 3rd ed., ed. by Japan Chemical Society, Maruzen, Tokyo, **1984**; Vol. II, p. 365.

(12) Mehta, M.; Waldo, P. J.; Larock, C. R. *J. Org. Chem.* **2009**, *74*, 1141.

(13) Huang, O.; Larock, C. R. *J. Org. Chem.* **2003**, *68*, 980.

(14) Shao, H.; Chen, X.; Wang, Z.; Lu, P. *J. Phys. Chem. B*, **2007**, *111*, 10386.

(15) Werz, B. D.; Fischer, R. F.; Kornmayer, C. S.; Rominger, F.; Gleiter, R. *J. Org. Chem.* **2008**, *73*, 8021.

Chapter 4

Direct Arylation Reaction of Heteroarenes Catalyzed by Palladium Complex Bearing Diimine-type Ligand

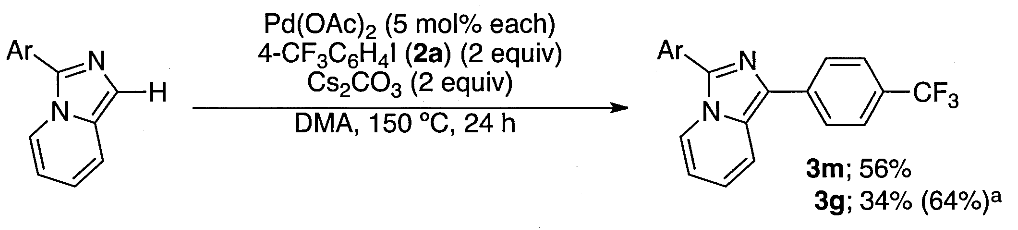
A cationic palladium complex bearing 1,10–phenanthroline ligand was found to catalyze direct C-H arylation reactions of heteroarenes with aryl iodides. The coupling of imidazo[1,5-*a*]pyridine with aryl iodide gave the corresponding C3-arylated imidazopyridines. Subsequent reaction of 3-arylimidazopyridines with aryl iodides gave the corresponding 1,3-diarylated imidazo[1,5-*a*]pyridines. Direct C-H arylation of benzazoles were also investigated under Pd-phenanthroline catalytic system to give the corresponding arylated products in good to high yields. In the case of 5-membered heteroarenes that have potentially reactive multiple C-H bonds, multiple arylations proceeded to give the corresponding di- or triarylated azoles in moderate to high yield. Mechanistic studies of present C-H arylation reaction was also described.

4.1. Introduction

Polyarylated heteroarenes are an important class of compounds that play significant roles in organic materials and bioactive compounds. The preparation of these substances is typically performed by means of transition metal catalyzed cross-coupling of (hetero)aryl metal reagents and (hetero)aryl halides. However, the efficiencies of these reactions remains a troublesome issue.[1] Recently, direct C-H bond functionalizations of heteroarenes have received growing attention in the context of streamlined chemical synthesis[2-7] since it has the potential of serving as an alternative to conventional cross-coupling reactions of heteroarenes. Unfortunately, the repertoire of applicable catalytic system for these processes remains limited.

4.2. Direct arylation reaction of imidazo[1,5-*a*]pyridines

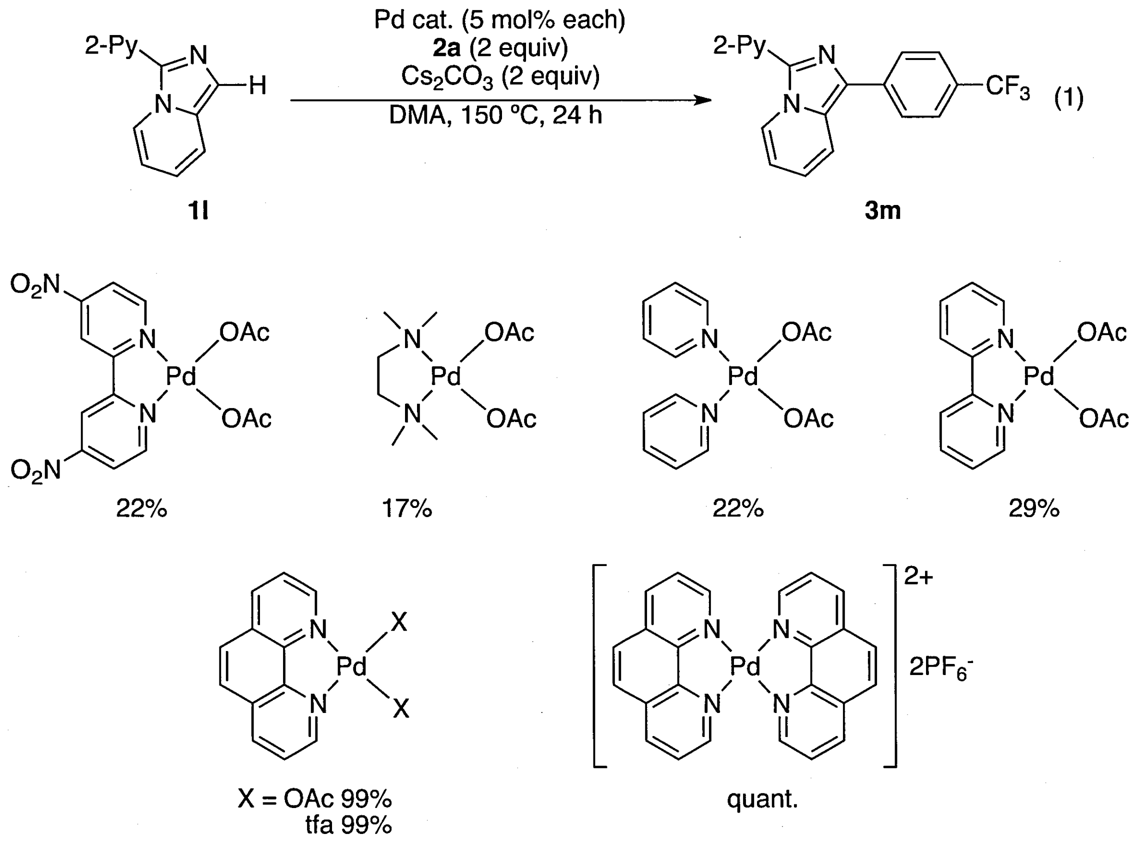
In the course of studies on the reactions of imidazo[1,5-*a*]pyridines,[8] the author employed a typical Pd-catalyzed C-H bond arylation reaction system[2c] to carry out arylation of 3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**1l**) at the 1-position. Importantly, conventional cross-coupling catalytic systems do not promote formation of products, a phenomenon that is probably a consequence of inhibition by chelation of the substrate to the catalyst.[8c] In contrast, reaction of **1l** and 4-trifluoromethylphenyl iodide (**2a**) gives the corresponding arylated product **3g** in moderate yield. However, the reaction of 4-methoxyphenylimidazo[1,5-*a*]pyridine (**1c**) with **2a** gives the corresponding product **3g** in a significantly lower yield (Scheme 1).



[a] With **1l** (5 mol%) instead of PPh_3.

Scheme 1 Reaction of imidazo[1,5-*a*]pyridines **1** and 4-iodotrifluoromethylbenzene **2a**

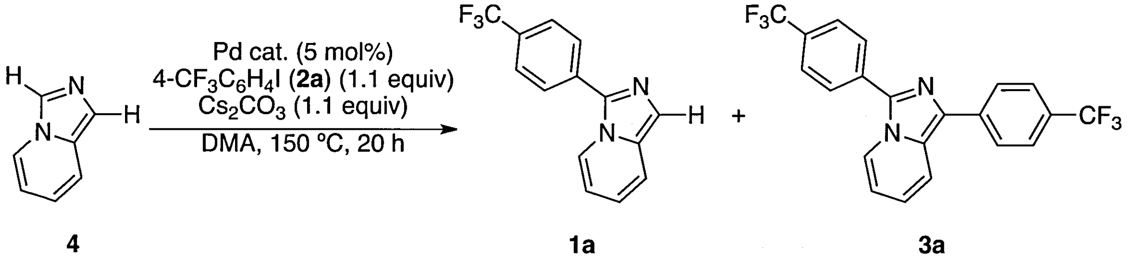
Interestingly, the use of **1l** as an additive in place of PPh_3 in the reaction of **1c** significantly improves the yield of **3g** suggesting that **1l** acts as a good ligand for Pd. Finally, under the screening of catalysts listed in scheme 2, the author found that a cationic complex bearing 1,10-phenanthroline ligand, $[Pd(phen)_2](PF_6)_2$[9] (phen = 1,10–phenanthroline), has excellent catalytic activity in the reaction of **1l** to give **3m** quantitatively (scheme 2).



Scheme 2. Screening of ligand for C-H arylation reaction

Owing to the unprecedented catalytic activity of such cationic Pd complex bearing a nitrogen-based ligand, the author investigated direct arylation reaction at 3-position of unsubstituted imidazo[1,5-*a*]pyridine **4** using Pd-phenanthroline system to achieve a direct synthesis of 1,3-diarylimidazo[1,5-*a*]pyridines **3** from **4** by sequential arylation. The results of initial investigation of the C-H direct arylation at 3-position of **4** and 4-iodotrifluoromethylbenzene **2a** are shown in Table 1.

Table. 1 Optimizing reaction conditions for C3 arylation of imidazo[1,5-*a*]pyridine **4**

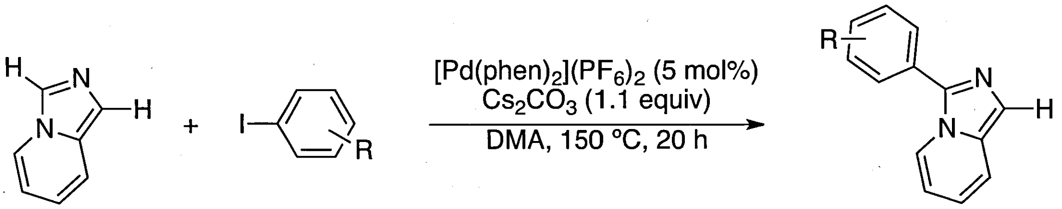


Entry	Pd cat.	**1a** (%)[a]	**3a** (%)[a]
1	$[Pd(phen)_2](PF_6)_2$	86	20
2	$Pd(phen)(OAc)_2$	81	22
3[b]	$[Pd(phen)_2](PF_6)_2$	74	20
4[c]	$[Pd(phen)_2](PF_6)_2$	98	trace

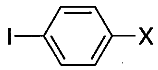
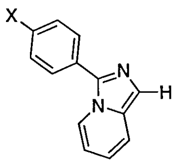
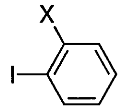
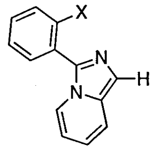
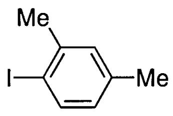
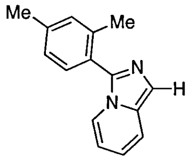
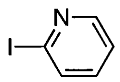
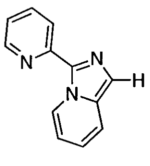
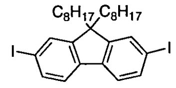
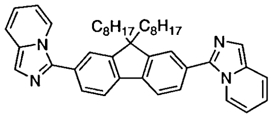
[a] Reactions were carried out using a imidazo[1,5-*a*]pyridine (0.5 mmol) and aryl iodide (1.1 equiv) in the presence of catalyst (5 mol%) and Cs_2CO_3 (1.1 equiv) in DMA (1 M) at 150 °C for 20 h. [b] Ar-Br was used. [c] Reaction was carried out in DMA (0.5 M).

The reaction of **4** and **2a** (1.1 equiv.) with Cs_2CO_3 (1.1 equiv.) and a catalytic amount of $[Pd(phen)_2](PF_6)_2$ (5 mol%) in DMA gave C3 arylated product **1c** in 86% yield and diarylated product **3a** in 20% yield (entry 1). Meanwhile, $Pd(phen)(OAc)_2$ also promoted the reaction but the efficiency was slightly lower than $[Pd(phen)_2](PF_6)_2$ (entry 2). When an aryl bromide was used instead of iodide, the yield of **1a** decreased (entry 3). The product ratio between **1a** and **3a** was improved under low concentration conditions and gave mono arylated product in 98% yield (entry 4). With the optimized reaction conditions in hand, direct arylation reaction of **4** and a variety of aryl halides **2** were examined. The results of reactions are summarized in Table 2.

Table 2. Reaction of a variety of **2** and imidazo[1,5-*a*]pyridine **4**



4 + **2** (1.1 equiv) → **1a**

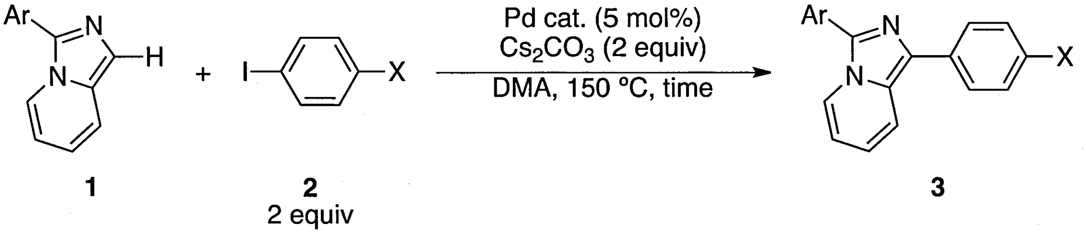
Entry	I-Ar (**2**)		Product	Yield (%)[a]
1		X = CF_3 **2a**		**1a**: 98
2		X = H **2b**		**1b**: 86
3		X = OMe **2c**		**1c**: 68
4		X = Me **2d**		**1d**: 74
5		X = NMe_2 **2e**		**1e**: 98
6		X = F **2f**		**1f**: 74
7		X = NO_2 **2g**		**1g**: 73[b]
8		X = COOEt **2h**		**1h**: 63[b]
9		X = Me **2i**		**1i**: 73
10		X = OMe **2j**		**1j**: 50
11		**2k**		**1k**: 70
12		**2l**		**1l**: 49
13		**2m**		**1m**: 90[c]

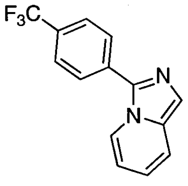
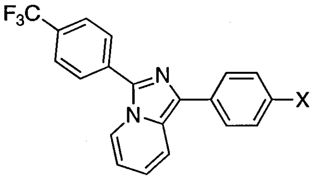
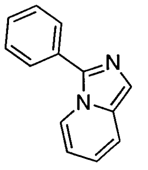
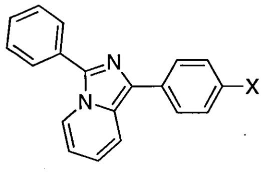
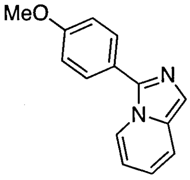
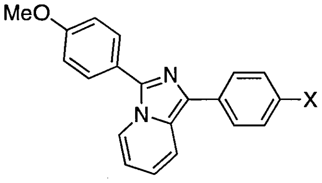
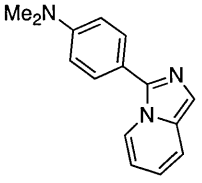
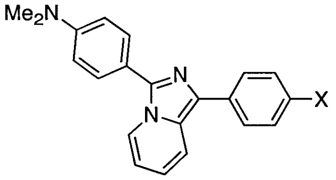
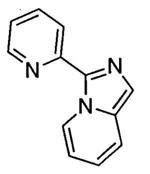
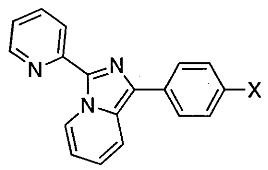
[a] Isolated yield. [b] K_2CO_3 was used instead of Cs_2CO_3. [c] 2.5 equiv of **4** was used.

Using the Pd-phenanthroline system, the desired arylated products **1** were obtained in moderate to high yields regardless of aryl iodides. The reaction proceeded efficiently with both electron-rich (entries 3-5) and poor (entries 1, 6-8) aryl iodides to give the monoarylated products **1** in good to high yields. When 4-nitro- (**2g**) and 4-ethoxycarbonyl-phenyl iodide (**2h**) were used as coupling partners, K_2CO_3 was a suitable base for these substrates (entries 7 and 8). Although, the reaction with sterically hindered 2-iodotoluene **2i** and 4-iodo-*m*-xylene **2k** also took place and gave the corresponding products **1i** and **1k** in good yields, the reaction of 2-iodoanisole **2j** did not proceed smoothly to give **1j** in a lower yield (entries 9-11). In the case of 2-iodopyridine **2l** as a coupling partner, the reaction was sluggish and afforded the product in only a moderate yield (entry 12). Finally, reaction of diiodofluorene (**2m**) with imidazopyridine gave the bis-coupling product **1m** in 90% yield (entry 13).

The author then turned his attention to the investigation of C1 arylation of 3-arylimidazopyridines **1** to lead to 1,3-diarylated imidazopyridines. The reaction of 3-arylimidazopyridines **1** with several aryl iodides **2** at 150 °C were carried out (Table 3).

Table 3. Reaction with a variety of **2** with 3-arylimidazopyridine **1**



Entry	1	2	Time (h)	Product	Yield (%)[a]
1		**2a**	24		**3a**: 59
2		**2b**	48		**3b**: 91
3		**2c**	48		**3c**: 82
4		**2a**	48		**3d**: 75
5		**2b**	48		**3e**: 74[b]
6		**2c**	48		**3f**: 90
7		**2a**	24		**3g**: 70[c]
8		**2b**	24		**3h**: 65
9		**2c**	48		**3i**: 68
10		**2a**	24		**3j**: 85[c]
11		**2b**	24		**3k**: 71
12		**2c**	48		**3l**: 60
13		**2a**	24		**3m**: 99
14		**2b**	24		**3n**: 90[c]
15		**2c**	24		**3o**: 93

[a] Isolated yield. [b] Pd(phen)$(OAc)_2$ was used. [c] Pd(phen)$(OCOCF_3)_2$ was used.

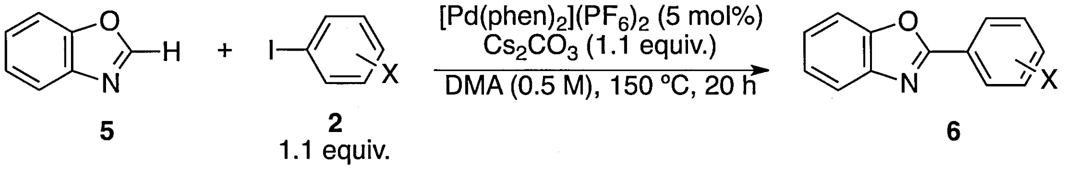
The Pd-phenanthroline complex could also promote C1 arylation of 3-arylimidazopyridines **1** with a variety of aryl iodides **2** to give

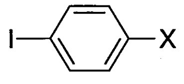
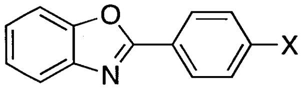
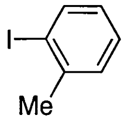
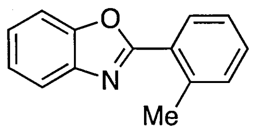
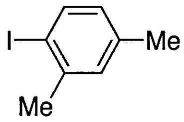
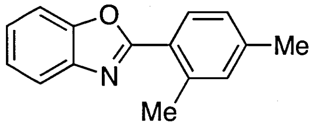
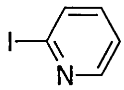
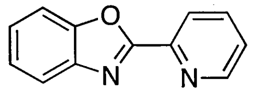
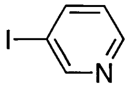
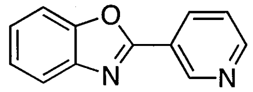
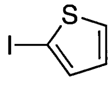
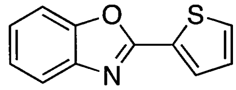
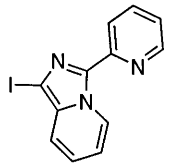
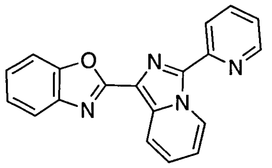
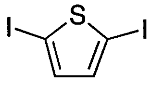
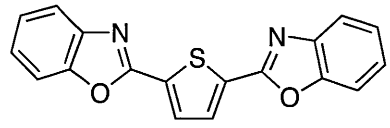
1,3-diarylimidazo[1,5-*a*]pyridines **3** in moderate to good yields. In the case of C1 arylation reaction of 3-arylimidazo[1,5-*a*]pyridines, the reaction behavior significantly changed depending on electronic properties of **1**. For example, 3-(4-trifluoromethylphenyl)imidazo[1,5-*a*]pyridine (**1a**) could be coupled with various aryl iodides (**2a-c**) to give the corresponding arylated products (**3a-c**) in moderate to high yields (entries1-3), though long reaction times were needed, comparing with electron-rich substrates such as **1c** and **1e** (entries 1-3 vs 7-12). In case of some combinations of **1** and **2**, $Pd(phen)(OAc)_2$ and $Pd(phen)(OCOCF_3)_2$ were suitable catalyst under the reaction conditions (entries 5, 7, 10, 14 and 15). Notably, imidazopyridine bearing 2-pyridyl group was crucial substrate under the present reaction conditions (entries 13-15).

4.3. Direct arylation reaction of benzazoles

To examine the applicability of the novel Pd-phenanthroline catalyst, the author chose the $[Pd(phen)_2](PF_6)_2$ as suitable catalyst due to its high reactivity for C-H arylation reaction of imidazo[1,5-*a*]pyridine. The reactions of benzoxazole (**4**) with several aryl iodides **2** at 150 °C for 20 h and 5 mol % of the $[Pd(phen)_2](PF_6)_2$ were carried out (Table 4).

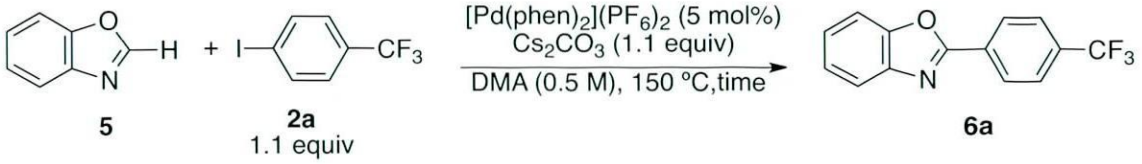
Table 4 Reaction of benzoxazole **5** and aryl iodides **2**[a]

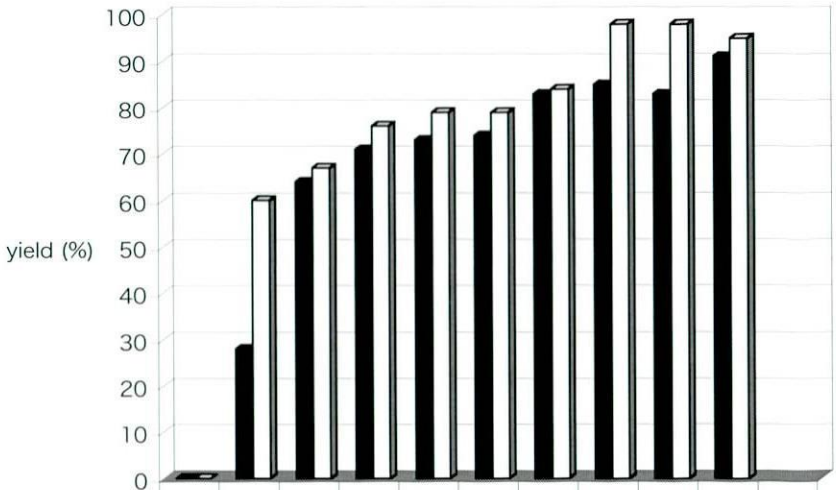


Entry	I-Ar (**2**)		Product	Yield(%)
1		X = CF_3: **2a**		**6a**: 94%
2		X = H: **2b**		**6b**: >99%
3		X = MeO: **2c**		**6c**: 89%
4		X = Me: **2d**		**6d**: 82%
5		**2i**		**6e**: 82%
6		**2k**		**6f**: 84%
7		**2l**		**6g**: 83%
8		**2n**		**6h**: 82%
9		**2o**		**6i**: 81%
10		**2p**		**6j**: >99%
11[b]		**2q**		**6k**: 89%

[a] Reactions were carried out with **4** (0.5 mmol), and aryl iodide (1.1 equiv) in the presence of $[Pd(phen)_2](PF_6)_2$ (5 mol%) and Cs_2CO_3 (1.1 equiv) in DMA at 150 °C for 20 h. [b]55 mol% of Ar-I was used.

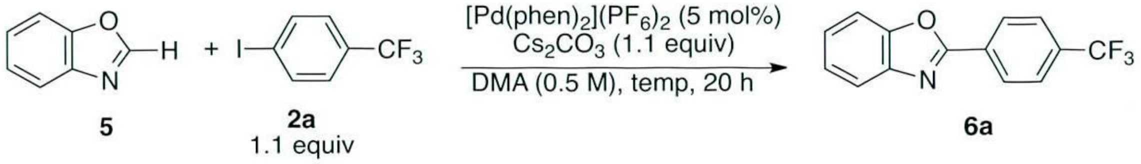
Aryl iodides **2a-d** undergo [Pd(phen)$_2$](PF$_6$)$_2$ promoted coupling reactions with **4** to give the corresponding products **6a-d** in high yields regardless of the nature of the electronic properties of the arene substituents (entries 1-4). Sterically hindered aryl iodides, *o*-tolyl iodide (**2i**) and 2,4-dimethylphenyl iodide (**2k**) also participate in coupling processes with **5** to give the respective products **6e-f** with high efficiency (entries 5,6). Furthermore, heteroaryl iodides, such as 2- and 3-pyridyl (**2l**, **2n**), 2-thienyl (**2o**), and 1-imidazo[1,5-*a*]pyridyl (**2p**) iodides, undergo reactions with **5** to generate the desired products **6g-j** in good to excellent yields (entries 7-10). Reaction of 2,5-diiodothiophene (**2q**) with **5** gives the bis-coupling product **6k** in 89% yield (entry 11). Notably, kinetic plots show that the reaction of high concentrations (1 M) of **5** and **2a** is complete within 40 min at 150 °C (Figure 1). Furthermore, this reaction proceeds even at 70 °C to give **6a** in 49% yield after 20 h (Figure 2). Finally, the cationic palladium complex [Pd(phen)$_2$](PF$_6$)$_2$ is stable in moist air and, as a result, reactions can be performed on a bench-top without Schlenk techniques. The catalyst [Pd(phen)$_2$](PF$_6$)$_2$ can be used to promote direct C-H bond arylation reactions of a wide variety of heteroarenes (Table 5).





	0	5	10	15	20	25	30	40	50	60
■ 0.5 M	0	28	64	71	73	74	83	85	83	91
1 M	0	60	67	76	79	79	84	98	98	95

Figure 1. Kinetic plots of the reaction under two concentrations.



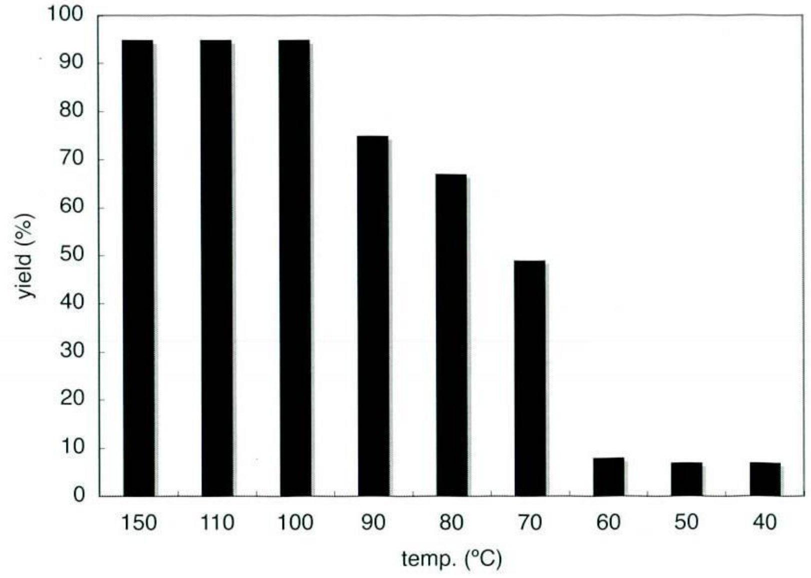
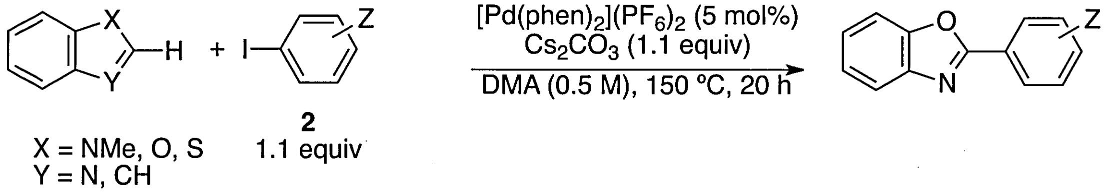
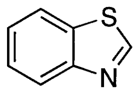
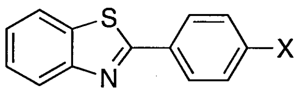
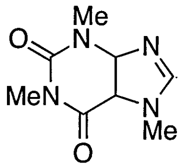
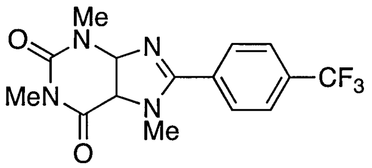
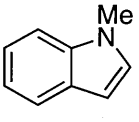
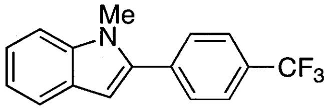


Figure 2. Temperature controlled experiments of direct arylation reaction of benzoxazole **5** and **2a**.

Table 5 Reaction of several heteroarenes and aryl iodides[a]



Entry	Ar-H	I-Ar' (**2**)	Ar–Ar'	Yield(%)
1	 **7**	**2a**		**8a**: 86%
2		**2b**		**8b**: 95%
3		**2c**		**8c**: 100%
4	 **9**	**2a**		**10**: 82%
5	 **11**	**2a**		**12**: 84%

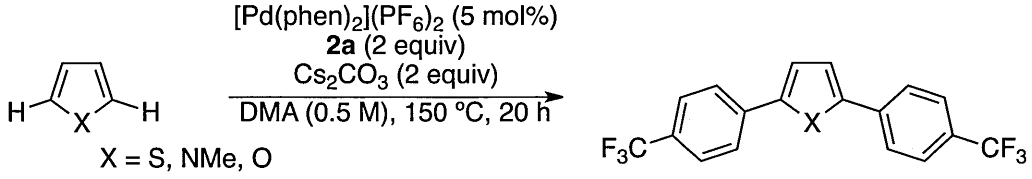
[a] Reactions were carried out using a heteroarene (0.5 mmol), and aryl iodide (1.1 equiv) in the presence of [Pd(phen)$_2$](PF$_6$)$_2$ (5 mol%) and Cs$_2$CO$_3$ (1.1 equiv) in DMA at 150 °C for 20 h.

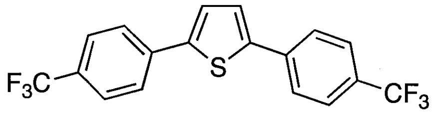
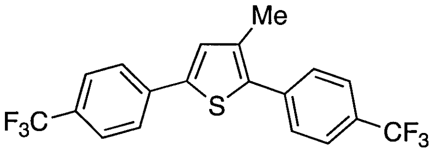
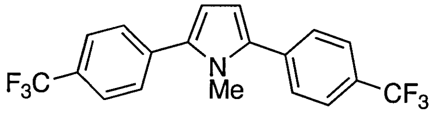
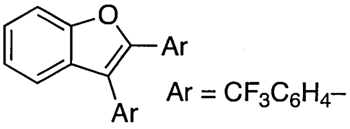
For example, benzothiazole (**7**) undergoes coupling with iodides **2a-c** to give the corresponding products **8a-c** in excellent yields (entries 1-3). Caffein (**9**) also participates in a reaction with **2a** to give the adduct **10** in high yield (entry 4). Finally, reaction of *N*-methylindole (**11**) and **2a** takes place in a regioselective fashion at the indole 1-position to give **12** in quantitative yield (entry 5).

4.4. Direct arylation reaction of 5-membered-heteroarenes

The catalytic system was found to be useful for carrying out multiple arylation reactions of heteroarenes. For example, thiophene reacts with 2 equiv of **2a** in the presence of [Pd(phen)$_2$](PF$_6$)$_2$ to give the 2,5-arylated product **13** exclusively in 80% yield on a 0.5 mmol scale (on a gram scale, the yield is 84%) (Table 6, entry 1).[10] In contrast, the reaction performed using the Pd-phosphine system[2a] affords **13** in only 11% yield (entry 2). Sterically hindered 3-methylthiophene also couples with **2a** at the 2- and 5-positions in high yield (entry 3). In addition, reaction of *N*-methylpyrrole takes place with a similar selectivity to that of thiophene to afford the bis-arylated product **15** in high yield (entry 4). Importantly, this straightforward and selective diarylation reaction of unsubstituted thiophene and *N*-methylpyrrole has only rarely been observed.[2a,b] Lastly, diarylation of benzofuran with 2 equiv of **2a** takes place to afford a 2,3-diaryl substituted benzofuran (entry 5).

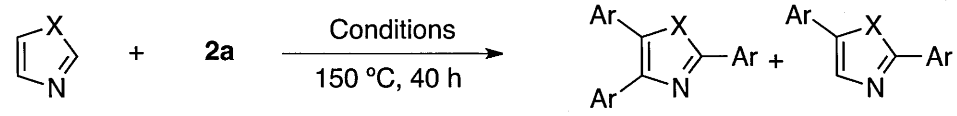
Table 6. Bis-arylation reactions of heteroarenes[a]



Entry	Product		Result
1		**13**	18 h, 80%
2			20 h, 11%[b]
3		**14**	20 h, 78%
4		**15**	12 h, 79%
5		**16**	20 h, 51%

[a] Reactions were carried out using a heteroarene (0.5 mmol), and aryl iodide (1.1 equiv) in the presence of $[Pd(phen)_2](PF_6)_2$ (5 mol%) and Cs_2CO_3 (1.1 equiv) in DMA at 150 °C for 20 h.

The author have also observed that the cationic Pd complex $[Pd(phen)_2](PF_6)_2$ catalyzes triarylation reactions of the simple heterocycles, oxazole (**17**) and *N*-methylimidazole (**18**) (scheme 3). In reactions of these substances with iodide **2a** which produce **19** and **21**, respectively, all of the arene hydrogens are substituted by aryl groups. The processes are accompanied by formation of minor amounts of the corresponding diarylated products **20** and **22**. The observations are in marked contrast to those made in studies of the related Pd-phosphine catalyzed reactions of **17** and **18** (Condition B), where **19** and **21** are the sole products generated. The processes described above are the first examples of triarylation reactions occurring by direct C–H arylation of simple heteroarenes.[2a]



17: X = O
18: X = NMe

3 equiv

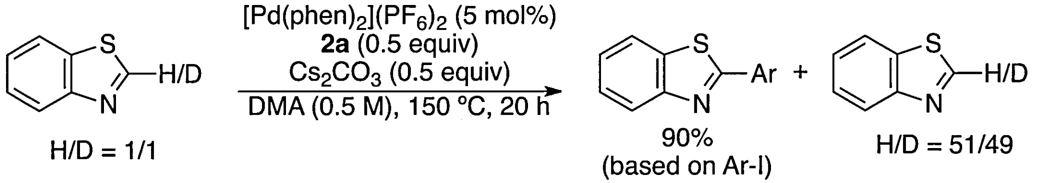
X = O	**19**	**20**
Condition A:	76%	21%
Condition B:	trace	59%
X = NMe	**21**	**22**
Condition A:	59%	39%
Condition B:	trace	41%

Condition A: $[Pd(phen)_2](PF_6)_2$ (5 mol%), Cs_2CO_3 (3 equiv), DMA
Condition B: $Pd(OAc)_2$ (5 mol%), P*t*Bu_3 (10 mol%), Cs_2CO_3 (3 equiv), xylene

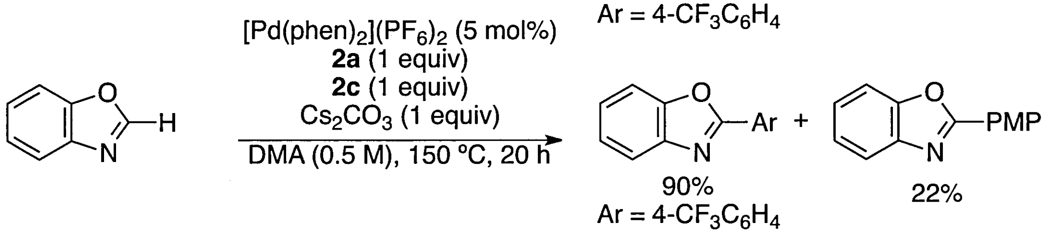
Scheme 3. Triple arylation of heteroarenes

4.5. Mechanistic studies of direct arylation reaction

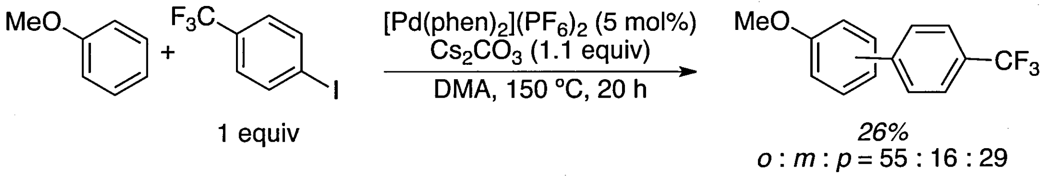
Although the mechanism of the catalytic process described above is not yet clear, several observations were made that provide insight into the mode of action of $[Pd(phen)_2](PF_6)_2$. The results of an intermolecular competitive reaction of deuterium-labeled **6** (H/D=1/1) with **2a** gives a KIE value of unity (eq 1). This finding clearly suggests that elimination of hydrogen from the heteroarene is not involved in the rate-limiting step. The results of a competitive reaction of **5** with an equimolar ratio of **2a** and **2c**, demonstrate that the electron deficient aryl halide **2a** undergoes coupling faster than its electron rich counterpart **2c** (eq 2). This observation suggests that either oxidative addition of the aryl iodide to the Pd catalyst or electrophilic addition of the resulting Pd complex to the heteroarene is rate-limiting provided that the reaction is taking place via a conventional pathway. Alternatively, the $[Pd(phen)_2](PF_6)_2$ catalyzed coupling reaction might follow a radical mechanism. Recently, an Ir-catalyzed reaction of anisole with iodobenzene was reported to give three regioisomeric monoarylated products with an unusually high *ortho* selectivity (*o* : *m* : *p* = 72 : 16 : 12). The intermediacy of a phenyl radical in this process has been proposed.[11] Interestingly, a similar *ortho* selectivity was observed in $[Pd(phen)_2](PF_6)_2$ promoted arylation reaction of anisole with **2a** (eq 3).



(1)



(2)



(3)

4.6. Summary

In conclusion, the Pd-phenanthroline system promotes efficient direct C-H bond arylation reactions of heteroarenes. A variety of 1,3-diarylimidazoles were obtained by sequential direct C3 and C1 arylation reactions of unsubstituted imidazopyridine. Arylation of benzazoles and variety of aryl iodides also proceed smoothly to give the corresponding arylated products in good to high yields. This catalytic system could be used to carry out highly selective multiple arylation reactions of unsubstituted azoles.

4.7. Experimental

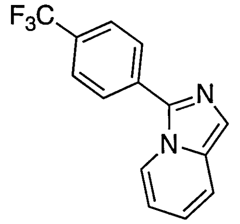
4.7.1 General information

Materials. Unless otherwise noted, reagents were commercially available and were used without purification. DMA was distilled over CaH_2 under reduced pressure. $Pd(phen)(OAc)_2$,[9c] $Pd(phen)(OCOCF_3)_2$,[9c] $[Pd(phen)_2](PF_6)_2$,[9c] $Pd(5,8\text{-dnbpy})(OAc)_2$,[12] $Pd(bpy)(OAc)_2$,[13] $Pd(tmeda)(OAc)_2$,[13] $Pd(py)_2(OAc)_2$,[13] 1-Methylindole,[14] imidazo[1,5-a]pyridine,[15] imidazo[1,5-a]pyridine derivatives[8d] and 2,7-diodo-9,9-dioctylfluorene[16] were prepared according the literature. Silica gel 60N (Spherical, Neutral, 40-50 mm) used was from Kanto Chemical Co., Inc.

4.7.2 General procedure for C-3 arylation of imidazo[1,5-*a*]pyridines

Cs_2CO_3 (1.1 equiv) was dried over *in vacuo* at 150 °C for 3 h imidazo[1,5-a]pyridine (0.5 mmol), aryliodide (1.1 equiv) and DMA (1 mL) were added under Ar atmosphere. The mixture was degassed for 3 times, $[Pd(phen)_2](PF_6)_2$ (5 mol%) was added to the mixture, and it was heated at 150 °C for 20 h. The resulting mixture was filtrated by cellite pad and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (*n*-Hex : AcOEt) to give a title compound.

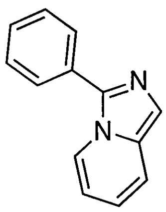
3-(4-Trifluoromethylphenyl)imidazo[1,5-a]pyridine **(1a)**[8a]



Chemical Formula: $C_{14}H_9F_3N_2$
Exact Mass: 262.0718
Molecular Weight: 262.2299

98% yield, yellow solid, Rf = 0.45 (hexane : AcOEt = 3 : 1). ^1H NMR ($CDCl_3$) δ 6.63 (t, *J* = 6.6 Hz, 1H, Ar), 6.77-6.80 (m, 1H, Ar), 7.52 (d, *J* = 9.3 Hz, 1H, Ar), 7.60 (s, 1H, Ar), 7.77 (d, *J* = 7.8 Hz, 2H, Ar), 7.94 (d, *J* = 7.8 Hz, 2H, Ar), 8.28 (d, *J* = 6.8 Hz, 1H, Ar).

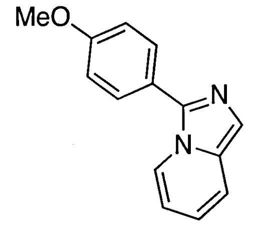
3-Phenylimidazo[1,5-a]pyridine **(1b)**[8a]



Chemical Formula: $C_{13}H_{10}N_2$
Exact Mass: 194.0844
Molecular Weight: 194.2319

86% yield, yellow solid, Rf = 0.38 (hexane : AcOEt = 2 : 1). ^1H NMR ($CDCl_3$) δ 6.57 (td, *J* = 6.8, 1.0 Hz, 1H, Ar), 6.64 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 1H, Ar), 7.33-7.49 (m, 5H, Ar), 7.01-7.73 (m, 2H, Ar), 8.18 (dd, *J* = 7.3, 1.0 Hz, 1H, Ar).

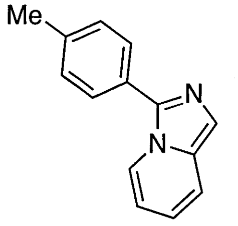
3-(4-Methoxyphenyl)imidazo[1,5-a]pyridine **(1c)**[8a]



Chemical Formula: $C_{14}H_{12}N_2O$
Exact Mass: 224.0950
Molecular Weight: 224.2579

68% yield, yellow solid, Rf = 0.18 (hexane : AcOEt = 2 : 1). ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, OMe), 6.49 (td, *J* = 6.9, 1.0 Hz, 1H, Ar), 6.65 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 7.02 (dq, *J* = 8.3, 4.7 Hz, 2H, Ar), 7.42 (dd, *J* = 9.3, 1.0 Hz, 1H, Ar), 7.49 (s, 1H, Ar), 7.68 (dq, *J* = 8.3, 4.7 Hz, 2H, Ar), 8.13-8.15 (m, 1H, Ar).

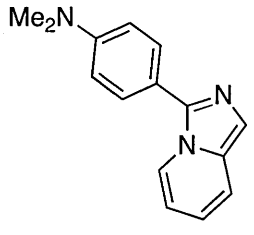
3-(4-Methylphenyl)imidazo[1,5-a]pyridine **(1d)**[8a]



Chemical Formula: $C_{14}H_{12}N_2$
Exact Mass: 208.1000
Molecular Weight: 208.2585

74% yield, yellow solid, Rf = 0.36 (hexane : AcOEt = 1 : 1). ^{1}H NMR ($CDCl_3$) δ 6.63 (t, *J* = 7.1 Hz, 1H, Ar), 6.82 (dd, *J* = 7.1, 9.1 Hz, 1H, Ar), 7.21-7.29 (m, 2H, Ar), 7.50 (d, *J* =9.1 Hz, 1H, Ar), 7.58 (s, 1H, Ar), 7.77-7.82 (m, 2H, Ar), 8.14 (d, *J* = 7.1 Hz, 1H, Ar).

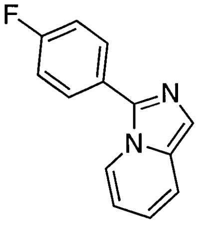
3-[4-(Dimethylamino)phenyl]imidazo[1,5-a]pyridine **(1e)**[8a]



Chemical Formula: $C_{15}H_{15}N_3$
Exact Mass: 237.1266
Molecular Weight: 237.2997

98% yield, yellow solid, Rf = 0.15 (hexane : AcOEt = 2 : 1). ^{1}H NMR ($CDCl_3$) δ 2.99 (s, 6H, NMe2), 6.45 (dd, *J* = 6.8, 6.3 Hz, 1H, Ar), 6.62 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 6.79 (d, *J* = 7.3 Hz, 2H, Ar), 7.40 (d, *J* = 9.3 Hz, Ar), 7.48 (s, 1H, Ar), 7.63 (d, *J* = 8.5 Hz, 2H, Ar), 8.17 (d, *J* = 6.8 Hz, 1H, Ar).

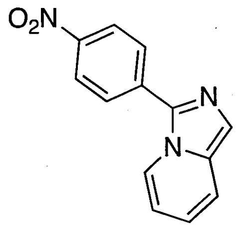
3-(4-Fluorophenyl)imidazo[1,5-a]pyridine **(1f)**[8a]



Chemical Formula: $C_{13}H_9FN_2$
Exact Mass: 212.0750
Molecular Weight: 212.2224

74% yield, yellow solid, Rf = 0.38 (hexane : AcOEt = 1 : 1). ^{1}H NMR ($CDCl_3$) δ 6.63 (t, *J* = 7.1 Hz, 1H, Ar), 6.82 (dd, *J* = 7.1, 9.1 Hz, 1H, Ar), 7.21-7.29 (m, 2H, Ar), 7.50 (d, *J* = 9.1 Hz, 1H, Ar), 7.58 (s, 1H, Ar), 7.77-7.82 (m, 2H, Ar), 8.14 (d, *J* = 7.1 Hz, 1H, Ar).

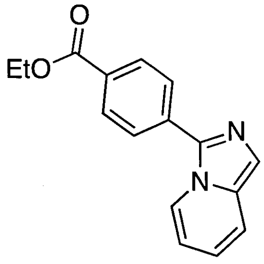
3-(4-Nitrolphenyl)imidazo[1,5-a]pyridine **(1g)**



Chemical Formula: $C_{13}H_9N_3O_2$
Exact Mass: 239.0695
Molecular Weight: 239.2295

73% yield, red solid, mp179-180 °C, Rf = 0.37 (hexane : AcOEt = 1 : 2). IR (KBr) 3079, 1591, 1509, 1341, 1255, 1099 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.74 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.87 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 7.58 (d, *J* = 9.3 Hz, 1H, Ar), 7.67 (s, 1H, Ar), 8.04 (d, *J* = 8.8 Hz, 2H, Ar), 8.37 (d, *J* = 7.3 Hz, 1H, Ar), 8.39 (d, *J* = 8.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 114.7, 119.4, 120.3, 121.6, 122.7, 124.7, 128.0, 133.2, 136.1, 136.8, 147.2 (Ar). MS (EI) *m/z* 239 (M$^+$); HRMS (EI): Exact mass calcd for $C_{13}H_9N_3O_2$ (M$^+$); 239.0695. Found: .239.0693.

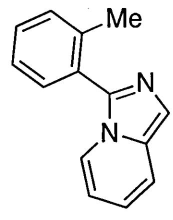
3-(4-Ethoxycarbonylphenyl)imidazo[1,5-a]pyridine **(1h)**



Chemical Formula: $C_{16}H_{14}N_2O_2$
Exact Mass: 266.1055
Molecular Weight: 266.2946

63% yield, yellow solid, mp 96-97 °C, Rf = 0.47 (hexane : AcOEt = 1 : 2). IR (KBr) 2980, 1705, 1609, 1308, 1273, 1126 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.42 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 4.41 (q, *J* = 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 6.61 (d, *J* = 7.3, 6.4 Hz, 1H, Ar), 6.76 (d, *J* = 9.3, 6.4 Hz, 1H, Ar), 7.49 (d, *J* = 9.3 Hz, 1H, Ar), 7.59 (s, 1H, Ar), 7.89 (d, *J* = 7.8 Hz, 1H, Ar), 8.18 (d, *J* = 7.8 Hz, 1H, Ar), 8.30 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.3 ($CH_2\underline{C}H_3$), 61.0 ($\underline{C}H_2CH_3$), 113.6, 118.8, 119.2, 121.3, 121.3, 127.2, 129.9, 130.1, 132.2, 134.4, 137.0 (Ar), 166.0 (C=O). MS (EI) *m/z* 266 (M$^+$); HRMS (EI): Exact mass calcd for $C_{16}H_{14}N_2O_2$ (M$^+$); 266.1055. Found: 226.1059.

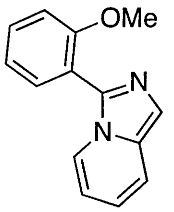
3-(2-Methylphenyl)imidazo[1,5-a]pyridine **(1i)**



Chemical Formula: $C_{14}H_{12}N_2$
Exact Mass: 208.1000
Molecular Weight: 208.2585

73% yield, brown sticky oil, Rf = 0.48 (hexane : AcOEt = 1 : 1). IR (KBr) 2926, 1632, 1468, 1351, 1250, 1044 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H, Me), 6.40 (dd, *J* = 8.8, 6.8 Hz, 1H, Ar), 6.64 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar), 7.19-7.55 (m, 7H, Ar).^{13}C NMR ($CDCl_3$) δ 19.6 (Me), 112.6, 118.5, 118.5, 119.7, 121.5, 126.0, 129.4, 129.5, 130.4, 130.5, 130.8, 136.4, 137.9 (Ar). MS (EI) *m/z* 208 (M$^+$); HRMS (EI): Exact mass calcd for $C_{14}H_{12}N_2$ (M$^+$); 208.1000. Found: 208.1012.

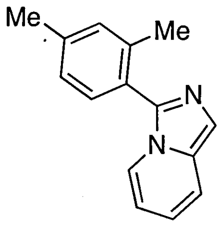
3-(2-Methoxylphenyl)imidazo[1,5-a]pyridine **(1j)**



Chemical Formula: $C_{14}H_{12}N_2O$
Exact Mass: 224.0950
Molecular Weight: 224.2579

50% yield, brown sticky oil, Rf = 0.10 (hexane : AcOEt = 1 : 1). IR (KBr) 2931, 1750, 1601, 1509, 1466, 1244, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H, OMe), 6.51 (dd, *J* = 7.3, 6.3 Hz, 1H, Ar), 6.72 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar), 7.05 (d, *J* = 8.8 Hz, 1H, Ar), 7.11 (dd, *J* = 7.8, 7.3 Hz, 1H, Ar), 7.44-7.49 (m, 2H, Ar), 7.58 (s, 1H, Ar), 7.60-7.63 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe), 111.2, 111.8, 118.2, 118.5, 119.4, 120.1, 121.5, 123.1, 130.6, 131.3, 132.5, 136.2, 157.3 (Ar). MS (EI) *m/z* 224 (M$^+$); HRMS (EI): Exact mass calcd for $C_{14}H_{12}N_2O$ (M$^+$); 224.0950. Found: 224.0956.

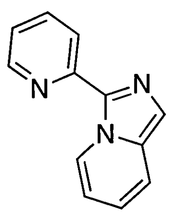
3-(2,4-Dimethylphenyl)imidazo[1,5-a]pyridine **(1k)**



Chemical Formula: $C_{15}H_{14}N_2$
Exact Mass: 222.1157
Molecular Weight: 222.2851

70% yield, brown sticky oil, Rf = 0.60 (hexane : AcOEt = 1 : 1). IR (KBr) 2919, 1614, 1461, 1351, 1136, 998 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H, Me), 2.40 (s, 3H, Me), 6.48 (dd, *J* = 7.8, 6.3 Hz, 1H, Ar), 6.70 (dd, *J* = 9.3, 6.3 Hz, 1H, Ar), 7.12 (d, *J* = 7.8 Hz, 1H, Ar), 7.18 (s, 1H, Ar), 7.33 (d, *J* = 7.3 Hz, 1H, Ar), 7.47 (d, *J* = 9.3 Hz, 1H, Ar), 7.56 (s, 1H, Ar), 7.63 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 19.2 (Me), 20.9 (Me), 112.1, 118.1, 118.2, 119.3, 1211.2, 126.2, 126.4, 129.9, 130.1, 131.2, 137.9, 138.9 (Ar). MS (EI) *m/z* 222 (M$^+$); HRMS (EI): Exact mass calcd for $C_{15}H_{14}N_2$ (M$^+$); 222.1157. Found: 222.1157.

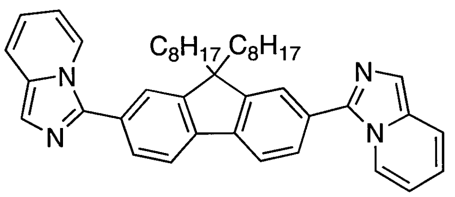
3-(2-Pyridyl)imidazo[1,5-a]pyridine **(1l)**[8a]



Chemical Formula: $C_{12}H_9N_3$
Exact Mass: 195.0796
Molecular Weight: 195.2200

49% yield, pale yellow solid, Rf = 0.37 (hexane : AcOEt = 2 : 1). ^{1}H NMR ($CDCl_3$) δ 6.66 (td, *J* = 5.1, 1.0 Hz, 1H, Ar), 6.79 (ddd, *J* = 9.3, 6.3, 1.0 Hz, 1H, Ar), 7.13 (ddd, *J* = 7.3, 4.9, 1.0 Hz, 1H, Ar), 7.46-7.48 (m, 1H, Ar), 7.55 (s, 1H, Ar), 7.72 (td, *J* = 7.8, 1.0 Hz, 1H, Ar), 8.28-8.30 (m, 1H, Ar), 8.57 (dd, *J* = 4.9, 1.0 Hz, 1H, Ar), 9.90 (d, *J* = 7.2 Hz, 1H Ar).

***2,7-Bis(3-imidazo[1,5-a]pyridinyl)-9,9'-dioctylfluorene* (1m)**



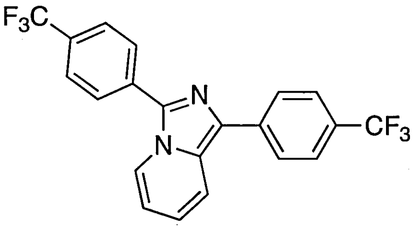
Chemical Formula: $C_{43}H_{50}N_4$
Exact Mass: 622.4035
Molecular Weight: 622.8839
Elemental Analysis: C, 82.91; H, 8.09; N, 8.99

90% yield, brawn oil, Rf = 0.13 (Hexane : EtOAc = 2 : 1). IR (neat) 2924, 2854, 2362, 1455, 1351, 1251, 1007, 903 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.74-0.77 (m, 10H, CH_2), 1.05-1.26 (m, 20H, CH_2), 2.04-2.08 (m, 4H, CH_2), 6.57 (dd, J = 7.3, 6.3 Hz, 2H, Ar), 6.72 (dd, J = 9.3, 6.3 Hz, 2H, Ar), 7.51 (d, J = 9.3 Hz, 2H, Ar), 7.59 (s, 2H, Ar), 0.74-0.77 (m, 10H, CH_2), 7.78 (d, J = 7.8 Hz, 2H, Ar), 7.81 (s, 2H, Ar), 7.86 (d, J = 7.8 Hz, 2H, Ar), 8.30 (d, J = 7.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 22.3, 23.8, 29.1, 29.1, 29.9, 31.5, 40.3 (CH_2), 55.6 (C), 113.1, 118.7, 118.8, 120.2, 120.6, 121.4, 122.7, 126.3, 129.2, 131.7, 138.7, 140.8, 152.0 (Ar). MS (EI) *m/z* 622 (M^+); HRMS (EI): Exact mass calcd for $C_{43}H_{50}N_4$, 622.4035 Found 622.4036.

4.7.3. General procedure for C-1 arylation of 3-arylimidazo[1,5-a]pyridines

Cs_2CO_3 (2.0 equiv) was dried over *in vacuo* at 150 °C for 3 h 3-arylimidazo[1,5-a]pyridine (0.5 mmol), aryliodide (2.0 equiv) and DMA (1 mL) were added under Ar atmosphere. The mixture was degassed for 3 times, Pd catalyst (5 mol%) was added to the mixture, and it was heated at 150 °C for period of time. The resulting mixture was filtrated by cellite pad and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel (hexane : AcOEt) to give a title compound.

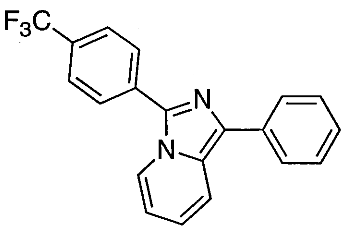
***1,3-bis(4-Trifluorophenyl)imidazo[1,5-a]pyridine* (3a)**[8d]



$C_{21}H_{12}F_6N_2$
Exact Mass: 406.0905
Mol. Wt.: 406.3238

57% yield, yellow solid, Rf = 0.48 (hexane : AcOEt = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 6.66-6.70 (m, 1H, Ar), 6.91 (dd, J = 9.3, 6.4 Hz, 1H, Ar), 7.68 (d, J = 8.8Hz, 2H, Ar), 7.78 (d, J = 8.1 Hz, 2H, Ar), 7.85 (d, J = 9.3 Hz, 1H, Ar), 7.96 (d, J = 8.8 Hz, 2H, Ar), 8.02 (d, J = 8.1 Hz, 2H, Ar), 8.26 (d, J = 7.3 Hz, 1H, Ar).

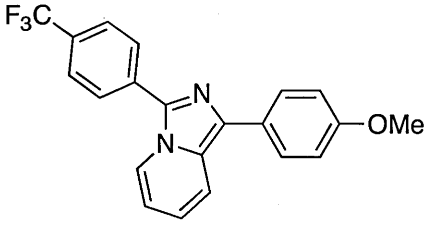
***1-(Phenyl)-3-(4-trifluorophenyl)imidazo[1,5-a]pyridine* (3b)**[8c]



$C_{20}H_{13}F_3N_2$
Exact Mass: 338.1031
Mol. Wt.: 338.3258

57% yield, yellow solid, Rf = 0.35 (*n*-Hex : AcOEt = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 6.60 (t, J = 6.3 Hz, 1H, Ar), 6.78 (dd, J = 6.3, 7.8 Hz, 1H, Ar), 7.26 (t, J = 7.8 Hz, 1H, Ar), 7.41 (t, J = 7.8 Hz, 2H, Ar), 7.72 (d, J = 8.3 Hz, 2H, Ar), 7.80-7.94 (m, 5H, Ar), 8.20 (d, J= 6.3 Hz, 1H, Ar).

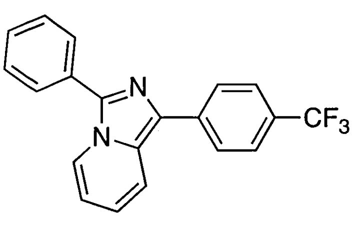
1-(4-Methoxyphenyl)-3-(4-trifluorophenyl)imidazo[1,5-a]pyridine **(3c)**[8c]



$C_{21}H_{15}F_3N_2O$
Exact Mass: 368.1136
Mol. Wt.: 368.3518

82% yield, yellow solid, Rf = 0.35 (hexane : AcOEt = 4 : 1). ^{1}H NMR (CDCl$_3$) δ 3.88 (s, 3H, OCH$_3$), 6.64 (t, *J* = 6.3 Hz, 1H, Ar), 6.81 (dd, *J* = 8.8, 5.9 Hz, 1H, Ar), 7.03 (dt, *J* = 8.3, 2.0 Hz, 2H, Ar), 7.78-7.87 (m, 5H, Ar), 7.99 (d, *J* = 8.3 Hz, 2H, Ar), 8.26 (d, *J* = 7.3 Hz 1H, Ar).

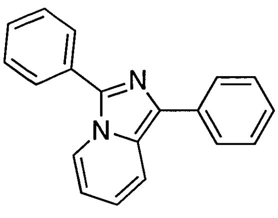
1-(4-Trifluorophenyl)-3-phenylimidazo[1,5-a]pyridine **(3d)**[8d]



$C_{20}H_{13}F_3N_2$
Exact Mass: 338.1031
Mol. Wt.: 338.3258

75% yield,yellow solid, Rf = 0.49 (*n*-Hex : EtOAc = 4 : 1). ^{1}H NMR (CDCl$_3$) δ 6.56 (td, *J* = 7.8, 1.0 Hz, 1H, Ar), 6.81 (ddd, *J* = 9.2, 6.3, 1.0 Hz, 1H, Ar), 7.70 (tt, *J* = 7.8, 1.0 Hz, 1H, Ar), 7.48 (tt, *J* = 7.4, 1.0 Hz, 2H, Ar), 7.62 (d, *J* = 8.3 Hz, 2H, Ar), 7.74-7.79 (m, 3H, Ar), 7.98 (d, *J* = 8.3 Hz, 2H, Ar), 8.19 (d, *J* = 7.3 Hz, 1H, Ar).

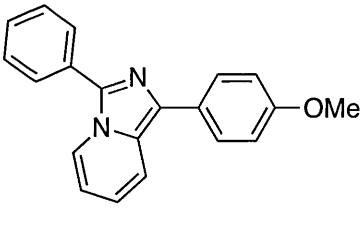
1,3-Diphenylimidazo[1,5-a]pyridine **(3e)**[8c]



$C_{19}H_{14}N_2$
Exact Mass: 270.1157
Mol. Wt.: 270.3279

74% yield, yellow solid, Rf = 0.45 (*n*-Hex : EtOAc = 4 : 1). ^{1}H NMR (CDCl$_3$) δ 6.50 (t, *J* = 6.5 Hz, 1H, Ar), 6.73 (dd, *J* = 6.5, 7.3 Hz, 1H, Ar), 7.23 (t, *J* = 7.3 Hz, 1H, Ar), 7.37-7.50 (m, 5H, Ar), 7.78 (dd, *J* = 1.7, 7.3 Hz, 3H, Ar), 7.87 (dd, *J* = 1.0, 7.3 Hz, 2H, Ar), 8.18 (d, *J* = 7.3 Hz, 1H, Ar).

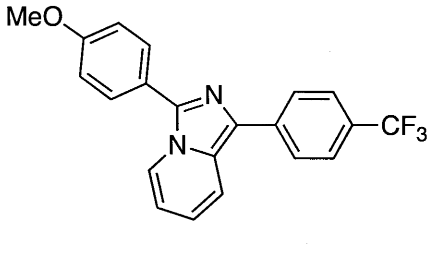
1-(4-Methoxyphenyl)-3-phenylimidazo[1,5-a]pyridine **(3f)**[8c]



$C_{20}H_{16}N_2O$
Exact Mass: 300.1263
Mol. Wt.: 300.3538

90% yield, yellow solid, Rf = 0.38 (*n*-Hex : EtOAc = 4 : 1). ^{1}H NMR (CDCl$_3$) δ 3.72 (s, 3H, OMe), 6.37 (t, *J* = 6.7 Hz, 1H, Ar), 6.57 (dd, *J* = 6.7, 9.1 Hz, 1H, Ar), 6.90 (d, *J* = 7.7 Hz, 2H, Ar), 7.30 (t, *J* = 6.8 Hz, 1H, Ar), 7.39 (d, *J* = 7.2 Hz, 2H, Ar), 7.62 (d, *J* = 9.1 Hz, 1H, Ar), 7.69-7.80 (m, 4H, Ar), 8.05 (d, *J* = 6.7 Hz, 1H, Ar).

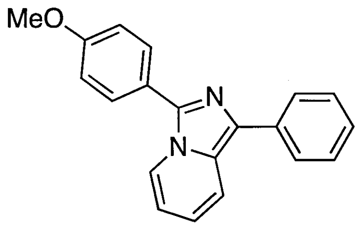
***3-(4-Methoxyphenyl)-1-(4-trifluorophenyl)imidazo[1,5-a]pyridines* (3g)**[8d]



$C_{21}H_{15}F_3N_2O$
Exact Mass: 368.1136
Mol. Wt.: 368.3518

70% yield, yellow solid, Rf = (*n*-Hex : AcOEt = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H, OCH_3), 6.61 (dd, *J* = 6.3, 7.4 Hz, 1H, Ar), 6.86 (dd, *J* = 9.1, 6.3 Hz, 1H, Ar), 7.07 (d, *J* = 8.3 Hz, 2H, Ar), 7.69 (d, *J* = 8.5 Hz, 2H, Ar), 7.75 (d, *J* = 8.5 Hz, 2H, Ar), 7.83 (d, *J* = 9.1 Hz, 1H, Ar), 8.05 (d, *J* = 8.3 Hz, 2H, Ar), 8.19 (d, *J* = 7.4 Hz, 1H, Ar).

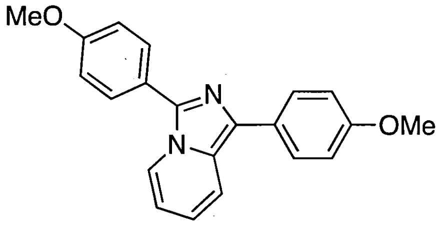
***3-(4-Methoxyphenyl)-1-phenylimidazo[1,5-a]pyridine* (3h)**[8c]



$C_{20}H_{16}N_2O$
Exact Mass: 300.1263
Mol. Wt.: 300.3538

68% yield, yellow solid, Rf = 0.35 (*n*-Hex : EtoAc = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 3H, OMe), 6.50 (t, *J* = 6.3 Hz, 1H, Ar), 6.71 (dd, *J* = 6.3, 8.8Hz, 1H, Ar), 7.01 (d, *J* = 8.8 Hz, 2H, Ar), 7.24(dd, *J* = 6.3, 7.8 Hz, 1H, Ar), 7.41 (d, *J* = 7.5 Hz, 2H, Ar), 7.71(d, *J* = 8.8 Hz, 2H, Ar), 7.77 (d, *J* = 8.8 Hz, 1H, Ar), 7.89 (d, *J* = 7.8 Hz, 2H, Ar), 8.11 (d, *J* = 6.3 Hz, 1H, Ar).

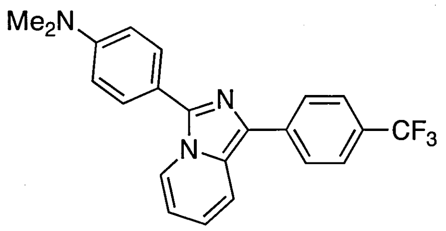
***1,3-bis(4-Methoxyphenyl)imidazo[1,5-a]pyridines* (3i)**[8c]



$C_{21}H_{18}N_2O_2$
Exact Mass: 330.1368
Mol. Wt.: 330.3798

68% yield, yellow solid, Rf = 0.24 (*n*-Hex : AcOEt = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.45 (t, *J* = 6.5 Hz, 1H, Ar), 6.65 (m, 1H, Ar), 6.91-6.97 (m, 4H, Ar), 7.64-7.68 (m, 3H, Ar), 7.78 (d, *J* = 8.3 Hz, 2H, Ar), 8.07 (d, *J* = 6.5 Hz, 1H, Ar).

***3-(4-N,N'Dimethylaminophenyl)-1-(4-trifluorophenyl)-imidazo[1,5-a]pyridine* (3j)**

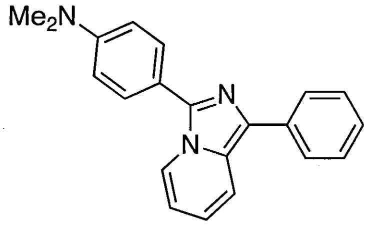


$C_{22}H_{18}F_3N_3$
Exact Mass: 381.1453
Mol. Wt.: 381.3936

85% yield, yellow solid, mp. 189-190 °C, Rf = 0.39 (hexane : AcOEt = 4 : 1). IR (KBr) 1613, 1361, 1159, 1104, 1065 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 6H, Me_2N), 6.39 (dd, *J* = 6.3, 7.0 Hz, 1H, Ar), 6.65 (dd, *J* = 6.3, 9.2 Hz, 1H, Ar), 6.71 (d, *J* = 8.8 Hz, 2H, Ar), 7.54 (d, *J* = 8.8 Hz, 2H, Ar), 7.57 (d, *J* = 8.3 Hz, 2H, Ar), 7.66 (d, *J* = 9.2 Hz, 1H, Ar), 7.94 (d, *J* = 8.3 Hz, 2H, Ar), 8.05 (d, *J* = 7.0 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 40.2 (Me_2N), 112.2, 112.7, 117.1, 118.4, 120.3, 122.2 (Ar), 124.5 (q, *J* = 271 Hz, $\underline{C}F_3$), 125.4 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 126.3 (Ar), 127.5 (q, *J* = 32.3 Hz, CF_3-$\underline{C}$), 128.0, 129.2, 129.4, 138.8, 139.5, 150.7 (Ar).

^{19}F NMR (CDCl$_3$) δ -62.4 (CF$_3$). MS (EI) *m/z* 381 (M$^+$); HRMS (EI) Calcd for $C_{22}H_{18}F_3N_3$ (M$^+$); 381.1453. Found: 381.1436.

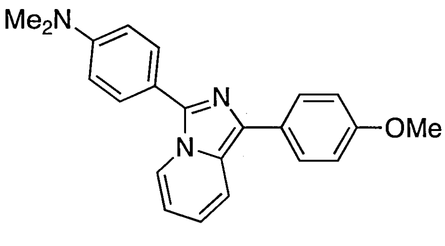
3-(4-N,N'-Dimethylaminophenyl)-1-phenylimidazo[1,5-a]pyridine (3k)



$C_{21}H_{19}N_3$
Exact Mass: 313.1579
Mol. Wt.: 313.3957

71% yield, yellow solid, mp 139-140 °C, Rf = 0.33 (hexane : AcOEt = 4 : 1). IR (KBr) 2929, 2727, 1614, 1536, 1360 cm^{-1}. ^{1}H NMR (CDCl$_3$) d 2.96 (s, 6H, Me$_2$N), 6.44 (dd, *J* = 6.5, 6.8 Hz, 1H, Ar), 6.66 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 6.77 (d, *J* = 8.3 Hz, 2H, Ar), 7.18-7.22 (m, 1H, Ar), 7.38 (t, *J* = 7.3 Hz, 2H, Ar), 7.62 (d, *J* = 8.3 Hz, 2H, Ar), 7.73 (d, *J* = 9.3 Hz, 1H, Ar), 7.86 (d, *J* = 7.3 Hz, 2H, Ar), 8.10 (d, *J* = 6.5 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 40.3 (Me$_2$N), 112.3, 112.7, 117.6, 119.0, 119.1, 122.0, 126.3, 126.8, 127.0, 128.6, 129.3, 131.2, 135.1, 139.0, 150.7 (Ar). MS (EI) *m/z* 313 (M$^+$); HRMS (EI) Calcd for $C_{21}H_{19}N_3$ (M$^+$); 313.1579. Found: 313.1566.

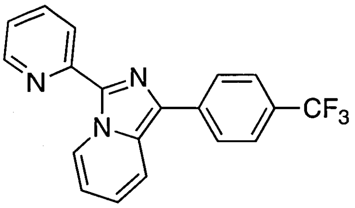
1-(4-Methoxyphenyl)-3-(4-N,N'dimethylaminophenyl)imidazo[1,5-a]pyridine (3l)



$C_{22}H_{21}N_3O$
Exact Mass: 343.1685
Mol. Wt.: 343.4216

60% yield, yellow slid, mp 189-190 °C, Rf = 0.27 (hexane : AcOEt = 4 : 1). IR (KBr) 2928, 1724, 1612, 1536, 1503, 1406, 1360, 1243 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.95 (s, 6H, Me$_2$N), 3.78 (s, 3H, OMe), 6.40 (dd, *J* = 6.6, 6.8 Hz, 1H, Ar), 6.60 (dd, *J* = 6.8, 9.1 Hz, 1H, Ar), 6.76 (d, *J* = 8.7 Hz, 2H, Ar), 6.93 (d, *J* = 8.3 Hz, 2H, Ar), 7.61 (d, *J* = 8.7 Hz, 2H, Ar), 7.66 (d, *J* = 9.1 Hz, 1H, Ar), 7.78 (d, *J* = 8.3 Hz, 2H, Ar), 8.01 (d, *J* = 6.6 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 40.3 (Me$_2$N), 55.3 (OMe), 112.3, 112.6, 114.1, 117.7, 118.6, 119.1, 121.8, 126.4, 127.8, 128.0, 129.3, 131.2, 138.6, 150.6, 158.3 (Ar). MS (EI) *m/z* 343 (M$^+$); HRMS (EI) Calcd for $C_{22}H_{21}N_3O$ (M$^+$); 343.1685. Found: 343.1660.

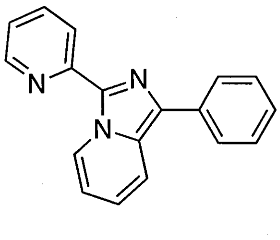
3-(2-Pyridyl)-1-(4-trifluorophenyl)imidazo[1,5-a]pyridine (3m)



$C_{19}H_{12}F_3N_3$
Exact Mass: 339.0983
Mol. Wt.: 339.3139

99% yield, yellow solid, mp 128-129 °C, Rf = 0.36 (hexane : AcOEt = 4 : 1), IR (KBr) 1615, 1589, 1324, 1124, 1067 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 6.60 (dd, *J* = 6.3, 6.8 Hz, 1H, Ar), 6.80 (dd, *J* = 6.8, 8.8 Hz, 1H, Ar), 7.07 (dd, *J* = 4.4, 6.3 Hz, 1H, Ar), 7.58 (d, *J* = 8.1 Hz, 2H, Ar), 7.62-7.70 (m, 2H, Ar), 7.92 (d, *J* = 8.1 Hz, 2H, Ar), 8.30 (d, *J* = 7.8 Hz, 1H, Ar), 8.49 (d, *J* = 4.4 Hz, 1H, Ar), 9.87 (d, *J* = 6.3 Hz, 1H, Ar). ^{13}C NMR (CDCl$_3$) δ 113.7, 117.7, 121.8, 121.9, 122.2 (Ar), 124.8 (q, *J* = 272 Hz, $\underline{C}F_3$), 125.5 (q, *J* = 3.3 Hz, $CF_3\text{-}C{=}\underline{C}$), 126.5, 126.6 (Ar), 128.0 (q, *J* = 32.3 Hz, $CF_3\text{-}\underline{C}$), 129.7, 130.2, 135.3, 136.4, 138.4, 148.0, 150.0 (Ar); ^{19}F NMR (CDCl$_3$) δ -58.7 (CF$_3$); MS (EI) *m/z* 339 (M^+); HRMS (EI) Calcd for $C_{19}H_{12}F_3N_3$ (M^+); 339.0983. Found: 339.0957.

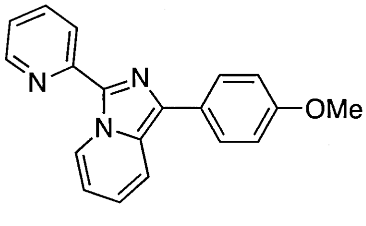
1-Phenyl-3-(2-pyridyl)imidazo[1,5-a]pyridine **(3o)**



$C_{18}H_{13}N_3$
Exact Mass: 271.1109
Mol. Wt.: 271.3159

90% yield, yellow solid, mp 98-99 °C, Rf = 0.33 (hexane : AcOEt = 4 : 1). IR (KBr) 1959, 1727, 1588, 1275, 1123 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.66 (dd, *J* = 6.3, 6.8 Hz, 1H, Ar), 6.85 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 7.13-7.16 (m, 1H, Ar), 7.32 (dd, *J* = 6.8, 7.8 Hz, 1H, Ar), 7.50 (t, *J* = 7.8 Hz, 2H, Ar), 7.74 (t, *J* = 7.8 Hz, 1H, Ar), 7.84 (d, *J* = 8.8 Hz, 1H, Ar), 7.98 (d, *J*= 7.8 Hz, 2H, Ar), 8.46 (d, *J* = 8.3 Hz, 1H, Ar), 8.60 (d, *J* = 4.4 Hz, 1H, Ar), 9.96 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 113.5, 118.1, 120.8, 121.4, 122.0, 126.2, 126.6, 126.8, 128.6, 129.0, 132.1, 134.7, 134.8, 136.2, 148.0, 150.9 (Ar). MS (EI) *m/z* 271 (M^+); HRMS (EI) Calcd for $C_{18}H_{13}N_3$ (M^+);271.1109. Found: 271.1092.

1-(4-Methoxyphenyl)-3-(2-pyridyl)imidazo[1,5-a]pyridine **(3o)**



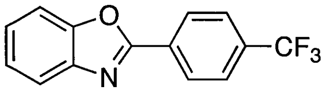
$C_{19}H_{15}N_3O$
Exact Mass: 301.1215
Mol. Wt.: 301.3419

93% yield, yellow solid, mp 126-128 °C, Rf = 0.29 (hexane : AcOEt = 4 : 1). IR (KBr) 2930, 1727, 2587, 1496, 1248, 1032 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H, OMe), 6.63 (dd, *J* = 6.8, 7.3 Hz, 1H, Ar), 6.80 (dd, *J* = 6.8, 8.3 Hz, 1H, Ar), 7.02 (d, *J* = 8.3 Hz, 2H, Ar), 7.12 (dd, *J* = 4.4, 6.2 Hz, 1H, Ar), 7.70-7.78 (m, 2H, Ar), 7.86 (d, *J* = 8.3 Hz, 2H, Ar), 8.43 (d, *J* = 7.8 Hz, 1H, Ar), 8.59 (d, *J* = 4.4 Hz, 1H, Ar), 9.93 (d, *J* = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.2 (OMe), 113.4, 114.1, 118.2, 120.3, 121.3, 121.9, 126.1, 127.6, 128.1, 128.5, 132.2, 134.5, 136.2, 147.9, 150.9, 158.5 (Ar). MS (EI) *m/z* 301 (M^+); HRMS (EI) Calcd for $C_{19}H_{15}N_3O$ (M^+); 301.1215. Found: 301.1215.

4.7.4. General procedure for the C-H arylation of heteroaromatics

In a screw-capped test tube was placed Cs_2CO_3 (1.1-3.0 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then, to the tube were added $[Pd(phen)_2](PF_6)_2$ (5 mol%), azole (0.5 mmol), aryl iodide (1.1-3.0 equiv) and DMA (1 mL). The resulting mixture was stirred under Ar atmosphere at 150 °C for 20 h. The resulting mixture was filtrated through celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give a title compound.

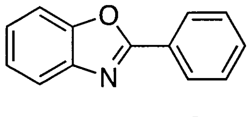
2-(4-Trifluoromethylphenyl)benzoxazole **(6a)**[17]



Chemical Formula: $C_{14}H_8F_3NO$
Exact Mass: 263.0558
Molecular Weight: 263.2146

94% yield, colorless solid, Rf = 0.30 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.37-7.40 (m, 2H, Ar), 7.58-7.59 (m, 1H, Ar), 7.80 (d, *J* = 8.2 Hz, 2H, Ar), 7.80-7.81 (m, 1H, Ar), 8.36 (d, *J* = 8.2 Hz, 2H, Ar).

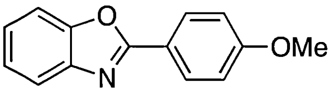
2-Phenylbenzoxazole (6b)[17]



Chemical Formula: $C_{13}H_9NO$
Exact Mass: 195.0684
Molecular Weight: 195.2167

99% yield, colorless solid, Rf = 0.43 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.33-7.38 (m, 2H, Ar), 7.51-7.54 (m, 3H, Ar), 7.56-7.59 (m, 1H, Ar), 7.78-7.81 (m, 1H, Ar), 8.26-8.28 (m, 2H, Ar).

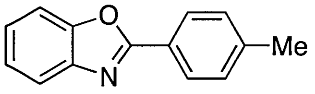
2-(4-Methoxyphenyl)benzoxazole (6c)[17]



Chemical Formula: $C_{14}H_{11}NO_2$
Exact Mass: 225.0790
Molecular Weight: 225.2426

89% yield, colorless solid, Rf = 0.2 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 4.08 (s, 3H, OMe), 7.01 (d, J = 8.8 Hz, 2H, Ar), 7.24-7.32 (m, 2H, Ar), 7.74 (m, 1H, Ar), 7.72 (m, 1H, Ar), 8.18 (d, J = 8.8 Hz, 2H, Ar).

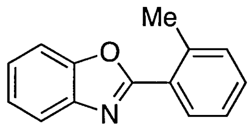
2-(4-Methylphenyl)benzoxazole (6d)[17]



Chemical Formula: $C_{14}H_{11}NO$
Exact Mass: 209.0841
Molecular Weight: 209.2432

82% yield, colorless solid, Rf = 0.38 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H, Me), 7.32 (d, J = 8.3 Hz, 2H, Ar), 7.34-7.35 (m, 1H, Ar), 7.55-7.58 (m, 2H, Ar), 7.76-7.79 (m, 2H, Ar), 8.15 (d, J = 8.3 Hz, 2H, Ar).

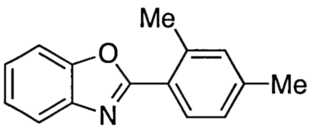
2-(2-Methylphenyl)benzoxazole (6e)[17]



Chemical Formula: $C_{14}H_{11}NO$
Exact Mass: 209.0841
Molecular Weight: 209.2432

82% yield, colorless solid, Rf = 0.39 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 7.18-7.27 (m, 5H), 7.45 (dd, J = 6.6, 2.4 Hz, 1H), 7.70 (dd, J = 6.6, 2.4 Hz, 1H), 8.05 (dd, J = 8.3, 2.0 Hz, 1H).

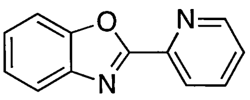
2-(2,4-Dimethylphenyl)benzoxazole (6f)



Chemical Formula: $C_{15}H_{13}NO$
Exact Mass: 223.0997
Molecular Weight: 223.2698

84% yield, colorless solid, mp 87-88 °C, Rf = 0.48 (hexane : AcOEt = 10 : 1). IR (KBr) 2921, 1546, 1490, 1455, 1247, 932 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, Ar), 2.62 (s, 3H, Ar), 7.16-7.17 (m, 2H, Ar), 7.35-7.37 (m, 2H, Ar), 7.59 (dd, J = 5.8, 4.8 Hz, 1H, Ar), 7.83 (dd, J = 5.8, 4.8 Hz, 1H, Ar), 8.11 (d, J = 9.2 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 21.3, 22.1 (Me), 110.3, 119.9, 123.4, 124.2, 124.7, 126.8, 129.8, 132.5, 138.7, 141.2, 142.2, 150.2, 163.6 (Ar). MS (EI) m/z 223 (M^+); HRMS (EI): Exact mass calcd for $C_{15}H_{13}NO_2$: 223.0997, Found: 223.0997.

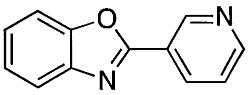
2-(2-Pyridyl)benzoxazole (6g)[18]



Chemical Formula: $C_{12}H_8N_2O$
Exact Mass: 196.0637
Molecular Weight: 196.2047

83% yield, colorless solid, Rf = 0. 10 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.32-7.39 (m, Ar, 3H), 7.59-7.62 (m, 1H, Ar), 7.77-7.83 (m, 2H, Ar), 8.29 (d, *J* = 9.1 Hz, 1H, Ar), 8.76 (d, *J* = 4.6 Hz, 1H, Ar).

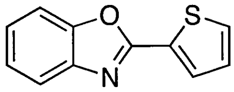
2-(3-Pyridyl)benzoxazole (6h)[17]



Chemical Formula: $C_{12}H_8N_2O$
Exact Mass: 196.0637
Molecular Weight: 196.2047

82% yield, colorless solid, Rf = 0. 10 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.36-7.38 (m, 2H, Ar), 7.45 (dd, *J* = 7.9, 4.8 Hz, 1H, Ar), 7.58-7.60 (m, 1H, Ar), 7.77-7.79 (m, 1H, Ar), 8.48 (td, *J* = 8.0, 1.8 Hz, 1H, Ar), 8.75 (d, *J* = 4.8, 1.7 Hz, 1H, Ar), 9.46 (d, *J* = 1.7 Hz, 1H, Ar).

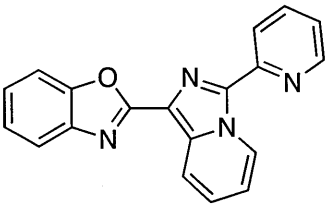
2-(2-Thienyl)benzoxazole (6i)[17]



Chemical Formula: $C_{11}H_7NOS$
Exact Mass: 201.0248
Molecular Weight: 201.2444

81% yield, colorless solid, Rf = 0.27 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.17 (dd, *J* = 4.9, 3.4 Hz, 1H, Ar), 7.32-7.34 (m, 2H, Ar), 7.52-7.54 (m, 2H, Ar), 7.72-7.75 (m, 1H, Ar), 7.90 (dd, *J* = 3.9, 1.4 Hz).

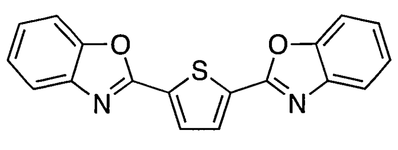
1-(2-Benzoxazolizyl)-3-(2-pyridyl)imidazo[1,5-a]pyridine (6j)



Chemical Formula: $C_{19}H_{12}N_4O$
Exact Mass: 312.1011
Molecular Weight: 312.3248

99% yield, yellow solid, mp 218-220 °C, Rf = 0.13 (hexane : AcOEt = 4 : 1). IR (KBr) 2360, 1618, 1580, 1505, 1454, 12456, 1018 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.85 (dd, *J* = 7.3, 6.4 Hz, 1H, Ar), 7.14-7.28 (m, 4H, Ar), 7.55 (dd, *J* = 7.3, 1.2 Hz, 1H, Ar), 7.71 (dd, *J* = 7.3, 1.0 Hz, 1H, Ar), 7.74 (ddt, *J* = 7.8, 1.8, 0.8, 1H, Ar) 8.46 (dd, *J* = 9.3, 1.0 Hz, 1H, Ar), 8.50 (dd, *J* = 7.8, 0.8 Hz, 1H, Ar), 8.58 (dd, *J* = 4.9, 1.0 Hz, 1H, Ar), 10.01 (dd, *J* = 7.3, 1.0 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 110.5, 114.9, 119.2, 119.3, 119.5, 122.5, 122.9, 124.2, 124.4, 124.5, 127.2, 134.0, 136.5, 136.6, 142.3, 148.1, 150.1, 150.2, 159.6 (Ar). MS (EI) *m/z* 312 (M^+); HRMS (EI): Exact mass calcd for $C_{19}H_{12}N_4O$ (M^+); 312.1011. Found: 312.1025.

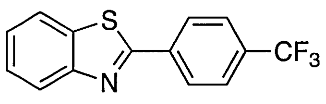
2,5-Bisbenzoxazolizylthiophene (6k)[17]



Chemical Formula: $C_{18}H_{10}N_2O_2S$
Exact Mass: 318.0463
Molecular Weight: 318.3492

89% yield, yellow solid. Rf = 0.13 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.38-7.40 (m, 4H, Ar), 7.59 (dd, *J* = 5.3, 3.6, 2H, Ar), 7.79 (dd, *J* = 5.7, 3.6 Hz, 2H, Ar), 7.95 (s, 2H, Ar).

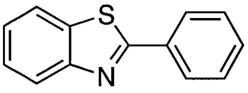
2-(4-Trifluoromethylphenyl)benzothiazole (8a)[19]



Chemical Formula: $C_{14}H_8F_3NS$
Exact Mass: 279.0330
Molecular Weight: 279.2802

86% yield, colorless solid, Rf = 0.35 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.44 (ddd, *J* = 7.9, 7.3, 0.9 Hz, 1H, Ar), 7.54 (ddd, *J* = 8.3, 7.3, 0.9 Hz, 1H, Ar), 7.76 (d, *J* = 7.8 Hz, 2H, Ar), 7.94 (d, *J* = 8.3 Hz, 1H, Ar), 8.12 (d, *J* = 7.9 Hz, 1H, Ar), 8.22 (d, *J* = 7.8 Hz, 2H, Ar).

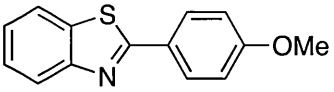
2-Phenylbenzothiazole (8b)[19]



Chemical Formula: $C_{13}H_9NS$
Exact Mass: 211.0456
Molecular Weight: 211.2823

95% yield, colorless solid, Rf = 0.31 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.40 (t, *J* = 7.4 Hz, 1H, Ar), 7.50-7.53 (m, 4H, Ar), 7.91 (d, *J* = 7.47 Hz, 1H, Ar), 8.10-813 (m, 3H, Ar).

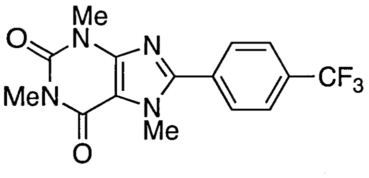
2-(4-Methoxyphenyl)benzothiazole (8c)[20]



Chemical Formula: $C_{14}H_{11}NOS$
Exact Mass: 241.0561
Molecular Weight: 241.3082

100% yield, colorless solid, Rf = 0.22 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OMe), 7.01 (d, *J* = 9.0 Hz, 2H, Ar), 7.36 (ddd, *J* = 7.8, 7.4, 1.3 Hz, 1H, Ar), 7.48 (ddd, *J* = 8.5, 7.4, 1.3 Hz, 1H, Ar), 7.88 (d, *J* = 8.5 Hz, 1H, Ar), 8.04-8.06 (m, 3H, Ar).

2-(4-Trifluoromethylphenyl)caffeine (10)

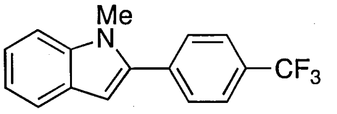


Chemical Formula: $C_{15}H_{13}F_3N_4O_2$
Exact Mass: 338.0991
Molecular Weight: 338.2845

82% yield, colorless solid, mp 200-202 °C, Rf = 0.05 (hexane : AcOEt = 10 : 1). IR (KBr) 3083, 1700, 1543, 1436, 1319, 1168 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, Me), 3.61 (s, 3H, Me), 4.09 (s, 3H, Me), 7.79 (d, *J* = 8.5 Hz, 2H, Ar), 7.85 (d, *J* = 8.5 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 28.0, 29.7, 33.9 (Me), 108.8 (Ar), 123.5 (q, *J* = 273.8 Hz, $\underline{C}F_3$), 125.8 (q, *J* = 3.3 Hz, CF_3-C=$\underline{C}$), 129.5, 131.8 (Ar), 132.2 (q, *J* = 33.1 Hz, CF_3-$\underline{C}$), 148.2, 150.2 (Ar), 151.5, 155.5 (C=O). ^{19}F NMR ($CDCl_3$) δ -63.3 (CF_3). MS (EI) *m/z* 338 (M^+); HRMS

(EI): Exact mass calcd for $C_{15}H_{13}F_3N_4O_2$ (M^+); 338.0991. Found: 338.0974.

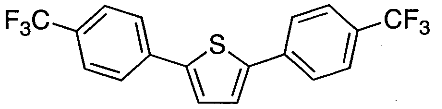
2-(4-Trifluoromethylphenyl)-N-methylindole (**12**)[21]



Chemical Formula: $C_{16}H_{12}F_3N$
Exact Mass: 275.0922
Molecular Weight: 275.2684

84% yield, colorless solid, Rf = 0.05 (hexane : AcOEt = 10 : 1). ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H, Me), 6.75 (s, 1H, Ar), 7.30 (t, J = 7.5 Hz, 1H, Ar), 7.42 (t, J = 7.5 Hz, 1H, Ar), 7.51 (d, J = 7.5 Hz, 1H, Ar), 7.74 (d, J = 8.3 Hz, 2H, AR), 7.77 (d, J = 7.5 Hz, 1H, Ar) 7.84 (d, J = 8.3 Hz, 2H, Ar).

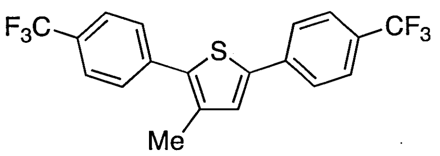
2,5-Bis(4-trifluoromethylphenyl)thiophene (**13**)



Chemical Formula: $C_{18}H_{10}F_6S$
Exact Mass: 372.0407
Molecular Weight: 372.3274

80% yield, yellow solid, mp 148-150 °C, Rf = 0.43 (hexane : AcOEt = 10 : 1). IR (KBr) 2925, 1612, 1321, 1164, 1129 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37 (s, 2H, Ar), 7.63 (d, J = 8.3 Hz, 4H, Ar), 7.70 (d, J = 8.3 Hz, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 124.1 (q, J = 272 Hz, $\underline{C}F_3$), 125.5, 125.7 (Ar), 126.0 (q, J = 4.1 Hz, CF_3-C=$\underline{C}$), 129.6 (q, J = 32.3 Hz, CF_3-$\underline{C}$), 137.2, 143.0 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.9 (CF_3). MS (EI) *m/z* 372 (M^+); HRMS (EI) Calcd for $C_{18}H_{10}F_6S$ (M^+); 372.0407. Found: 372.0402.

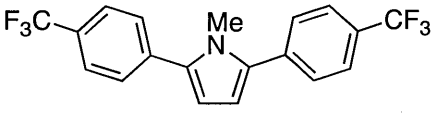
3-Methyl-2,5-bis(4-trifluoromethylphenyl)thiophene (**14**)



Chemical Formula: $C_{19}H_{12}F_6S$
Exact Mass: 386.0564
Molecular Weight: 386.3540

78% yield, colorless solid, mp 59.5-60.5 °C, Rf = 0.48 (hexane : AcOEt = 10 : 1). IR (KBr) 2924, 2360, 1409, 1068, 1015, 862 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H, Me), 7.16 (s, 1H, Ar), 7.50-7.60 (m, 8H, Ar). ^{13}C NMR ($CDCl_3$) δ 15.2 (Me), 124.1 (q, J = 271.3 Hz, $\underline{C}F_3$)*, 126.6 (Ar), 125.6 (q, J = 3.3 Hz, CF_3-C=$\underline{C}$), 125.9 (q, J = 3.3 Hz, CF_3-C=$\underline{C}$), 128.7, 128.9 (Ar), 129.4 (q, J = 33.2 Hz, F_3C-$\underline{C}$)*, 135.7, 137.0, 137.3, 137.8, 141.0 (Ar) (*two carbon peaks are overlapped.). ^{19}F NMR ($CDCl_3$) δ -62.9, -62.9 (CF_3). MS (EI) *m/z* 386 (M^+); HRMS (EI) Calcd for $C_{19}H_{12}F_6S$ (M^+); 386.0564. Found: 386.0551.

2,5-Bis(4-trifluoromethylphenyl)-N-methylpyrrole (**15**)

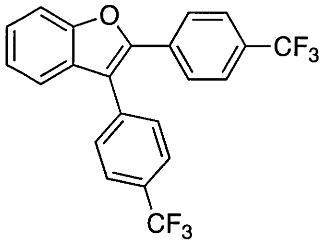


Chemical Formula: $C_{19}H_{13}F_6N$
Exact Mass: 369.0952
Molecular Weight: 369.3036

79% yield, colorless solid, mp 155-157 °C, Rf = 0.50 (hexane : AcOEt = 10 : 1). IR (KBr) 1610, 1456, 1416, 1321, 1179, 1132, 1109, 848 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.54 (s, 3H, Me), 6.32 (s, 2H, Ar), 7.49 (d, J = 8.3 Hz, 4H, Ar), 7.59 (d, J = 8.3 Hz, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 34.6 (Me), 110.4 (Ar), 124.1 (q, J = 272 Hz, $\underline{C}F_3$), 125.5 (q, J = 3.3 Hz, CF_3-C=$\underline{C}$), 128.6 (Ar), 128.9 (q, J = 32.6 Hz, CF_3-$\underline{C}$), 136.5, 136.6 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.8 (CF_3). MS (EI) *m/z* 369 (M^+); HRMS (EI) Calcd for

$C_{19}H_{13}F_6N$ (M^+); 369.0952. Found: 369.0973.

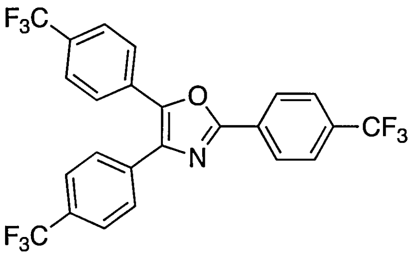
2,3-Bis(4-trifluoromethylphenyl)-2-benzofuran (**16**)



Chemical Formula: $C_{22}H_{12}F_6O$
Exact Mass: 406.0792
Molecular Weight: 406.3205

51% yield, colorless solid, mp 118-120 °C, Rf = 0.43 (hexane : AcOEt = 10 : 1). IR (KBr) 2360, 1930, 1475, 1258, 1210, 1015 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33 (dd, J = 7.8, 7.3 Hz, 1H, Ar), 7.44 (dd, J = 7.8, 7.4 Hz, 1H, Ar), 7.52 (d, J = 7.8 Hz, 1H, Ar), 7.61-7.66 (m, 1H, Ar), 7.63 (d, J = 7.8 Hz, 2H, Ar), 7.65 (d, J = 7.8 Hz, 2H, Ar), 7.76 (d, J = 7.8 Hz, 2H, Ar), 7.80 (d, J = 7.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 111.5, 118.0, 120.1, 123.7 (Ar), 124.0 (q, J = 272.3 Hz, $\underline{C}F_3$), 124.2 (q, J = 271.1 Hz, $\underline{C}F_3$), 125.6 (q, J = 3.5 Hz, CF_3-C=$\underline{C}$) , 125.8 (q, J = 3.5 Hz, CF_3-C=$\underline{C}$), 126.2, 127.2, 129.4, 130.1 (Ar), 130.4 (q, J = 33.1 Hz, CF_3-$\underline{C}$), 130.5 (q, J = 32.8 Hz, CF_3-$\underline{C}$), 133.6, 136.3, 149.5, 154.3 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.9, -63.2 (CF_3). MS (EI) *m/z* 406 (M^+); HRMS (EI): Exact mass calcd for $C_{22}H_{12}F_6O$ (M^+); 406.0792. Found: 406.0789.

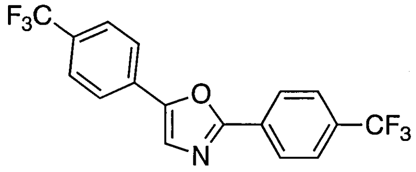
2,3,5-Tris(4-trifluoromethylphenyl)oxazole (**19**)



Chemical Formula: $C_{24}H_{12}F_9NO$
Exact Mass: 501.0775
Molecular Weight: 501.3438

76% yield, mp 148-150 °C, colorless solid. Rf = 0.34 (hexane : AcOEt = 10 : 1). IR (KBr) 2360, 1561, 1326, 1161, 1109, 1016 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.68 (m, 4H, Ar), 7.75-7.78 (m, 4H, Ar), 7.82 (d, J = 7.8 Hz, 2H, Ar), 8.25 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 123.8 (q, J = 272.9 Hz, $F_3\underline{C}$)*, 124.0 (q, J = 272.2 Hz, $F_3\underline{C}$), 125.9 (q, J = 3.3 Hz, CF_3-C=$\underline{C}$), 126.1 (q, J = 3.4 Hz, CF_3-C=$\underline{C}$), 126.1 (q, J = 3.3 Hz, CF_3-C=$\underline{C}$), 126.8, 126.9, 128.4, 129.8 (Ar), 130.7 (q, J = 33.1 Hz, F_3C-$\underline{C}$), 131.1 (q, J = 33.0 Hz, F_3C-$\underline{C}$), 131.4 (Ar), 132.5 (q, J = 33.1 Hz, F_3C-$\underline{C}$), 135.3, 137.3, 145.7, 159.7 (Ar) (* two carbon peaks are overlapped.). ^{19}F NMR ($CDCl_3$) δ -63.1, -63.3, -63.3 (CF_3). MS (EI) *m/z* 501 (M^+); HRMS (EI): Exact mass calcd for $C_{24}H_{12}F_9NO$ (M^+); 501.0775. Found: 501.0767.

2,5-Bis(4-trifluoromethylphenyl)oxazole (**20**)

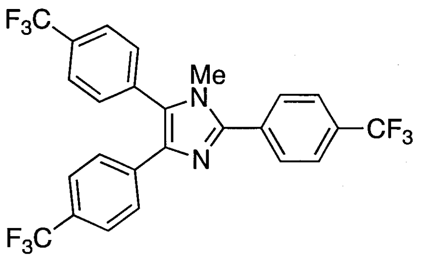


Chemical Formula: $C_{17}H_9F_6NO$
Exact Mass: 357.0588
Molecular Weight: 357.2499

21% yield, colorless solid, mp 115-116 °C, Rf = 0.23 (hexane : AcOEt = 10 : 1). IR (KBr) 3129, 1619, 1494, 1420, 1320, 1166, 1140, 1107, 1073, 1057, 1014, 952, 852, 837 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.52 (s, 1H, Ar), 7.63-7.69 (m, 4H, Ar), 7.76 (d, J = 8.3 Hz, 2H, Ar), 8.15 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 123.8 (q, J = 272.0 Hz, $F_3\underline{C}$), 123.9 (q, J = 272.0 Hz, $F_3\underline{C}$), 124.4, 125.5 (Ar), 125.9 (q, J = 3.3 Hz, F_3C-C=$\underline{C}$), 126.1 (q, J = 3.3 Hz, F_3C-C=$\underline{C}$), 126.7, 130.1 (Ar), 130.4 (q, J = 32.3 Hz, F_3C-$\underline{C}$), 130.9 (Ar) 132.2 (q, J = 33.1 Hz, F_3C-$\underline{C}$), 150.6, 160.5 (Ar). ^{19}F NMR

($CDCl_3$) δ -59.1, -59.2 (CF_3). MS (EI) *m/z* 357 (M^+); HRMS (EI): Exact mass calcd for $C_{17}H_9F_6NO$ (M^+); 357.0588. Found: 357.0571.

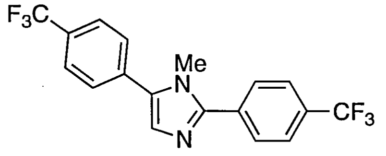
2,3,5-Tris(4-trifluoromethylphenyl)-1-methylimidazole (**21**)



Chemical Formula: $C_{25}H_{15}F_9N_2$
Exact Mass: 514.1092
Molecular Weight: 514.3856

59% yield, colorless solid, mp 200-202 °C, Rf = 0.52 (hexane : AcOEt = 4 : 1). IR (KBr) 2926, 2361, 1928, 1470, 1455, 1324, 1132, 1073, 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.57 (s, 3H, Me), 7.51 (d, *J* = 8.8 Hz, 2H, Ar), 7.57 (d, *J* = 8.5 Hz, 2H, Ar), 7.62 (d, *J* = 8.5 Hz, 2H, Ar), 7.79-7.80 (m, 4H, Ar), 7.91 (d, *J* = 8.0 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.4 (Me), 123.7 (q, *J* = 272.1 Hz, $F_3\underline{C}$), 123.8 (q, *J* = 271.2 Hz, $F_3\underline{C}$), 124.1 (q, *J* = 272.1 Hz, $F_3\underline{C}$), 125.2 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 125.6 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 126.3 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 127.0 (Ar), 128.7 (q, *J* = 32.2 Hz, $F_3C\text{-}\underline{C}$), 129.2, 130.6 (Ar), 131.0 (q, *J* = 33.3 Hz, $F_3C\text{-}\underline{C}$), 131.2, (Ar), 131.2 (q, *J* = 33.1 Hz, $F_3C\text{-}\underline{C}$), 133.8, 134.0, 137.5, 137.7, 147.4 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.9, -63.0, -63.0 (CF_3). MS (EI) *m/z* 514 (M^+); HRMS (EI): Exact mass calcd for $C_{25}H_{15}F_9N_2$ (M^+); 514.1092. Found: 514.1090.

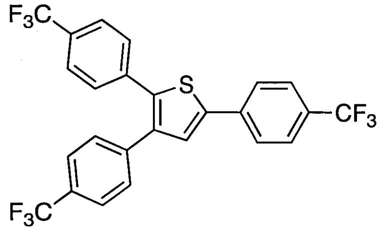
2,5-Bis(4-trifluoromethylphenyl)-1-methylimidazole (**22**)



Chemical Formula: $C_{18}H_{12}F_6N_2$
Exact Mass: 370.0905
Molecular Weight: 370.2917

39% yield, colorless solid, mp 155-157 °C, Rf = 0.23 (hexane : AcOEt = 4 : 1). IR (KBr) 2359, 1414, 1179, 1132, 1072, 851 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H, Me), 7.31 (s, 1H, Ar), 7.59 (d, *J* = 7.8 Hz, 2H, Ar), 7.74 (d, *J* = 7.8 Hz, 2H, Ar), 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 7.85 (d, *J* = 8.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.9 (Me), 123.9 (q, *J* = 272.1 Hz, $F_3\underline{C}$), 124.0 (q, *J* = 271.2 Hz, $F_3\underline{C}$), 125.4 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 125.8 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 128.6, 128.9, 129.0 (Ar), 130.0 (q, *J* = 32.3 Hz, $F_3C\text{-}\underline{C}$), 130.6 (q, *J* = 33.1 Hz, $F_3C\text{-}\underline{C}$), 133.4, 133.9, 134.8, 148.7 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.02, -63.09 (CF_3). MS (EI) *m/z* 370 (M^+); HRMS (EI): Exact mass calcd for $C_{18}H_{12}F_6N_2$ (M^+); 370.0905. Found: 370.0893.

2,3,5-Tris(4-trifluoromethylphenyl)thiophene



Chemical Formula: $C_{25}H_{13}F_9S$
Exact Mass: 516.0594
Molecular Weight: 516.4213

Cs_2CO_3 (326 mg, 1 mmol, 2.0 equiv) was dried over *in vacuo* at 150 °C for 3 h and **12** (186 mg, 0.5 mmol), 4-trifluoromethylphenyl iodide (0.14 mL, 1 mmol, 2.0 equiv) and DMA (1 mL) were added under Ar atmosphere. The mixture was degassed for 3 times, $[Pd(phen)_2](PF_6)_2$ (19 mg, 0.025 mmol, 5 mol%) was added to the mixture, and this was heated at 150 °C for 20 h. The resulting mixture was filtrated through celite pad and concentrated *in vacuo.*

The residue was purified by preparative recycling GPC to give the title compound (86 mg, 0.16 mmol, 33%) as a colorless solid. mp 182-184 °C; IR (KBr) 2928, 2360, 1417, 1240, 1193, 869 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.31 (d, J = 8.3 Hz, 2H, Ar), 7.34 (d, J = 8.3 Hz, 2H, Ar), 7.35 (s, 1H, Ar), 7.47 (d, J = 8.3 Hz, 2H, Ar), 7.51 (d, J = 8.3 Hz, 2H, Ar), 7.85 (d, J = 8.3 Hz, 2H, Ar), 7.65 (d, J = 8.3 Hz, 2H, Ar); ^{13}C NMR (CDCl$_3$) δ 123.9 (q, J = 272.1 Hz, $F_3\underline{C}$), 124.0 (q, J = 271.2 Hz, $F_3\underline{C}$), 124.0 (q, J = 271.2 Hz, $F_3\underline{C}$), 125.6 (q, J = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 125.7 (q, J = 3.8 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 125.8 (Ar), 126.1 (q, J = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 127.4, 129.4, 129.4 (Ar), 129.5 (q, J = 30.8 Hz, $F_3C\text{-}\underline{C}$), 130.0 (q, J = 33.0 Hz, $F_3C\text{-}\underline{C}$), 130.1 (q, J = 32.8 Hz, $F_3C\text{-}\underline{C}$), 136.7, 137.0, 138.5, 138.9, 139.4, 142.5 (Ar); ^{19}F NMR (CDCl$_3$) δ -62.8, -63.1, -63.1 (CF$_3$); MS (EI) *m/z* 516 (M$^+$); HRMS (EI): Exact mass calcd for $C_{25}H_{13}F_9S$ (M$^+$); 516.0594. Found: 516.0601.

References and notes

(1) For recent reviews of cross-coupling reactions, see: (*a*) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, M.; Lemaire, E. *Chem. Rev.* **2002**, *102*, 1359. (*b*) *Metal–Catalyzed Cross-Coupling Reactions*, 2nd Ed; Meijere, de A.; Diederich, F. Eds.; Wiley-VHC: Weinheim, 2004. (*c*) Corbet, J.-P.: Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (*d*) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.

(2) Selected examples of Pd catalysis: (*a*) Okazawa, T.: Satoh, T.: Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (*b*) Kalyani, D.; Deprez, N. R. Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (*c*) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (*d*) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (*e*) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (*f*) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (*g*) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996. (*h*) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (*i*) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (*j*) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (*k*) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (*l*) Mori, 1.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (*m*) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 201. (*n*) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622.

(3) Selected examples of Rh catalysis: (*a*) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (*b*) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (*c*) Proch, S.; Kempe, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 3135. (*d*) Kanbe, M.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2007**, *129*, 8080. (*e*) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (*f*) Berman, A. M.; Lewis, J. C.; Bergman, R. G. J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926.

(4) Selected examples of Ni catalysis: Canvient, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733.

(5) Selected examples of Ir catalysis: (*a*) Fujita, K.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926. *(b)* Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem. Int. Ed.* **2009**, *48,* 3644.

(6) Selected examples of Cu catalysis: (*a*) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (*b*) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (*c*) Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598. (*d*) Besselivre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett. 2008*, 10, 4029.

(7) Selected examples of Ru catalysis: (*a*) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (*b*) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (*c*) Oi, S.; Funayama, R.; Hattori, T.; Inoue, Y. *Tetrahedron* **2008**, *64*, 6051.

(8) (*a*) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621. (*b*) Shibahara, F.; Yoshida, A.; Murai, T. *Chem. Lett.* **2008**, *37*, 646. (*c*) Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron* **2009**, *65*, 5062. (*d*) Shibahara, F.; Sugiura, R.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566. (*e*) Tahara, S.; Shibahara, F.; Maruyama, T.; Murai, T. *Chem. Commum.* **2009**, 7009.

(9) $[Pd(phen)_2](PF_6)_2$ has been used as a catalyst for copolymerization of CO and olefins, see: (*a*) Durand, J.; Scarel, A.; Milani, B.; Seraglia, R.; Gladiali, S.; Carfagna, C.; Binotti, B. *Helv, Chim. Acta* **2006**, *89*, 1752. and for reductive carbonylation of nitroarenes, see: (*b*) Bontempi, A.; Alessio, E.; Chanos, A.; Mestroni, G. *J. Mol. Catal.* **1987**, *42*, 67. (*c*) Izumi, Y.; Satoh, Y.; Kondoh, K.; Urabe, K. *J. Mol. Catal.* **1992**, *72*, 37.

(10) Diarylated thiophene **12** was coupled with another aryl iodide **2a** under the identical conditions, but the reaction is significantly slow (33% yield for 20 h).

(11) A similar *ortho*-site selectivity is observed for uncatalyzed radical aromatic substitution reactions reported by Davies, see: D. I. Davies, D. H. Hey and B. Summers, *J. Chem. Soc. (C)*, **1971**, 2681.

(12) Brink, J. G.; Arends, I.; Hoogenraad, M.; Verspui, G.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 497.

(13) Trend, R. M.; Ramtohul, K. Y.; Stoltz, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

(14) Roy, S.; Eastman, A.; Gribble, G. W. *Tetrahedron* **2006**, *62*, 7838.

(15) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834.

(16) Geng, Y.; Culligan, S.; Trajkovska, A.; Wallace, J.; Chen, S. *Chem. Mater.* **2003**, *15*, 542. (b) Jo, J.; Chi, C.; Höger, S.; Wegner, G.; Yoon, D. *Chem. Eur. J.* **2004**, *10*, 2681. (c) Geng, Y.; Trajkovska, A.; Katsis, D.; Ou, J.; Culligan, S.; Chen, S. *J. Am. Chem. Soc.* **2002**, *124*, 8337. (d) Ding, J.; Day, M.; Robertson, G; Roovers, J. *Macromolecules* **2002**, *35*, 3474. (e) Grisorio, R.; Mastrorilli, P.; Nobile, C.; Romanazzi, G..; Suranna, G.; Meijer, E. *Tetrahedron Letters* **2004**, *45*, 5367. (f) Lee, S.; Toshikazu, N.; Tetsuo, T. *Org. Lett.* **2001**, *3*, 2005.

(17) F. Derridj; S. Djebbar; O. Benali-Baitich; H. Doucet, *J. Organomet. Chem.* **2008**, *693*, 135.

(18) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

(19) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.

(20) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835.

(21) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897.

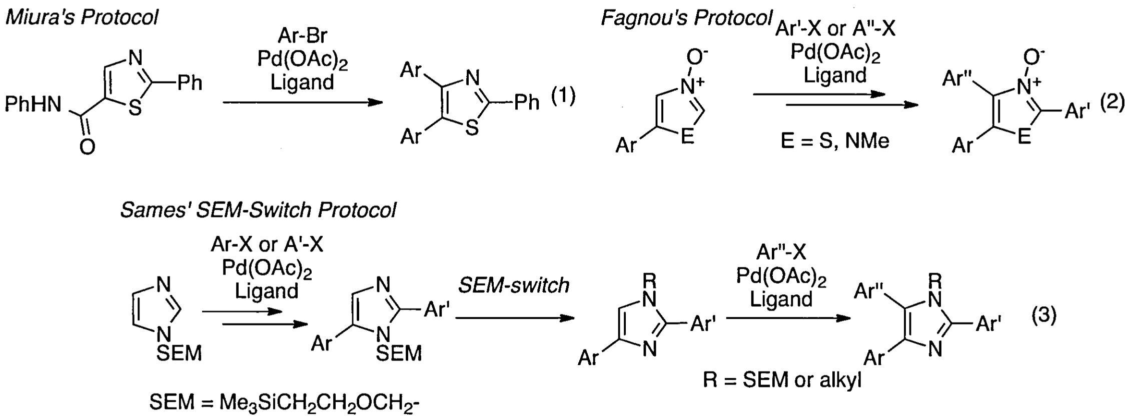
Chapter 5

A Sequential Direct Arylation Reaction of Azoles Catalyzed by Phenanthroline-modified Palladium Complexes

A sequential direct C-H bond arylation reactions of simple azoles by phenanthroline-modified Pd complex were carried out. Direct C5 and C2 arylation reactions of azoles were achieved by $[Pd(phen)_2](PF_6)_2$ under controlled conditions, respectively. Direct C4 arylation of azoles was also achieved by using the present Pd-phenanthroline system. Moreover, the synthesis of Tie-2 tyrosine kinase inhibitor was achieved by the present sequential arylation strategy. Mechanistic studies on the C2 and C4 direct arylation reaction of azoles are also described.

5.1. Introduction

In chapter 4, the author described syntheses of a wide variety polyarylated heteroaromatics by means of Pd-phenanthroline catalyzed direct multiple C-H bonds arylation reaction. Meanwhile, syntheses of polyarylated heteroaromatics from unsubstituted heteroaromatics with programmable manner have been attractive protocols due to applicable to rapid and diversity-oriented synthesis of bioactive compounds[1] and optoelectronic compounds.[2] In this regard, Miura has recently described a procedure for the synthesis of triarylated azoles that involves 4,5-diarylation of 2-aryl-azoles that contain a directing and sacrificial 5-carboxanilide group (eq 1).[3] Fagnou also reported a method for preparation of triarylated azoles containing three different aryl groups that employs sequential C–H bond arylation of azole *N*-oxides (eq 2).[4]



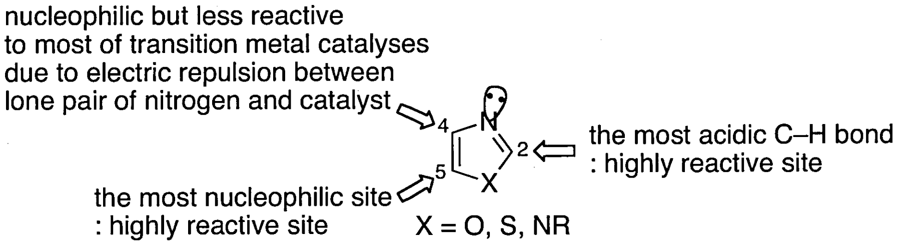


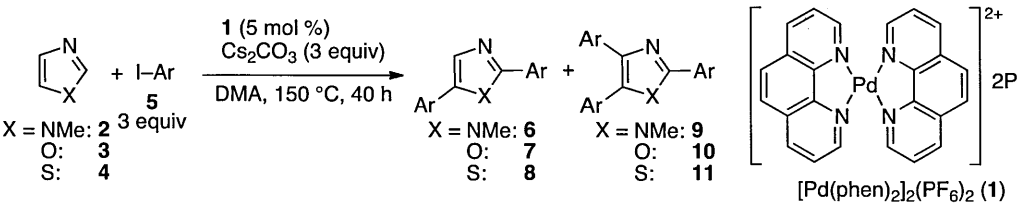
Figure 1. General reaction profiles for azoles in transition metal catalysis

In light of these recent developments, studies of sequential arylation reactions that can be performed using simple and readily available azoles and that overcome problems associated with the low reactivity at C4 azole positions are worthwhile (Figure 1).[5] To circumvent the C4 reactivity issue, Sames has devised a SEM-switch strategy that employs an indirect method for introduction of a C4 aryl group in imidazole.[5] However, this protocol requires SEM protection and deprotection of nitrogen to achieve selective C4 arylation (eq 3). The chapter 4 described that a palladium complex, bearing an sp^2-nitrogen-based ligand, such as 1,10-phenantroline, displays excellent catalytic activity in C–H bond arylation reactions of simple azoles. Moreover, by using $[\mathrm{Pd(phen)_2}](\mathrm{PF_6})_2$ (**1**) as a catalyst for these processes all three sites including C4 in imidazole and oxazole are sequentially arylated in moderately efficient one-pot processes.[6] Furthermore, no additives, such as carboxylic acids,[4a] metal salts,[7] and ammonium salts,[8] are needed in these reactions except for a stoichiometric amount of a base to neutralize the formed hydrogen halides. It is important to note that prior to these findings, metal catalysts with nitrogen-based ligands have rarely been applied to direct C–H arylation reactions. The auther's studies with $[\mathrm{Pd(phen)_2}](\mathrm{PF_6})_2$ have revealed that arylation reactions take place smoothly even at the C4 positions of simple 2,5-diaryl-azoles. Below, the full details of the investigation the author has carried out in this area are described. The observations made in this effort demonstrate the significant synthetic potential of reactions promoted by the new catalytic system. This utility of this methodology is shown by its application to a concise three-step synthesis of the Tie-2 Tyrosine Kinase Inhibitor starting with commercially available *N*-methylimidazole.

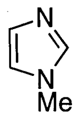
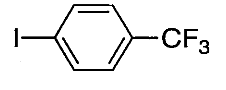
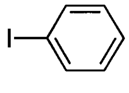
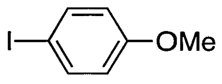
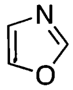
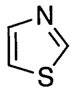
5.2. One-pot multiple C–H direct arylation of azoles

In chapter 4, the author described that a palladium catalyst bearing an sp^2-nitrogen-based ligand, such as 1,10-phenantroline shows excellent catalytic activity for C–H bond arylation of simple azoles, and the author also found that all three C–H bonds even at C4 position in imidazole and oxazole were arylated with *p*-trifluoromethylphenyl iodide at once by $[Pd(phen)_2](PF_6)_2$ (**1**) as a catalyst.[9] Notably, the reaction does not need any additives such as carboxylic acid,[10] metal salt,[11] and ammonium salt[8] except a stoichiometric amount of base to abstract hydrogen halide formed. Subsequently, scope of the triarylation of azoles with aryl iodides was examined. The results are summarized in Table 1. Reactions of *N*-methylimidazole (**2**) with 3 equiv of the aryl iodides **5a-c** in DMA solutions containing catalyst **1** (5 mol %) and Cs_2CO_3 (3 equiv) gave the corresponding triarylated products **9** in good yields along with diarylated products **6** in 40-44% yields (Table 1, entries 1-3). Reactions of oxazole (**3**) with aryl iodides under these conditions also gave the triarylated products **10** in moderate to high yields (entries 4-6). In contrast, triarylated products **11** were not produced when thiazole (**4**) and aryl iodides were subjected to the palladium catalyzed reaction conditions. Instead, diarylated products **8** were generated exclusively in 73-99% yields (entries 7-9). The finding that *N*-methylimidazole and oxazole undergo triarylation reactions demonstrates that by using the $[Pd(phen)_2](PF_6)$ catalyst C4 arylation of 1,3-azoles takes place. In addition, the triarylation process can be applied to the other types of azoles, exemplified by transformation of *N*-methylpyrazole (**12**) to the tris-*p*-trifluoromethylphenyl adduct **13** in a moderate yield (eq. 4).

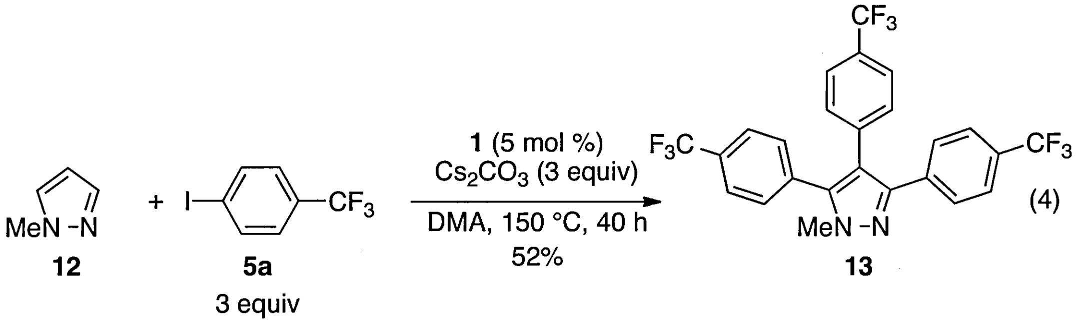
Table 1. One-pot Direct Multiple Arylation Reactions of Azoles Catalyzed by $[Pd(phen)_2](PF_6)_2$[a]



$[Pd(phen)_2]_2(PF_6)_2$ (**1**)

Entry	Azoles	5	Product (isolated yield)	
			di	tri
1	 **2**	 **5a**	**6a**(39%)	**9a**(59%)
2		 **5b**	**6b**(31%)	**9b**(61%)
3		 **5c**	**6c**(40%)	**9c**(44%)
4	 **3**	**5a**	**7a**(21%)	**10a**(76%)
5		**5b**	**7b**(34%)	**10b**(55%)
6		**5c**	**7c**(30%)	**10c**(49%)
7	 **4**	**5a**	**8a**(73%)[b]	**11a**(trace)
8		**5b**	**8b**(93%)[b]	**11b**(trace)
9		**5c**	**8c**(99%)[b]	**11c**(trace)

[a] The reactions were carried out with 0.5 mmol of azoles **2**-**4**. [b] The reaction was carried out with 6 equiv of aryl iodide for 20 h.



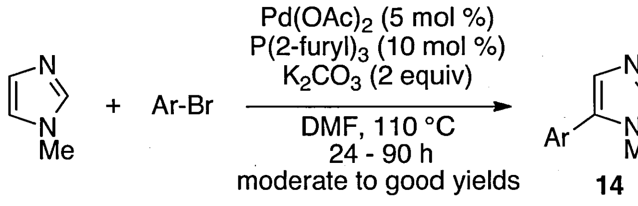
5.3. Sequential arylation of azoles

In order to explore further the unprecedented reactions promoted by the catalytic system described above, stepwise sequential arylation reactions of azoles that enable introduction of three different aryl groups into the azole skeleton were investigated. Inspection of the observations made in earlier efforts suggests that the positional reactivity profile of azoles, in particular imidazole, in palladium-catalyzed C–H bond arylation processes is either C5 ≥ C2 >> C4 or C2 ≥ C5 >> C4 depending on the catalytic system employed.[8,12] As a result, selective arylation at C5 or C2 can be achieved by using the reported catalytic systems. Nevertheless, undesired secondary reactions of the initially formed C5 and C2 arylated products that lead to diarylation and the low efficiencies of arylation reactions of monoarylated substrates are issues that need to be solved in order to promote efficient sequential arylation processes. Therefore, further investigations of the reaction conditions for arylation on each three positions of *N*-methylimidazole were carried out.

5.3.1. C5-arylation of *N*-methylimidazole

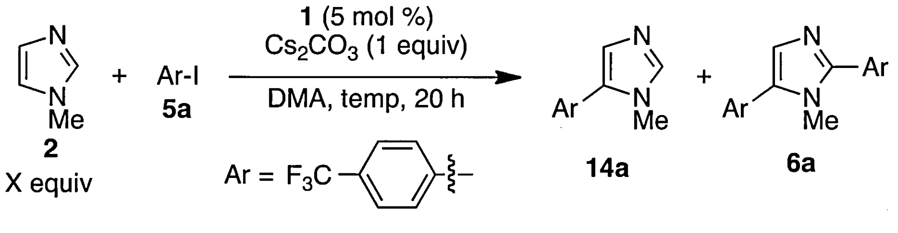
A number of C5 arylation reactions of azoles have been described previously.[3,6,13] In the reported processes, C5-aryl-azoles often display a higher reactivity at C2 positions compared to those of unsubstituted azoles. Thus C5,C2 diarylation of azoles often serves as a yield diminishing side reaction in processes designed to form mono-C5 arylated products. In this context, Bellina and Rossi developed a selective C5 arylation reaction that employs $Pd(OAc)_2/P(2\text{-furyl})_3/K_2CO_3$ as the catalytic system (eq. 5).[13] Although this process is relatively slow, it does furnish the C5-arylated imidazoles **14** selectively and in good yield.

To investigate the applicability of $[Pd(phen)_2](PF_6)_2$ to monoarylation reactions, the author has examined reactions of *N*-methylimidazole (**2**) under controlled conditions. The results, displayed in Table 2, show that reaction of **2** with a nearly stoichiometric amount of arly iodide **5a** at 150 °C for 20 h gave the diaryl-imidazole **6a** in quantitative yield based on **5a** (entry 1). Reaction under the same conditions carried out at the 140 °C led to formation of the monoarylated product **14a** in 46% yield, but the diarylated product **6a** is still formed in 54% yield. Although lowering the temperature further (130 °C) enables **14a** to be produced in higher yield than **6a**, the total yield of **14a** and **6a** at this temperature is lower (entry 3). The quantity of *N*-methylimidazole (**2**) has an impact on ratio of monoarylated **14a** and diarylated **6a** products. Specifically, the selectivity for formation of **14a** was increased when increasing amounts of **2** were employed (entries 4-6) and the use of 10 equiv of **2** resulted in exclusive generation of the monoarylation product (entry 6). Owing to ready availability of **2**, reactions of 10 equiv of **2** with several aryl iodides were probed. As the results in Scheme 1 show, each of these reactions gave the corresponding monoarylated product **14** in high yield.



(5)

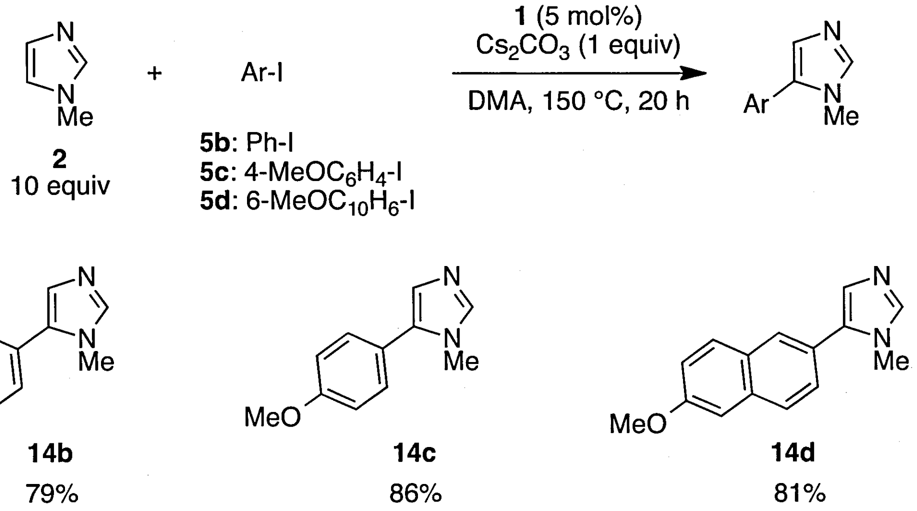
Table 2. Optimization of C5 Direct Monoarylation of *N*-Methylimidazole Catalyzed by $[Pd(phen)_2](PF_6)_2$[a]



Entry	equiv of **2**	Temp (°C)	Yield(%)[a]	
			14a	**6a**
1	1.1	150	trace	93
2	1.1	140	46	54
3	1.1	130	40	36
4	2	150	33	58
5	3	150	59	40
6	10	150	74	trace

[a] The reactions were carried out with 0.5 mmol of *p*-$CF_3C_6H_4$-I. [b] Isolated yields based on the amount of *p*-$CF_3C_6H_4$-I.

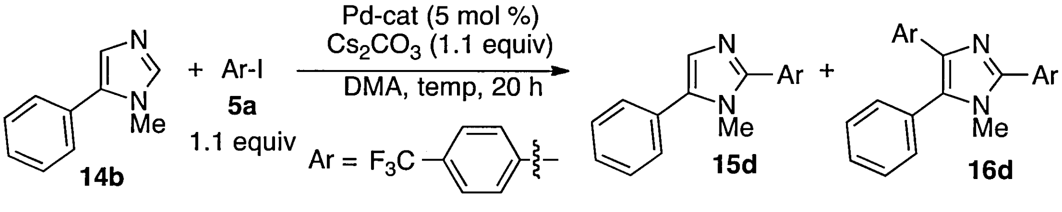
Scheme 1. Scope of C5-Monoarylation Reaction of *N*-Methylimidazole



5.3.2. C2-arylation of *N*-methylimidazole

Selective C2 arylation reactions of C5-aryl-imidazoles **14** was investigated next. As the results previously shown in Table 2, the reactions of these substrates with aryl iodides employing catalyst **1** preferentially generated diarylated products. These observations clearly show that the new catalytic system is effective for conducting efficient C2 arylation reactions. Optimization of the conditions used for this process were carried out employing *N*-methyl-5-phenylimidazole (**14b**) and *p*-trifluoromethylphenyl iodide (**5a**). During the investigation, formation of the undesired triarylated product **16d** was an issue. The results displayed in Table 3 indicate that reactant concentration has an effect on the selectivity for production of the monoarylated product **15d** versus the triaryl-adduct **16d** (entries 1 and 2). The counter anion of the catalysts also governs the outcome of this process with the highest yield and selectivity for formation of **15d** being attained when the hexafluorophosphate containing catalyst **1** was used (entries 2-4). The optimum temperature for this reaction is 150 °C, since the use of both higher (160 °C) and lower (140 °C) temperatures led to lower yields of **15d** (entries 5 and 6). Thus, the reaction conditions listed in entry 2 were used in subsequent reactions. In addition, as part of mechanistic investigations described below, the author observed that the triarylation reaction (further C4-arylation) is significantly suppressed when galvinoxyl is employed as an additive, as demonstrated by the formation of **15d** in 74% yield and no triarylated product (entry 7). This effect is likely the consequence of the operation of different mechanisms for the reactions occurring at different imidazole positions (see below).

Table 3. Optimization of the Direct C2 Arylation of *N*-Methyl-5-phenylimidazole[a]

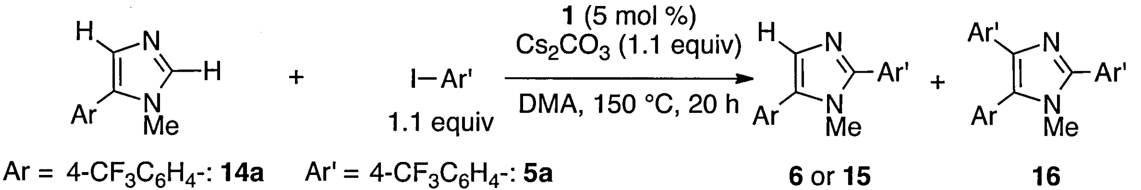


Entry	Pd-cat	conc.(M)	Temp (°C)	Yields(%)[b]	
				15d	**16d**
1	**1**	1	150	46	22
2	**1**	**0.5**	**150**	**58**	**14**
3	Pd(phen)(OAc)$_2$	0.5	150	57	29
4	Pd(phen)(tfa)$_2$	0.5	150	42	16
5	**1**	0.5	160	43	22
6	**1**	0.5	140	37	27
7[c]	**1**	0.5	150	74	not detected

[a] The reactions were carried out with 0.25 mmol of **14b**. [b] Isolated yields. [c] Galvinoxyl (1 equiv) was added as an additive.

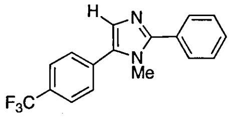
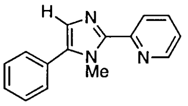
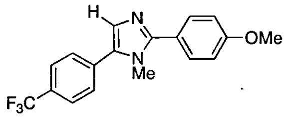
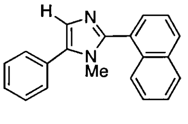
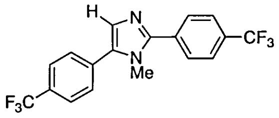
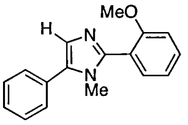
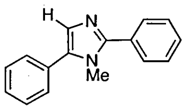
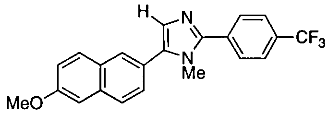
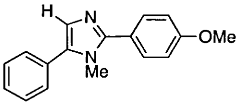
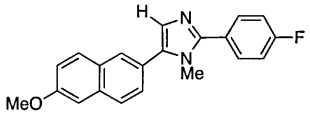
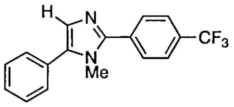
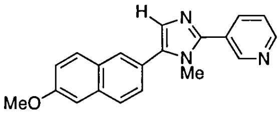
An exploration of the substrate scope of the process provided the results summarized in Table 4. Firstly, the electronic effects of substituents in both the aryl iodides **5** and the C5 aryl ring of imidazoles **14** on the reaction were examined (entries 1-9). The results indicate that the yields of products **6** and **15** are relatively higher when an electron-rich halide **5c** is used as the substrate (entries 2, 5, 8). In addition, the imidazole **14a**, which possesses an electron-withdrawing *p*-trifluoromethylphenyl group at C5, reacted sluggishly independent of the aryl iodide used and, as a result, longer times were needed to obtain satisfactory yields (entries 1-3). By using the new catalytic system, heteroaryl iodides, such as 2- or 3-pyridyl iodide, undergo coupling with imidazoles **14** (entries 10, 15). Sterically hindered 1-naphthyl and 2-tolyl iodide also react with imidazoles to give the corresponding arylated products **15h**, **15m**, and **15n** in moderate to high yields (entries 11,16,17). In addition, the presence of an *o*-methoxy group on the aryl halides, which can possibly bind to the catalyst, does not impede the reaction as demonstrated by the production of **15h** and **15n** in moderate to excellent yields (entries 12, 18). In this case also, the yields were improved when galvinoxyl is used as an additive (entries 1, 5, 6, 10, 13, 14).

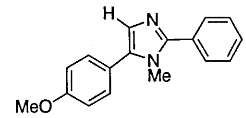
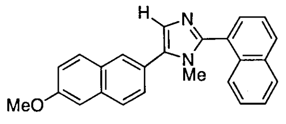
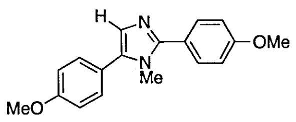
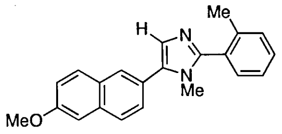
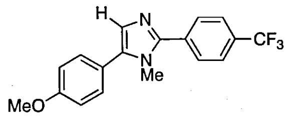
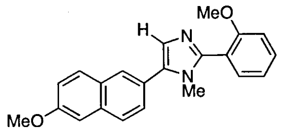
Table 4. Scope of the Direct C2 Arylation reactions of C5-ArylImazoles[a]



Ar = 4-$CF_3C_6H_4$-: **14a**
Ph-: **14b**
4-$MeOC_6H_4$-: **14c**
6-$MeOC_{10}H_6$-: **14d**

Ar' = 4-$CF_3C_6H_4$-: **5a**
Ph-: **5b**
4-$MeOC_6H_4$-: **5c**
6-$MeOC_{10}H_6$-: **5d**

Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **15a**	59 (12)	10	 **15g**	48 (nd)
2	 **15b**	quant (–)	11	 **15j**	69 (nd)
3	 **6a**	54 (12)	12	 **15h**	52 (nd)
4	 **6b**	71 (13)	13	 **15i**	53 (nd)
5	 **15c**	76 (13)	14	 **15j**	59 (nd)
6	 **15d**	58 (29)	15	 **15k**	69 (nd)

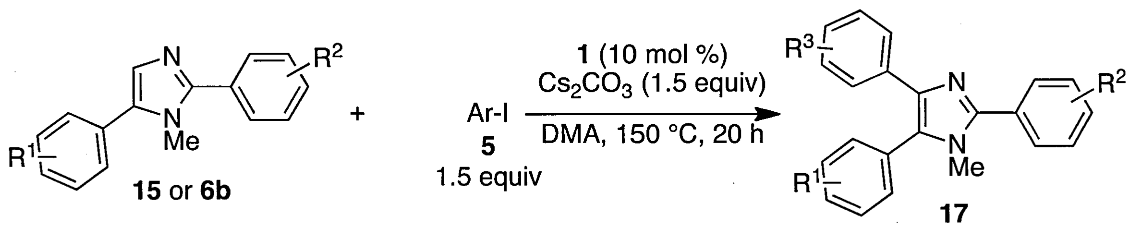
7	 **15e**	59 (20)	16	 **15l**	82 (nd)
8	 **6c**	71 (9)	17	 **15m**	68 (nd)
9	 **15f**	55 (19)	18	 **15n**	92 (nd)

[a] The reactions were carried out with 0.25 mmol of **14.** [b] Isolated yields. The yields of the triarylated byproduct are shown in parentheses. Also, nd in parentheses indicates not determined. [c] The reaction was carried out for 40 h. [d] Galvinoxyl (1 equiv) was used as an additive. [e] Small amounts of the corresponding triarylated products were observed in the crude mixtures probably due to

5.3.3. C4-arylation of *N*-methylimidazole

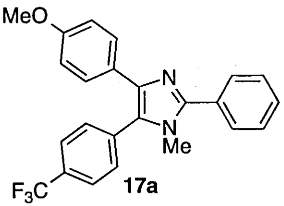
C4 arylation reactions of the azoles studied in the past have been promoted by using directing groups or substrate activation as shown in eq 2.[3,4] The reaction of 2,5-diphenyloxazole with bromobenzene, which affords the C4 arylated product, described by Fagnou was the sole example of a direct C4 arylation process.[4a] As a result of this void, the auther's attention turned to an investigation of C4 arylation reactions of azoles using [Pd(phen)$_2$](PF$_6$)$_2$ as the catalyst. The initial reactions were carried out with imidazole **15a**, 1.5 equiv of 4-methoxyphenyl iodide **5c**, and 10 mol % of catalyst **1**. As the author expected, the C4 arylation process proceeded efficiently to give the triaryl product **17a** in quantitative yield (Table 5). In addition, reactions of several substrates bearing electron donating and withdrawing groups on the imidazole C2 and C5 aryl groups were carried out under these conditions. The observations show that the new catalytic system is highly compatible with processes that yield adducts **17b-f** in good to excellent yields. Furthermore, this process can be used to couple the diphenyl-imidazole **6b** with the strong electron-withdrawing (*eg*., *p*-nitrophenyl, *p*-ethoxycarbonylphenyl) and electron-donating (*eg*., *p*-dimethylaminophenyl) group substituted iodides **5k**, **5l**, and **5m** to give the corresponding products **17g**, **17h**, and **17i** in good to high yields. Moreover, the reaction takes place when sterically crowded aryl iodide substrates are utilized, as exemplified by the reactions of **6b** with *o*-tolyl and 1-napthyl iodides, **5j** and **5f**, respectively. In these cases the coupling product **17k** and **17l** are produced without significant loss of efficiency.

Table 5. Direct C4 Arylation Reactions of 2,5-Diaryl-*N*-Methylimidazoles[a]

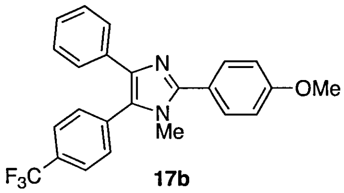


R^1, R^2 = *p*-CF_3, H: **15a**
p-CF_3, *p*-MeO: **15b**
H, *p*-MeO: **15c**
H, *p*-CF_3: **15d**
p-MeO, H: **15e**
p-MeO, *p*-CF_3: **15f**
H, H: **6b**

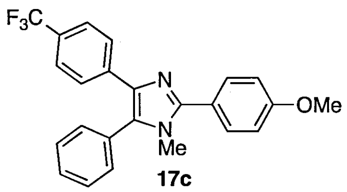
Ar = 4-$CF_3C_6H_4$-: **5a**
Ph-: **5b**
4-$MeOC_6H_4$-: **5c**
1-naphthyl: **5f**
2-MeC_6H_4-: **5j**
4-$NO_2C_6H_4$-: **5k**
4-EtOC(O)C_6H_4-: **5l**
4-$Me_2NC_6H_4$-: **5m**
3-$MeOC_6H_4$-: **5n**



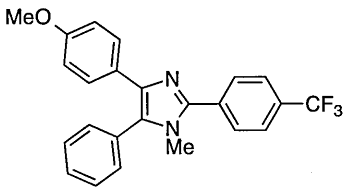
17a
quant.



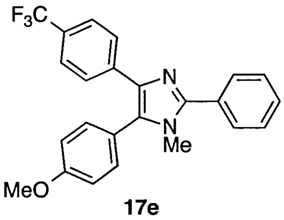
17b
80%



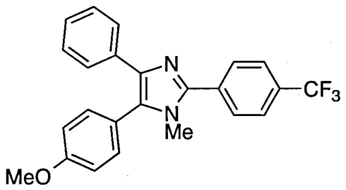
17c
84%



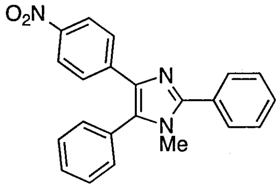
17d
97%



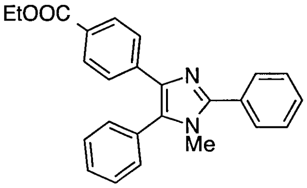
17e
79%



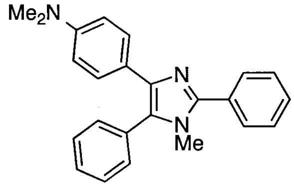
17f
92%



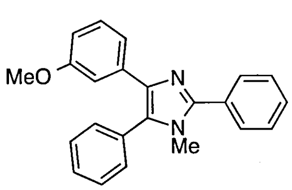
17g
75%



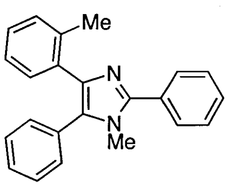
17h
56%[b]



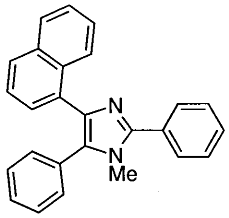
17i
84%[b]



17j
66%



17k
56%



17l
74%

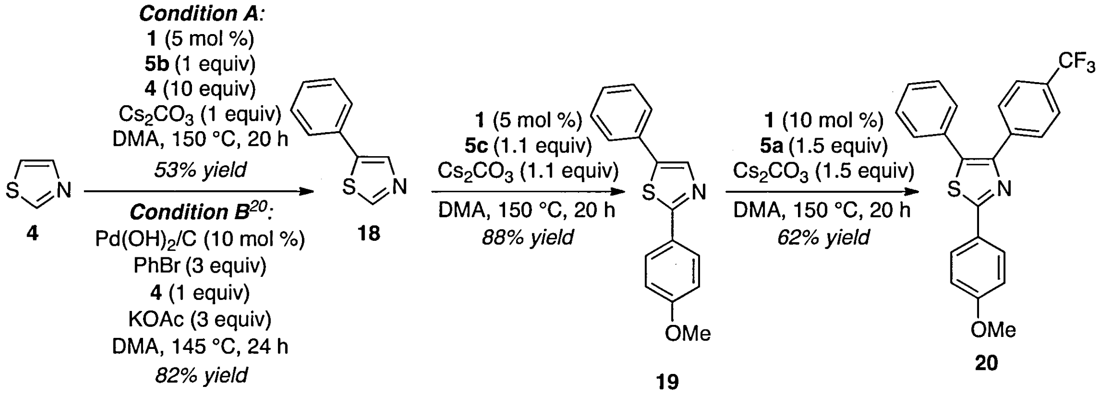
---

[a] The reactions were carried out with 0.125 mmol of **15** or **6b**. Isolated yields are shown. [b] K_2CO_3 (1.5 equiv)

5.3.4. Sequential arylations of thiazole

Previously, Mori[6,14] and Fagnou[15] have observed excellent levels of selectivity in respective direct C2 and C5 monoarylation reactions of thiazole. The author has also examined the applicability of the new catalytic system based on the palladium complex **1** to monoarylation reactions of thiazole. As the results shown in Scheme 2 indicate, C5 selective phenylation of thiazole occurs but only in a moderate yield (Condition A). Therefore, the $Pd(OH)_2/C$ and KOAc system, described by Fagnou, was used to generate phenylthiazole **18** (Condition B). In contrast, selective C2 arylation of **18** with *p*-anisyl iodide with catalyst **1** proceeds smoothly to give the diaryl-thiazole **19** in high yield. Earlier, the author had observed that one-pot triarylation reactions of thiazole take place inefficiently and that the generated product mixtures contain predominantly diaryl-thiazoles (Table 1, entries 7-9). These findings show that C4 arylation reactions of thiazole **18** employing the new catalyst system are slow. In contrast, C4 arylation of the isolated diaryl-thiazole **19** occurred efficiently to give the triarylated product **20** in good yield.

Scheme 2. Sequential Direct Arylation Reactions of Thiazole



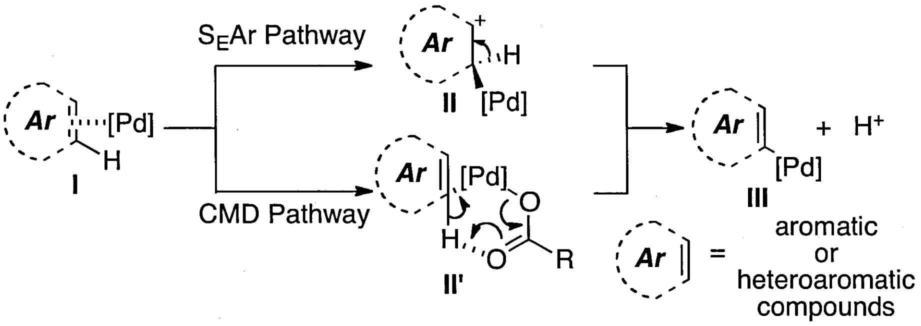
5.4. Mechanistic studies on direct arylations

Mechanisms for closely related direct C-H arylation reactions have been suggested to involve palladation of the aromatic components via electrophilic aromatic substitution (S_EAr) or concerted metallation-deprotonation (CMD) pathways in which carboxylates in the catalyst serve as the base (Scheme 3).[16] An alternative involving radical intemediates has been suggested (Scheme 4).[17,18,19] Although, most of the recent examples of direct C-H arylation reactions can be understood in terms of the CMD pathway, this mechanism is not applicable to the system explored in this study since no carboxylates are present in the catalyst $[Pd(phen)_2](PF_6)_2$. In contrast to these proposals, the author has suggested in previous chapter that, depending on the nature of the substrate, $[Pd(phen)_2](PF_6)_2$ promoted arylation reactions could proceed via radical pathways. This suggestion was based in part on the observed ortho, meta, and para product distributions that match those arising from known radical reactions between aryl iodides and an arenes.[6] In addition, operation of a radical pathway is consistent with the slight perturbation of the product distribution when galvinoxyl was added as to the reaction mixture of benzoxazole (**21**) and **5a** (Scheme 5). Therefore, a radical pathway remains as a plausible alternative for the reactions probed in this effort, even though it is known that radical scavengers like galvinoxyl can decompose[20] or ligate to[21] Pd complexes and influence their catalytic activities.

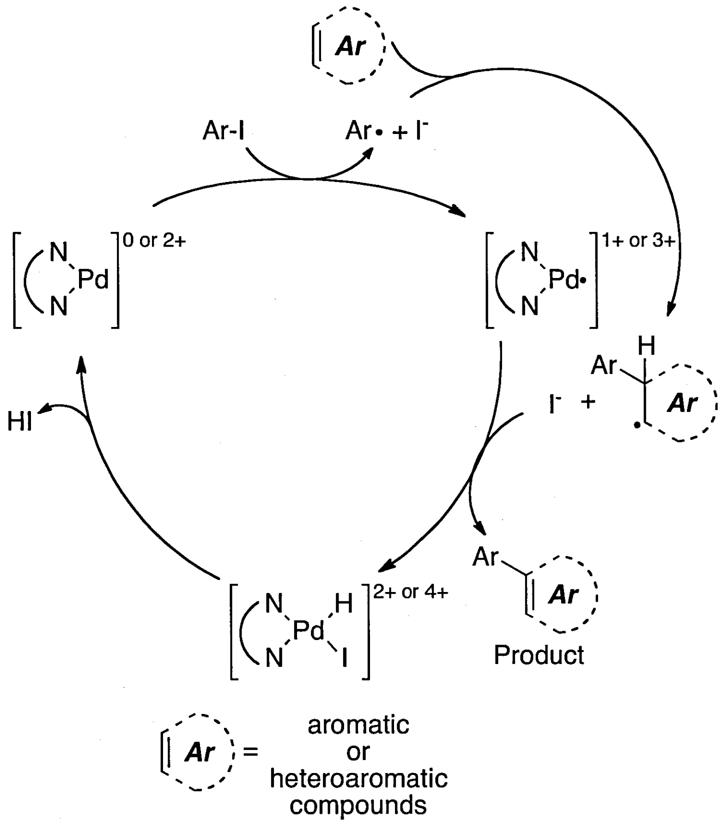
Another consideration is that the $[Pd(phen)_2](PF_6)_2$ catalyzed direct arylation reactions at three different azole positions could follow different mechanistic pathways. In order to gain additional information about the mechanism(s) of these pocessess and, in particular, those that take place at the C2 and C4 positions of azoles, several experiments were carried out. For example, when the C5-aryl-imidazole **14d** was treated with an excess of D_2O under the standard reaction conditions in the absence of an aryl halide, proton-exchange rapidly occurs at the C2 position to give mono-deuterated **14d**-*d* quantitatively (Scheme 6, upper). Since this exchange reaction does not take place in the absence of catalyst **1**, it is clear that it is promoted by the palladium complex through a sequence involving S_EAr type C2 palladation of the imidazole and protonolysis of the resulting Pd-imidazole intermediate.[22] Therefore, electrophilic palladation at C2 takes place smoothly to give Pd-aryl species (**III** in Scheme 3). In addition, the reaction of the relatively electron-deficient imidazole **14a** promoted by $[Pd(phen)_2](PF_6)_2$ takes place more slowly than those of its electron rich analogs (see Table 4, entries 1-3). Based on these results, it is likely that reactions of imidazoles with the catalyst take place preferentially at the C2 position via an S_EAr fashion.

In contrast, the H–D exchange reaction at the C4 position of the diaryl-imidazole **15p** proceeds much more slowly than the C2 exchange process (Scheme 6, lower). Also, reaction of a 1:1 mixture of the electron-deficient and electron-rich diaryl-imidazoles **6a** and **6c** with iodide **5a** affords almost equal amounts of the respective C4-arylated products **9a** and **17m** (Scheme 7). Furthermore, the C4 arylation process was inhibited to an observable degree by the radical trap galvinoxyl, yet C2 arylation reactions were not affected by this substance (Table 3, entries 7, 8 and Scheme 8). These observations suggest that reactions at C2 and C4 pass through different mechanistic pathways. The combined results appear to support the plausible conclusion that the palladation at C4 occurs by an electrophilic aromatic substitution route, whereas, a radical pathway is followed in the reaction at C4. Further investigations are needed to elucidate fully the mechanism of the C4 arylation reactions.

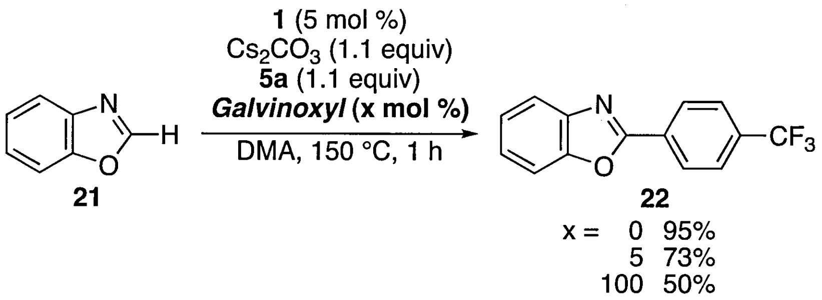
Scheme 3. Concise Mechanism for Palladation via the S_EAr Pathway and CMD Pathways.



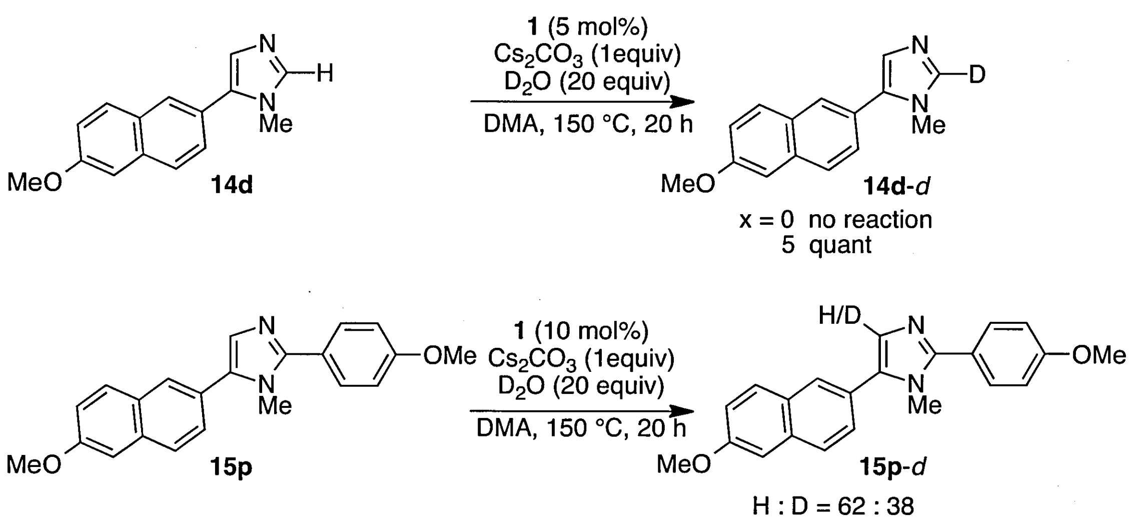
Scheme 4. Radical Mechanism for C4 Arylation.



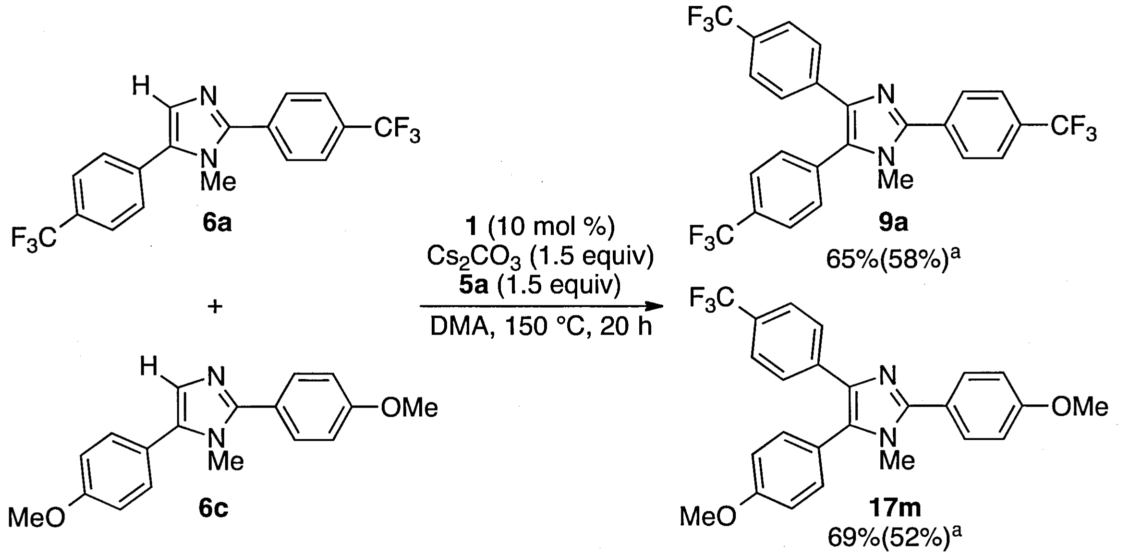
Scheme 5. Radical Trap Experiment on the Reaction of Benzoxazole (**21**).



Scheme 6. H-D Exchange Reactions Catalyzed by **1**.



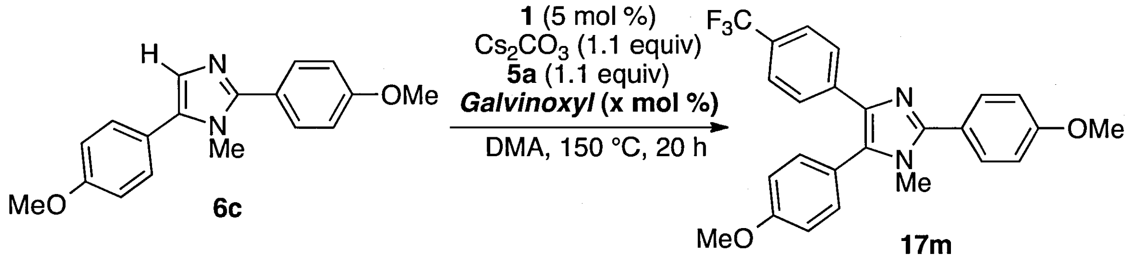
Scheme 7. Competitive Direct C4 Arylation Reactions of Diaryl-imidazoles.



6a : **6c** = 1 : 1

[a] NMR yields. Isolated yields are shown in parentheses.

Scheme 8. Radical Trap Experiments of the Reaction of **6c**.



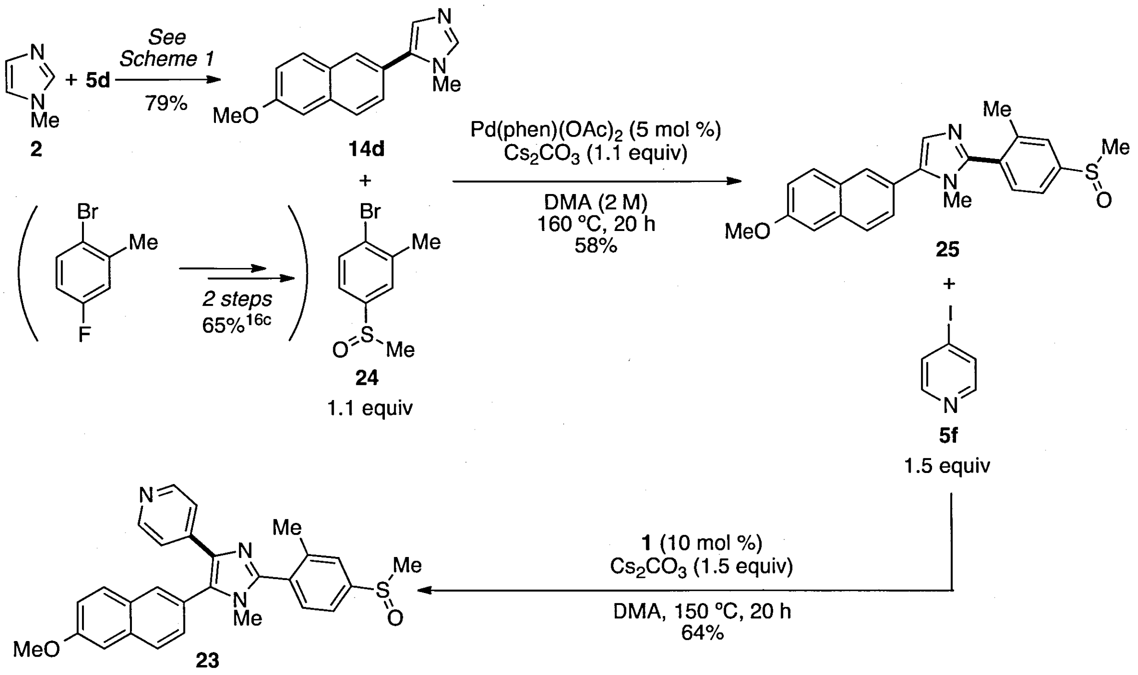
		17m	**6c**
x =	0	86%	trace
	100	73%	28%

5.5. Direct synthesis of Tie2 Tyrosine Kinase Inhibitor

To demonstrate the synthetic utility of the new arylation methodology, a synthesis of the medicinally important substance, the Tie-2 Tyrosine Kinase Inhibitor (**23**), was explored. The previous strategy employed to prepare **23** involves construction of the imidazole core by using a classical condensation strategy starting with fragments that already contain the requisite substituents in the target at C2, C4, and C5.[23] As a result, multistep syntheses of the fragments were needed. More recently, Fagnou et.al. developed a synthesis of **23** that relies on direct arylation of an imidazole *N*-oxide.[4c] In this case, owing to the instability of the imidazole core under oxidation conditions, the catalytic reactions were performed on the *N*-oxide of **14d**, which was synthesized by utilizing a classical condensation approach from a corresponding glyoxal oxime and 1,3,5-triazine.

The author envisioned that the three arene fragments present in **23** could be directly and sequentially installed starting with commercially available *N*-methylimidazole (**2**) by using the new catalytic arylation process (Scheme 9). Execution of a route following this plan, began with the high yield preparation of the C5-aryl-imidazole **14d** from **2** by using the process shown in Scheme 1. In order to avoid diarylation at C2 and C4, coupling of **14d** with the relatively slowly reacting substrate, 2-methyl-4-methylsulfonylphenyl bromide (**24**),[4c] was attempted using **1** as the catalyst but the yield of the desired product **25** was low. A brief reinvestigation of the reaction conditions revealed that the use of Pd(phen)$(OAc)_2$ as a catalyst instead of **1** enables efficient and selective C2 arylation of **14d** with **24** to produce **25** in 58% yield. Finally, the target compound **23** was generated in pure form in 64% yield by reaction of **25** and 4-iodopyridine (**5f**). This three step sequential arylation route for preparation of **23** takes place with an overall yield of 29%. To the best of the auther's knowledge, this is the first example of a synthesis of **23** from commercially available **2** by using palladium catalyzed direct C-H arylation reactions.

Scheme 9. Synthesis of Tie-2 Tyrosine Kinase Inhibitor (**23**).



Overall yields of
3 steps of direct arylations: 29%
The longest liner 4 steps: 25%

5.6. Summary

In the studies described above, the author has developed an efficient direct C–H arylation reaction of simple azoles that is catalyzed by the 1,10-phenanthroline–Pd complex **1**. Although nitrogen-based ligands have rarely been used in catalysts that promote direct C–H arylation reactions, the author's efforts clearly reveal the significant potential of these types of catalysts. In fact, the catalytic system developed in this investigation even can be used to promote efficient direct C4 arylation reactions of simple azoles. Sequential arylations of simple azoles using the new catalytic system serves as the most simple and efficient method for preparation of triaryl-azoles bearing three different aryl groups. The advent of this versatile procedure for preparation of mono-, di-, and triaryl-azoles should enable wider screening and exploration of these potentially biological active substances.

5.7. Experimental

5.7.1. General

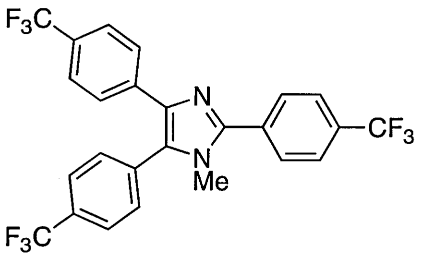
Materials: Unless otherwise noted, reagents were commercially available and were used without purification. DMA was distilled over calcium hydride under reduced pressure. Pd(phen)(OAc)$_2$,[24] Pd(phen)(OCOCF$_3$)$_2$,[24] Pd(phen)$_2$(PF$_6$)$_2$,[24] and **5e-Br**[4c] were prepared according the literature. Silica gel 60N (Spherical, Neutral, 40-50 mm) used from Kanto Chemical Co., Inc.

5.7.2. General procedure for 1-pot tri or diarylation of azoles

In a screw-capped test tube was placed Cs$_2$CO$_3$ (3 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then Pd(phen)$_2$(PF$_6$)$_2$ (5 mol%), azole (0.5 mmol), aryliodide (3 equiv) and DMA (1 mL) were added. The resulting mixture was stirred under Ar atmosphere at 150 °C for 40 h. The resulting mixture was filtrated by celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography to give a title compound as a white solid.

Products of One-Pot Triarylations

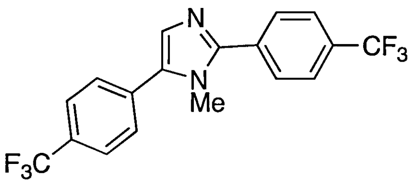
1-Methyl-2,4,5-tris(4-trifluoromethylphenyl)-*1H*-imidazole (9a)[6]



Chemical Formula: $C_{25}H_{15}F_9N_2$
Exact Mass: 514.1092
Molecular Weight: 514.3856

59% yield, white solid, Rf = 0.52 (hexane : AcOEt = 4 : 1). ^{1}H NMR (CDCl$_3$) δ 3.57 (s, 3H, Me), 7.51 (d, *J* = 8.8 Hz, 2H, Ar), 7.57 (d, *J* = 8.5 Hz, 2H, Ar), 7.62 (d, *J* = 8.5 Hz, 2H, Ar), 7.79-7.80 (m, 4H, Ar), 7.91 (d, *J* = 8.0 Hz, 2H, Ar).

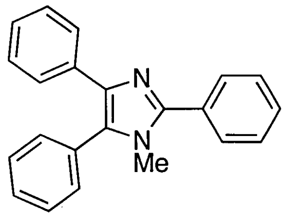
1-Methyl-2,5-bis(4-trifluoromethylphenyl)-*1H*-imidazole (6a)[6]



Chemical Formula: $C_{18}H_{12}F_6N_2$
Exact Mass: 370.0905
Molecular Weight: 370.2917

39% yield, white solid, Rf = 0.58 (*n*-Hex : EtOAc = 1 : 2). ^{1}H NMR (CDCl$_3$) δ 3.74 (3H, NMe), 7.32 (s, 1H, Ar), 7.60 (d, *J* = 8.3 Hz, 2H, Ar), 7.44-7.78 (m, 4H, Ar), 7.85 (d, *J* = 8.3 Hz, 2H, Ar).

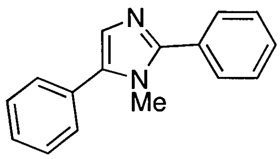
1-Methyl-2,4,5-triphenyl-*1H*-imidazole (9b)[25]



Chemical Formula: $C_{22}H_{18}N_2$
Exact Mass: 310.1470
Molecular Weight: 310.3917

61% yield, white solid, Rf = 0.58 (*n*-Hex : EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H, NMe), 7.27 (t, *J* = 7.3 Hz, 1H, Ar), 7.24 (t, *J* = 7.3 Hz, 2H, Ar), 7.42-7.53 (m 8H, Ar), 7.59 (d, *J* = 8.3 Hz, 2H, Ar), 7.78 (d, *J* = 7.3 Hz, 2H, Ar).

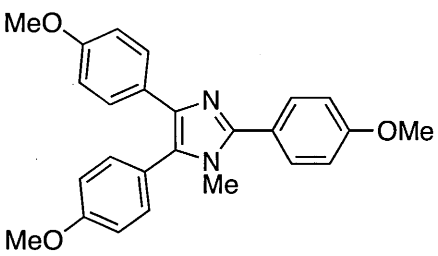
1-Methyl-2,5-diphenyl-*1H*-imidazole (6b)[26]



Chemical Formula: $C_{16}H_{14}N_2$
Exact Mass: 234.1157
Molecular Weight: 234.2958

31% yield, white solid, Rf = 0.35 (*n*-Hex : EtOAc = 1 : 2). ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H, NMe), 7.13 (s, 1H, Ar), 7.29-7.41 (m, 8H, Ar), 7.62 (d, *J* = 7.8 Hz, 2H, Ar).

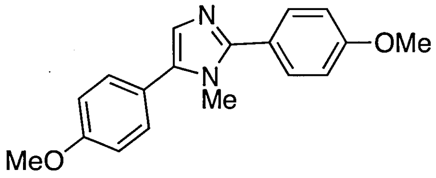
1-Methyl-2,4,5-tris(4-methoxyphenyl)-*1H*-imidazole (9c)



Chemical Formula: $C_{25}H_{24}N_2O_3$
Exact Mass: 400.1787
Molecular Weight: 400.4697

44% yield, white solid, mp 55-57 °C, Rf = 0.30 (DCM : MeOH = 100 : 3). IR (KBr) 2935, 2834, 1612, 1578, 1517, 1494, 1246 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H, NMe), 3.77 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.78 (d, *J* = 8.8 Hz, 2H, Ar), 7.00 (d, *J* = 8.8 Hz, 2H, Ar), 7.02 (d, *J* = 8.8 Hz, 2H, Ar), 7.32 (d, *J* = 8.8 Hz, 2H, Ar), 7.50 (d, *J* = 8.8 Hz, 2H, Ar), 7.67 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.9 (NMe), 55.1, 55.3, 55.3 (OMe), 113.5, 113.9, 114.3, 114.4, 123.4, 127.4, 128.0, 128.9, 130.3, 132.1, 136.9, 147.3, 158.1, 159.6, 159.9 (Ar). MS (EI) *m*/*z*: 400 (M^+). HRMS (EI): Exact mass calcd for $C_{25}H_{24}N_2O_3$ (M^+); 400.1787. Found: 400.1786.

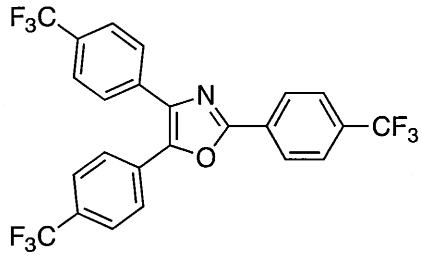
1-Methyl-2,5-bis(4-methoxyphenyl)-*1H*-imidazole (6c)



Chemical Formula: $C_{18}H_{18}N_2O_2$
Exact Mass: 294.1368
Molecular Weight: 294.3477

40% yield, white solid, mp 204-207 °C, Rf = 0.10 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) = 3010, 2954, 2933, 2835, 1612, 1576, 1553, 1249cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H, NMe), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.99 (d, *J* = 8.8 Hz, 2H, Ar), 7.00 (d, *J* = 8.8 Hz, 2H, Ar), 7.11 (s, 1H, Ar), 7.36 (d, *J* = 8.8 Hz, 2H, Ar), 7.61 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.5 (NMe), 55.3, 55.3 (OMe), 113.9, 114.2, 122.8, 123.5, 126.6, 130.0, 130.1, 134.8, 148.8, 159.3, 159.9 (Ar). MS (EI) *m*/z: 294 (M^+). HRMS (EI): Exact mass calcd for $C_{18}H_{18}N_2O_2$ (M^+); 294.1368. Found: 294.1373.

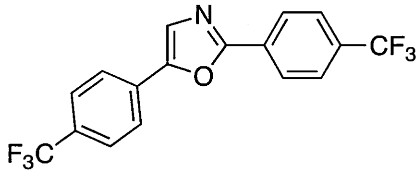
2,4,5-Tris(4-trifluoromethylphenyl)oxazole (10a)[6]



Chemical Formula: $C_{24}H_{12}F_9NO$
Exact Mass: 501.0775
Molecular Weight: 501.3438

76% yield, white solid, Rf = 0.34 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4H, Ar), 7.75-7.78 (m, 4H, Ar), 7.82 (d, *J* = 7.8 Hz, 2H, Ar), 8.25 (d, *J* = 8.3 Hz, 2H, Ar).

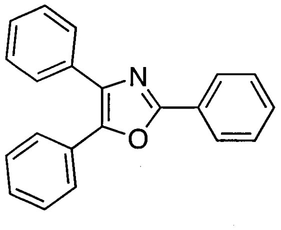
2,5-Bis(4-trifluoromethylphenyl)oxazole (7a)[6]



Chemical Formula: $C_{17}H_9F_6NO$
Exact Mass: 357.0588
Molecular Weight: 357.2499

21% yield, white solid, Rf = 0.23 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1H, Ar), 7.63-7.69 (m, 4H, Ar), 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 8.15 (d, *J* = 8.3 Hz, 2H, Ar).

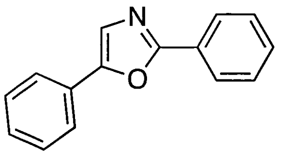
2,4,5-Triphenyloxazole (10b)[1]



Chemical Formula: $C_{21}H_{15}NO$
Exact Mass: 297.1154
Molecular Weight: 297.3499

55% yield, white solid, Rf = 0.35 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.33-7.48 (m, 9H, Ar), 7.67 (d, *J* = 6.8 Hz, 2H, Ar), 7.72 (d, *J* = 7.3 Hz, 2H, Ar), 8.15 (d, *J* = 7.8 Hz, 2H, Ar).

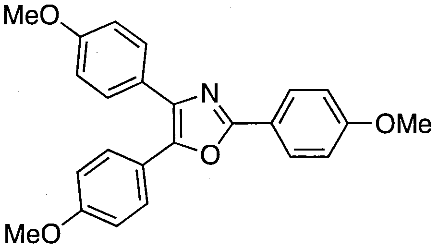
2,5-Diphenyloxazole (7b)[27]



Chemical Formula: $C_{15}H_{11}NO$
Exact Mass: 221.0841
Molecular Weight: 221.2539

34% yield, white solid, Rf = 0.22 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.32 (t, *J* = 7.3 Hz, 1H, Ar), 7.41-7.47 (m, 6H, Ar), 7.71 (d, *J* = 7.3 Hz, 2H, Ar), 8.11 (d, *J* = 6.8 Hz, 2H, Ar).

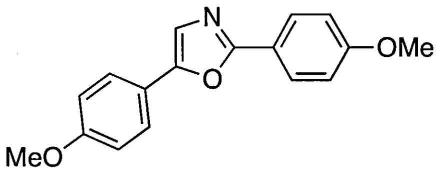
2,4,5-Tris(4-methoxyphenyl)oxazole (10c)



Chemical Formula: $C_{24}H_{21}NO_4$
Exact Mass: 387.1471
Molecular Weight: 387.4278

49% yield, white solid, mp 140-142 °C, Rf = 0.23 (hexane : AcOEt = 4 : 1). IR (KBr) 3041, 2999, 1613, 1517, 1500, 1298, 1247, 1172, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.84-6.93 (m, 4H, Ar), 6.97 (d, *J* = 8.8 Hz, 2H, Ar), 7.56 (d, *J* = 8.5 Hz, 2H, Ar), 7.62 (d, *J* = 8.5 Hz, 2H, Ar), 8.05 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.2, 55.3, 55.3 (OMe), 114.0, 114.2, 114.2, 120.4, 121.9, 125.3, 127.8, 127.9, 129.2, 135.1, 144.3, 159.3, 159.5, 159.6, 161.2 (Ar). MS (EI) *m*/*z*: 387 (M$^+$). HRMS (EI): Exact mass calcd for $C_{24}H_{21}NO_4$ (M$^+$); 387.1417. Found: 387.1413.

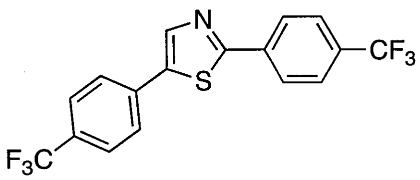
2,5-Bis(4-methoxyphenyl)oxazole (7c)



Chemical Formula: $C_{17}H_{15}NO_3$
Exact Mass: 281.1052
Molecular Weight: 281.3059

30% yield, white solid, mp 105-107 °C, Rf = 0.23 (hexane : AcOEt = 4 : 1). IR (KBr) 1615, 1494, 1304, 1251, 1173, 1057, 1024, 951, 834, 820 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.91-6.95 (m, 4H, Ar), 7.23 (s, 1H, Ar), 7.59 (d, *J* = 8.3 Hz, 2H, Ar), 7.99 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.3, 55.3 (OMe), 114.2, 114.3, 120.4, 121.0, 121.7, 125.5, 127.7, 150.7, 159.6, 160.6, 161.1 (Ar). MS (EI) *m*/*z* : 281 (M$^+$). HRMS (EI): Exact mass calcd for $C_{17}H_{15}NO_3$ (M$^+$); 281.1052. Found: 281.1043.

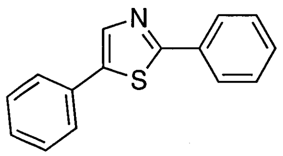
2,5-Bis(4-trifluoromethylphenyl)thiazole (8a)



Chemical Formula: $C_{17}H_9F_6NS$
Exact Mass: 373.0360
Molecular Weight: 373.3155

73% yield, yellow solid, mp 155-156 °C, Rf = 0.20 (hexane : AcOEt = 10 : 1). IR (KBr) 1613, 1434, 1320, 1172, 1136, 1108, 1066, 835 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.56-7.62 (m, 6H, Ar), 7.96 (d, *J* = 8.3 Hz, 2H, Ar), 8.00 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 123.8 (q, *J* = 272.1 Hz, $F_3\underline{C}$), 123.9 (q, *J* = 272.1 Hz, $F_3\underline{C}$), 126.0 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 126.2 (q, *J* = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 126.6, 126.8 (Ar), 130.4 (q, *J* = 33.1 Hz, $F_3C\text{-}\underline{C}$), 131.0 (q, *J* = 33.1 Hz, $F_3C\text{-}\underline{C}$), 134.4, 136.4, 138.7, 140.7, 166.2 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.1, -63.2 (CF_3). MS (EI) *m*/*z*: 373 (M$^+$). HRMS (EI): Exact mass calcd for $C_{17}H_9F_6NS$ (M$^+$); 373.0360. Found: 373.0349.

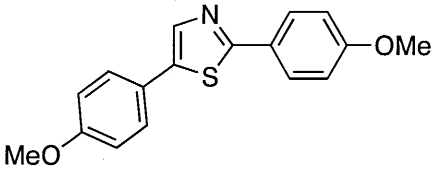
2,5-Diphenylthiazole (8b)[1]



Chemical Formula: $C_{15}H_{11}NS$
Exact Mass: 237.0612
Molecular Weight: 237.3195

93%yield, white solid, Rf = 0.24 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 7.31-7.47 (m, 6H, Ar), 7.59 (d, J = 7.8 Hz, 2H, Ar), 7.97 (d, J = 8.3 Hz, 2H, Ar), 8.02 (s, 1H, Ar).

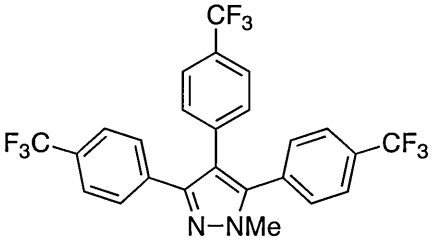
2,5-Bis(4-methoxyphenyl)thiazole (8c)[27]



Chemical Formula: $C_{17}H_{15}NO_2S$
Exact Mass: 297.0823
Molecular Weight: 297.3715

99% yield, yellow solid, Rf = 0.10 (hexane : AcOEt = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.91-6.95 (m, 4H, Ar), 7.49 (d, J = 8.1 Hz, 2H, Ar), 7.84-7.88 (m, 3 H, Ar).

1-Methyl-3,4,5-tris(4-trifluoromethylphenyl)pyrazole (13)



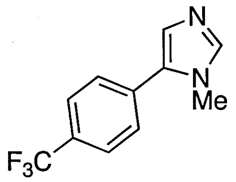
Chemical Formula: $C_{25}H_{15}F_9N_2$
Exact Mass: 514.1092
Molecular Weight: 514.3856

52% yield, white solid, mp 156-157.5 °C, Rf = 0.62 (n-Hex : EtOAc = 4 : 1). IR (KBr) 3046, 2944, 1689, 1619, 1574, 1330 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, NMe), 7.14 (d, J = 7.8 Hz, 2H, Ar), 7.38 (d, J = 7.8 Hz, 2H, Ar), 7.49 (d, J = 8.3 Hz, 2H, Ar), 7.54-7.59 (m, 4H, Ar), 7.79 (d, J = 8.3 HZ, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 37.3 (NMe), 118.4 (Ar), 123.5 (q, J = 272.1 Hz, $F_3\underline{C}$), 123.8 (q, J = 272.1 Hz, $F_3\underline{C}$), 123.9 (q, J = 272.1 Hz, $F_3\underline{C}$), 125.1 (q, J = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 125.3 (q, J = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 125.6 (q, J = 3.3 Hz, $F_3C\text{-}C\text{=}\underline{C}$), 128.0 (Ar), 128.9 (q, J = 33.1 Hz, $F_3C\text{-}\underline{C}$), 129.5 (q, J = 32.3 Hz, $F_3C\text{-}\underline{C}$), 130.2 , 130.2 (Ar), 130.9 (q, J = 32.3 Hz, $F_3C\text{-}\underline{C}$), 132.7, 136.0, 141.1, 147.2 (Ar). One carbon atom was overlapped. ^{19}F NMR ($CDCl_3$) δ -62.9, -63.0, -63.3 (CF_3). MS (EI) m/z: 514 (M^+). HRMS (EI): Exact mass calcd for $C_{25}H_{15}F_9N_2$ (M^+); 514.1092. Found: 514.1074

5.7.3. General procedure for C-5 arylation of azoles

In a screw-capped test tube was placed Cs_2CO_3 (1 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then $Pd(phen)_2(PF_6)_2$ (5 mol%), azole (10 equiv), aryliodide (1 equiv) and DMA were added. The resulting mixture was stirred under Ar atmosphere at 150 °C for 20 h. The resulting mixture was filtrated by celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography (DCM : MeOH = 100 : 1- 100 : 5) to give a title compound.

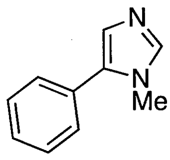
1-Methyl-5-(4-trifluoromethylphenyl)-1H-imidazole (14a)[13]



Chemical Formula: $C_{11}H_9F_3N_2$
Exact Mass: 226.0718
Molecular Weight: 226.1978

74% yield, colorless oil, Rf = 0.10 (DCM : MeOH = 100 : 1). ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H. NMe), 7.18 (s, 1H, Ar), 7.52 (d, *J* = 8.3 Hz, 2H, Ar), 7.56 (s, 1H, Ar), 7.70 (d, *J* = 8.3 Hz, 2H, Ar).

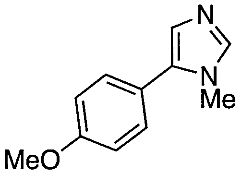
1-Methyl-5-phenyl-*1H*-imidazole (14b)[13]



Chemical Formula: $C_{10}H_{10}N_2$
Exact Mass: 158.0844
Molecular Weight: 158.1998

79% yield, brown solid, Rf = 0.10 (DCM : MeOH = 100 : 1). ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H, NMe), 7.11 (s, 1H, Ar), 7.37-7.44 (m, 5H, Ar), 7.53 (s, 1H, Ar).

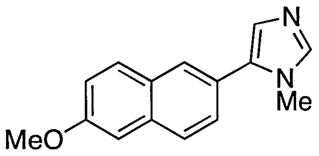
1-Methyl-5-(4-methoxyphenyl)- *1H*-imidazole (14c)[13]



Chemical Formula: $C_{11}H_{12}N_2O$
Exact Mass: 188.0950
Molecular Weight: 188.2258

86% yield, brown solid, Rf = 0.05 (DCM : MeOH = 100 : 1). ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H, NMe), 3.86 (s, 3H, OMe), 6.98 (d, *J* = 8.8 Hz, 2H, Ar), 7.05 (s, 1H, Ar), 7.32 (d, *J* = 8.8 Hz, 2H, Ar), 7.50 (s, 1H, Ar).

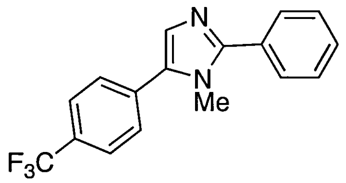
1-Methyl-5-(6-methoxy-2-naphtyl)-*1H*-imidazole (14d)[13]



Chemical Formula: $C_{15}H_{14}N_2O$
Exact Mass: 238.1106
Molecular Weight: 238.2845

81% yield, colorless solid, Rf = 0.07 (DCM : MeOH = 100 : 1). ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H, Me), 3.96 (s, 3H, Me), 7.17-7.22 (m, 3H, Ar), 7.48 (dd, *J* = 8.5 Hz, 1.7 Hz, 1H, Ar), 7.70 (s, 1H, Ar), 7.77-7.82 (m, 3H, Ar).

1-Methyl-2-phenyl-5-(4-trifluoromethylphenyl)-*1H*-imidazole (15a) (Method I)



Chemical Formula: $C_{17}H_{13}F_3N_2$
Exact Mass: 302.1031
Molecular Weight: 302.2937

59% yield, white solid, mp 172-173 °C, Rf = 0.63 (*n*-Hex : EtOAc = 1 : 2). IR (KBr) 2956, 1613. 1551, 1462, 1448, 1331 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, NMe), 7.28 (s, 1H, Ar), 7.44-7.52 (m, 3H, Ar), 7.59 (d, *J* = 7.8 Hz, 2H, Ar), 7.69-7.73 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.9 (NMe), 124.1 (q, *J* = 271.3 Hz, $\underline{C}F_3$), 125.8 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 128.6, 128.6, 128.7, 128.9, 129.0 (Ar), 129.8 (q, *J* = 33.1 Hz, $\underline{C}$-CF_3), 130.6, 133.9, 134.1, 150.5 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.9 (CF_3). MS (EI) *m*/*z*: 302 (M$^+$). HRMS (EI): Exact mass calcd for $C_{17}H_{13}F_3N_2O$ (M$^+$); 302.1031. Found: 302.1028.

5.7.4. General procedure for the C2 arylation of 5-arylazoles

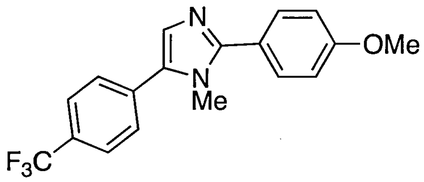
Method I (no additive)

In a screw-capped test tube was placed Cs_2CO_3 (1.1 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then Pd(phen)$_2$(PF_6)$_2$ (5 mol%), 5-arylaimidazoles (0.25 mmol), aryliodides (1.1 equiv) and DMA (1 mL) were added. The resulting mixture was stirred under an Ar atmosphere at 150 °C for 20-40 h. The residue was subjected to flash column chromatography on silica gel to give the 2,5-diarylated product as a white solid.

Method II (addition of Galvinoxyl)

In a screw-capped test tube was placed Cs_2CO_3 (1.1 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then Pd(phen)$_2$(PF_6)$_2$ (5 mol%), 5-arylaimidazoles (0.25 mmol), aryliodides (1.1 equiv), Galvinoxyl (1 equiv) and DMA (1 mL) were added. The resulting mixture was stirred under Ar atmosphere at 150 °C for 20 h. The residue was subjected to flash column chromatography on silica gel to give the 2,5-diarylated product as a white solid.

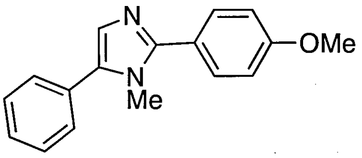
1-Methyl-2-(4-methyoxyphenyl)-5-(4-trifluoromethylphenyl)-*1H*-imidazole (15b) (Method I)



Chemical Formula: $C_{18}H_{15}F_3N_2O$
Exact Mass: 332.1136
Molecular Weight: 332.3197

quantitative yield, white solid, mp 177-179 °C, Rf 0.33 (*n*-Hex : EtOAc = 1 : 2). IR (KBr) 2958, 2838, 1613, 1575, 1328, 1256 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H, NMe), 3.87 (s, 3H, OMe), 7.02 (d, *J* = 8.8 Hz, 2H, Ar), 7.27 (s, 1H, Ar), 7.57 (d, *J* = 8.8 Hz, 2H, Ar), 7.63 (d, *J* = 8.8 Hz, 2H, Ar), 7.72 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.9 (NMe), 55.3 (OMe), 114.1, 123.0 (Ar), 124.1 (q, *J* = 271.3 Hz, $\underline{C}F_3$), 125.7 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 128.4, 128.4 (Ar), 129.6 (q, *J* = 32.3 Hz, $\underline{C}$-CF_3), 130.3, 133.8, 134.0, 150.5, 160.3 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.9 (CF_3). MS (EI) *m*/*z*: 332 (M$^+$). HRMS (EI): Exact mass calcd for $C_{18}H_{15}F_3N_2$ (M$^+$); 332.1136. Found: 332.1115.

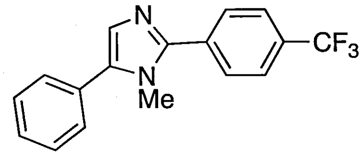
1-Methyl-2-(4-methoxyphenyl)-5-phenyl-*1H*-imidazole (15c) (Method II)



Chemical Formula: $C_{17}H_{16}N_2O$
Exact Mass: 264.1263
Molecular Weight: 264.3217

85% yield, white solid, mp 176-177.5 °C, Rf = 0.23 (*n*-Hex : EtOAc = 1 : 2). IR (KBr) 2953, 2834, 1612, 1577, 1252 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.64 (s, 3H, NMe), 3.85 (s, 3H, OMe), 7.00 (d, *J* = 9.1 Hz, 2H, Ar), 7.17 (s, 1H, Ar), 7.35-7.45 (m, 5H, Ar), 7.62 (d, *J* = 9.1 Hz, 2H, Ar). ^{13}C NMR (CDCl$_3$) δ 33.6 (NMe), 55.2 (OMe), 114.0, 123.4, 127.2, 127.7, 128.5, 128.7, 130.2, 130.4, 130.1, 149.4, 160.0 (Ar). MS (EI) *m*/z: 264 (M$^+$). HRMS (EI): Exact mass calcd for $C_{17}H_{16}N_2O$ (M$^+$); 264.1263. Found: 264.1269.

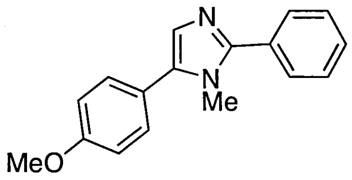
1-Methyl-2-(4-trifluoromethylphenyl)-5-phenyl-*1H*-imidazole (15d) (Method II)



Chemical Formula: $C_{17}H_{13}F_3N_2$
Exact Mass: 302.1031
Molecular Weight: 302.2937

74% yield, white solid, mp 178-179 °C, Rf = 0.68 (*n*-Hex : EtOAc = 1 : 2). IR (KBr) 3069, 2956, 1613, 1550, 1332 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.71 (s, 3H, NMe), 7.24 (s, 1H, Ar), 7.41-7.50 (m, 5H, Ar), 7.59 (d, *J* = 8.3 Hz, 2H, Ar), 7.85 (d, *J* = 8.3 Hz, 2H, Ar). ^{13}C NMR (CDCl$_3$) δ 33.8 (NMe), 55.3 (OMe), 124.1 (q, *J* = 271.3 Hz, $\underline{C}F_3$), 125.6 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF$_3$), 128.0, 128.1, 128.8, 128.9, 128.9, 129.8 (Ar), 130.4 (q, *J* = 33.1 Hz, $\underline{C}$-CF$_3$), 134.4, 136.3, 147.8 (Ar). ^{19}F NMR (CDCl$_3$) δ -63.0 (CF$_3$). MS (EI) *m*/z: 302 (M$^+$). HRMS (EI): Exact mass calcd for $C_{17}H_{13}F_3N_2O$ (M$^+$); 302.1031. Found :302.1022.

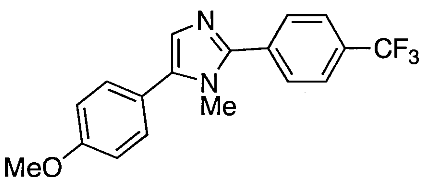
1-Methyl-2-phenyl-5-(4-methoxyphenyl)-*1H*-imidazole (15e) (Method I)



Chemical Formula: $C_{17}H_{16}N_2O$
Exact Mass: 264.1263
Molecular Weight: 264.3217

59% yield, white solid, mp 194-196 °C, Rf = 0.46 (*n*-Hex : EtOAc = 1 : 3). IR (KBr) 3058, 2952, 2834, 1610, 1575, 1248 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.64 (s, 3H, NMe), 3.86 (s, 3H, OMe), 7.00 (d, *J* = 8.8 Hz, 2H, Ar), 7.15 (s, 1H, Ar), 7.38 (d, *J* = 8.8 Hz, 2H, Ar), 7.43 (t, *J* = 7.3 Hz, 1H, Ar), 7.48 (t, *J* = 7.3 Hz, 2H, Ar), 7.70 (d, *J* = 7.3 Hz, 2H, Ar). ^{13}C NMR (CDCl$_3$) δ 33.5 (NMe), 55.3 (OMe), 114.0, 114.2, 122.7, 127.0, 128.5, 128.7, 130.2, 131.1, 135.2, 148.9, 159.5 (Ar). MS (EI) *m*/z: 264 (M$^+$). HRMS (EI): Exact mass calcd for $C_{17}H_{16}N_2O$ (M$^+$); 264.1263. Found 264.1261.

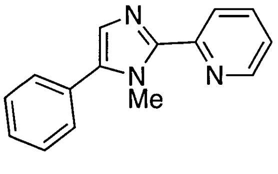
1-Methyl-2-(4-trifluoromethylphenyl)-5-(4-methyoxyphenyl)-*1H*-imidazole (15f) (Method II)



Chemical Formula: $C_{18}H_{15}F_3N_2O$
Exact Mass: 332.1136
Molecular Weight: 332.3197

61% yield, white solid, mp 185-186 °C, Rf = 0.38 (*n*-Hex : EtOAc = 1 : 3). IR (KBr) 2958, 1612, 1573, 1337, 1257 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.67 (s, 3H, NMe), 3.87 (s, 3H, OMe), 7.01 (d, *J* = 8.8 Hz, 2H, Ar), 7.18 (s, 1H, Ar), 7.38 (d, *J* = 8.8 Hz, 2H, Ar), 7.74 (d, *J* = 8.3 Hz, 2H, Ar), 7.84 (d, *J* = 8.3 Hz, 2H, Ar). ^{13}C NMR (CDCl$_3$) δ 33.6 (NMe), 55.3 (OMe), 114.3, 122.2, 124.1 (q, J = 271.3 Hz, $\underline{C}F_3$), 125.6 (q, J = 3.3 Hz, $\underline{C}$=C-CF_3), 127.5, 128.8, 130.3 (Ar), 130.3 (q, J = 32.3 Hz, $\underline{C}$-CF_3), 134.5, 136.1, 147.4, 159.7 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m/z*: 332 (M^+). HRMS (EI): Exact mass calcd for $C_{18}H_{15}F_3N_2O$ (M^+); 332.1136. Found: 332.1135.

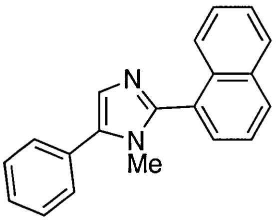
1-Methyl-2-(2-pyridyl)-5-phenyl-*1H*-imidazole (15g) (Method II)



Chemical Formula: $C_{15}H_{13}N_3$
Exact Mass: 235.1109
Molecular Weight: 235.2838

87% yield, brown oil, Rf = 0.26 (*n*-Hex : EtOAc = 1 : 1). IR (neat) 2954, 1631, 1568, 1458, 1411 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H, NMe), 7.13-7.18 (m, 2H, Ar), 7.31-7.42 (m, 5H, Ar), 7.71 (t, J = 7.8 Hz, 1H, Ar), 8.12 (d, J = 7.8 Hz, 1H, Ar), 8.55 (brs, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 30.8 (NMe), 122.5, 123.3, 127.7, 128.1, 128.8, 129.1*, 130.0, 136.7, 146.4, 148.3, 150.9 (Ar). *Two carbon atoms are overlapped. MS (EI) *m/z*: 235 (M^+). HRMS (EI): Exact mass calcd for $C_{15}H_{13}N_3$ (M^+); 235.1109. Found: 235.1103.

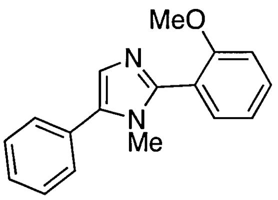
1-Methyl-2-(1-naphtyl)-5-phenyl-*1H*-imidazole (15h) (Method I)



Chemical Formula: $C_{20}H_{16}N_2$
Exact Mass: 284.1313
Molecular Weight: 284.3544

68% yield, yellow sticky oil, Rf = 0.38 (*n*-Hex : EtOAc = 1 : 1). IR (neat) 3050, 2949, 1644, 1603, 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3H, NMe), 7.39 (s, 1H, Ar), 7.46 (d, J = 6.8 Hz, 1H, Ar), 7.52-7.65 (m, 7H, Ar), 7.71 (d, J = 6.8 Hz, 1H, Ar), 7.90 (dd, J = 6.3, 4.4 Hz, 1H, Ar), 7.97-8.03 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.8 (NMe), 125.1, 125.7, 126.2, 127.0, 127.6, 127.9, 128.4, 128.7, 128.8, 128.9, 129.0, 129.7, 130.4, 132.6, 133.7, 134.5, 148.1 (Ar). MS (EI) *m/z*: 284 (M^+). HRMS (EI): Exact mass calcd for $C_{20}H_{16}N_2$ (M^+); 284.1313. Found: 284.1307.

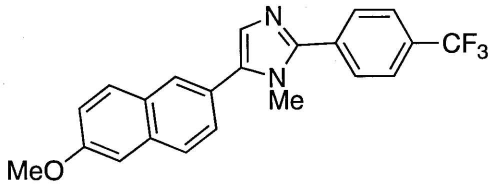
1-Methyl-2-(2-methoxyphenyl)-5-phenyl-*1H*-imidazole (15i) (Method I)



Chemical Formula: $C_{17}H_{16}N_2O$
Exact Mass: 264.1263
Molecular Weight: 264.3217

52% yield, yellow sticky oil, Rf = 0.20 (*n*-Hex : EtOAc = 1 : 1). IR (neat) 3059, 2951, 2835, 1604, 1580, 1552, 1248 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H, NMe), 3.91 (s, 3H, OMe), 7.05 (d, J = 8.3 Hz, 1H, Ar), 7.12 (t, J = 7.3 Hz, 1H, Ar), 7.27 (s, 1H, Ar), 7.41 (dd, J = 7.3, 6.8 Hz, 1H, Ar), 7.47-7.54 (m, 5H, Ar), 7.58 (d, J = 7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.5 (NMe), 55.5 (OMe), 110.9, 120.4, 120.9, 127.5, 127.7, 128.6, 128.7, 130.6, 130.9, 132.5, 134.4, 147.2, 157.5 (Ar). MS (EI) *m/z*: 264 (M^+). HRMS (EI): Exact mass calcd for $C_{17}H_{16}N_2O$ (M^+); 264.1263. Found: 264.1269.

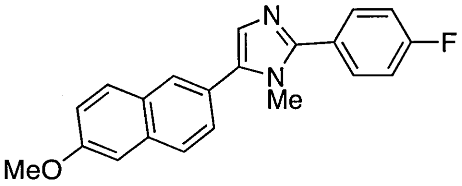
1-Methyl-2-(4-trifluoromethylphenyl)-5-(6-methoxyphenylnaphtyl)-*1H*-imidazole (15j) (Method II)



Chemical Formula: $C_{22}H_{17}F_3N_2O$
Exact Mass: 382.1293
Molecular Weight: 382.3784

83% yield, white solid, mp 222-224 °C, Rf = 0.43 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3031, 1629, 1455, 1338, 1269, 1123 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, NMe), 3.91 (s, 3H, OMe), 7.14-7.16 (m, 2H, Ar), 7.27 (s, 1H, Ar), 7.49 (d, *J* = 8.3 Hz, 1H, Ar), 7.70-7.84 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.3 (NMe), 55.7 (OMe), 106.1, 120.0 (Ar), 124.4 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.2 (Ar), 125.9 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 127.4, 127.7, 128.0, 128.4, 129.1, 129.2, 129.9 (Ar), 130.3 (q, *J* = 32.7 Hz, $\underline{C}$-CF_3), 134.5, 134.7, 136.8, 148.1, 158.7 (Ar).^{19}F NMR ($CDCl_3$) δ -63.3 (CF_3). MS (EI) *m*/*z*: 382 (M^+). HRMS (EI): Exact mass calcd for $C_{22}H_{17}F_3N_2O$ (M^+); 382.1293. Found: 382.1295.

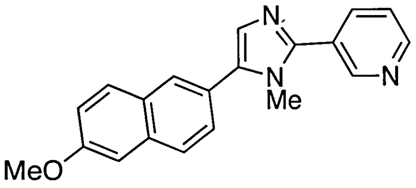
1-Methyl-2-(4-fluorophenyl)-5-(6-methoxy-2-naphtyl)-*1H*-imidazole (15k) (Method I)



Chemical Formula: $C_{21}H_{17}FN_2O$
Exact Mass: 332.1325
Molecular Weight: 332.3709

93% yield, white solid, mp 205-208 °C, Rf = 0.33 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 2957, 2840, 1628, 1602, 1550, 1452, 1246, 1216 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, NMe), 3.96 (s. 3H, OMe), 7.17-7.23 (m, 4H, Ar), 7.27 (s, 1H, Ar), 7.53 (d, *J* = 8.3 Hz, 1H, Ar), 7.69-7.73 (m, 2H, Ar), 7.79 (d, *J* = 8.8 Hz, 1H, Ar), 7.83 (d, *J* = 8.8 Hz, 1H, Ar), 7.84 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.7 (NMe), 55.3 (OMe), 105.7 (Ar), 115.7 (d, *J* = 21.5 Hz, F-C=$\underline{C}$), 119.6, 125.3, 127.1 (Ar), 127.2 (d, *J* = 3.3 Hz, F-C=C-C=$\underline{C}$), 127.3, 127.4, 127.6, 128.8, 129.6 (Ar), 130.7 (d, *J* = 9.1 Hz, F-C=C-$\underline{C}$), 134.0, 135.7, 148.5, 158.2 (Ar), 163.1 (d, *J* = 249.0 Hz, F-$\underline{C}$). ^{19}F NMR ($CDCl_3$) δ -112.7 (F). MS (EI) *m*/*z*: 332 (M^+). HRMS (EI): Exact mass calcd for $C_{21}H_{17}N_2O$ (M^+); 332.1325. Found:332.1328.

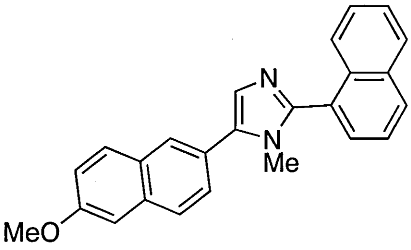
1-Methyl-2-(3-pyridyl)-5-(6-Methoxy-2-naphtyl)-*1H*-imidazole (15l) (Method I)



Chemical Formula: $C_{20}H_{17}N_3O$
Exact Mass: 315.1372
Molecular Weight: 315.3685

69% yield, white solid, mp 186-187 °C, Rf = 0.05 (n-Hex : EtOAc = 1 : 1). IR (KBr) 3038, 2957, 2844, 1630, 1606, 1572, 1262 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H, NMe), 3.95 (s. 3H, OMe), 7.18 (d, *J* = 2.4 Hz, 1H, Ar), 7.21 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar), 7.32 (s, 1H, Ar), 7.43 (dd, *J* = 8.8, 4.4 Hz, 1H, Ar), 7.52 (d, *J* = 8.3 Hz, 1H, Ar), 7.79 (d, *J* = 8.8 Hz, 1H, Ar), 7.83 (d, *J* = 8.8 Hz, 1H, Ar), 7.84 (s, 1H, Ar), 8.09 (d, *J* = 8.3 Hz, 1H, Ar), 8.67 (brs, 1H, Ar), 9.00 (brs, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.8 (NMe), 55.3 (OMe), 105.7, 119.6, 123.6, 124.9, 127.0, 127.3, 127.4, 127.7, 128.3, 128.8, 129.6, 134.1, 136.1, 136.4, 146.3, 149.3, 149.6, 158.3 (Ar). MS (EI) *m*/*z*: 315 (M^+). HRMS (EI): Exact mass calcd for $C_{20}H_{17}N_3O$ (M^+); 315.1372. Found: 315.1377.

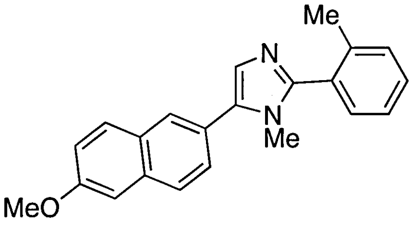
1-Methyl-2-(1-naphtyl)-5-(6-methoxy-2-naphtyl)-*1H*-imidazole (15m) (Method I)



Chemical Formula: $C_{25}H_{20}N_2O$
Exact Mass: 364.1576
Molecular Weight: 364.4391

82% yield, white solid, mp 146-148 °C, Rf = 0.35 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3050, 3001, 2936, 2840, 1629, 1606, 1560, 1261 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H, NMe), 3.96 (s, 3H, OMe), 7.20 (m, 2H, Ar), 7.43 (s, 1H, Ar), 7.54-7.63 (m, 4H, Ar), 7.79 (d, *J* = 5.9 Hz, 1H, Ar), 7.81-8.00 (m, 6H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.9 (NMe), 55.3 (OMe), 105.7, 119.5, 125.1, 125.5, 125.7, 126.2, 127.0, 127.1, 127.3, 127.4, 127.7, 128.4, 128.7, 128.9, 129.3, 129.6, 129.7, 132.5, 133.7, 133.9, 134.7, 148.0, 158.2 (Ar). MS (EI) *m*/*z*: 364 (M$^+$). HRMS (EI): Exact mass calcd for $C_{25}H_{20}N_2O$ (M$^+$); 364.1576. Found: 364.1565.

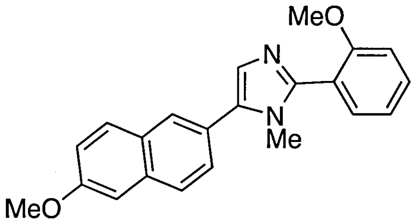
1-Methyl-2-(2-methylphenyl)-5-(6-methoxynaphtyl)-*1H*-imidazole (15n) (Method I)



Chemical Formula: $C_{22}H_{20}N_2O$
Exact Mass: 328.1576
Molecular Weight: 328.4070

68% yield, white solid, mp 122-123 °C, Rf = 0.40 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3057, 1605, 1450, 1260, 1244, 1024 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, Me), 3.67 (s, 3H, NMe), 3.92 (s, 3H, OMe), 7.14-7.19 (m, 3H, Ar), 7.24-7.38 (m, 3H, Ar), 7.53 (t, *J* = 8.4 Hz, 1H, Ar), 7.67 (dd, *J* = 8.4 Hz, 5.2 Hz, 1H), 7.74-7.82 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$) δ 19.7 (Me), 32.4 (NMe), 55.3 (OMe), 105.7, 119.5, 125.6, 125.7, 127.1, 127.2, 127.2, 127.9, 128.8, 129.3, 129.5, 130.4, 130.6, 130.9, 133.9, 134.0, 138.4, 148.9, 158.1 (Ar). MS (EI) *m*/*z*: 328 (M$^+$). HRMS (EI): Exact mass calcd for $C_{22}H_{20}N_2O$ (M$^+$); 328.1576. Found: 328.1576.

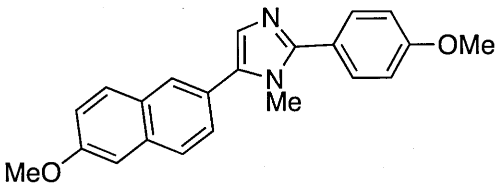
1-Methyl-2-(2-methoxyphenyl)-5-(6-methoxynaphtyl)-*1H*-imidazole (15o) (Method I)



Chemical Formula: $C_{22}H_{20}N_2O_2$
Exact Mass: 344.1525
Molecular Weight: 344.4064

92% yield, white solid, mp 159-161 °C, Rf = 0.13 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3026, 1606, 1470, 1449, 1259, 1021 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.54 (s, 3H, NMe), 3.89 (s, 3H, OMe), 3.95 (s, 3H, OMe), 7.03 (d, *J* = 7.8 Hz, 1H, Ar), 7.09 (dd, *J* = 7.8, 7.3 Hz, 1H, Ar), 7.19-7.22 (m, 2H, Ar), 7.30 (s, 1H, Ar), 7.46 (dd, *J* = 8.3, 7.5 Hz, 1H, Ar), 7.55-7.59 (m, 2H, Ar), 7.78-7.87 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.3 (OMe), 55.0 (NMe), 55.2 (NMe), 105.4, 110.6, 119.1, 120.1, 120.6, 125.4, 126.8, 126.9, 126.9, 127.2, 128.5, 129.2, 130.5, 132.2, 133.5, 134.2, 146.8, 157.2, 157.7 (Ar). MS (EI) *m*/*z*: 344 (M$^+$). HRMS (EI): Exact mass calcd for $C_{22}H_{20}N_2O_2$ (M$^+$); 344.1525. Found: 344.1522.

1-Methyl-2-(2-methoxyphenyl)-5-(6-Methoxynaphtyl)-*1H*-imidazole (15p) (Method I)



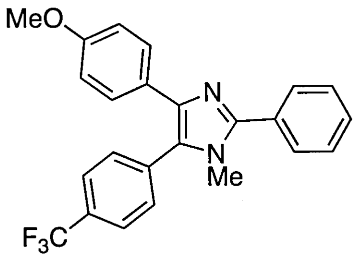
Chemical Formula: $C_{22}H_{20}N_2O_2$
Exact Mass: 344.1525
Molecular Weight: 344.4064

68% yield, white solid, mp 200-202 °C, Rf = 0.38 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 2951, 1604, 1452, 1251, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H, NMe), 3.77 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.92 (d, *J* = 8.8 Hz, 2H, Ar), 7.08-7.13 (m, 2H, Ar), 7.17 (s, 1H, Ar), 7.44 (d, *J* = 8.8 Hz, 1H, Ar), 7.57 (d, *J* = 8.8 Hz, 2H, Ar), 7.68-7.76 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.5 (NMe), 55.0 (OMe), 105.3, 113.7, 119.1, 123.2, 125.2, 126.7, 126.9, 128.5, 129.1, 129.6, 129.9, 132.0, 133.6., 135.0, 149.0, 157.8, 159.6 (Ar). MS (EI) *m*/*z*: 344 (M^+). HRMS (EI): Exact mass calcd for $C_{22}H_{20}N_2O_2$ (M^+); 344.1524. Found: 344.1511.

5.7.5. General procedure for the C-4 arylation of 2,5-diarylazoles

In a screw-capped test tube was placed Cs_2CO_3 (1.5 equiv), which was then dried at 150 °C *in vacuo* for 3 h. Then Pd(phen)$_2$(PF$_6$)$_2$ (5 mol%), 2,5-diarylazole (0.25 mmol), aryliodide (1.5 equiv) and DMA (0.5 mL) were added. The resulting mixture was stirred under Ar atmosphere at 150 °C for 20 h. The residue was subjected to flash column chromatography on silica gel to give the 2,4,5-triarylated product **17**.

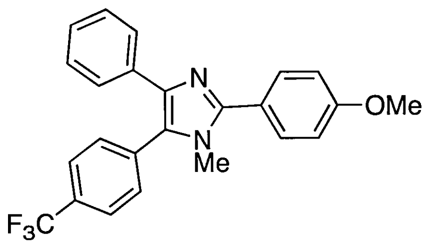
1-Methyl-2-phenyl-4-(4-methoxyphenyl)-5-(4-trifluoromethylphenyl)-*1H*-imidazole (17a)



Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

quantitative yield, white solid, mp 130-131 °C, Rf = 0.45 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3068, 2973, 2937, 1614, 1575, 1322 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H, NMe), 3.79 (s, 3H, OMe), 6.79 (d, *J* = 8.8 Hz, 2H, Ar), 7.43-7.56 (m, 7H, Ar), 7.74 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.3 (NMe), 55.1 (OMe), 113.7 (Ar), 124.1 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 126.0 (q, *J* = 4.1 Hz, $\underline{C}$=C-CF_3), 126.9, 128.0, 128.5, 128.7, 129.0, 129.1 (Ar), 130.3 (q, *J* = 33.1 Hz, $\underline{C}$-CF_3), 130.7, 131.2, 135.1, 138.7, 148.6, 158.6 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m*/z: 408 (M^+). HRMS (EI): Exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1447.

1-Methyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-trifluoromethylphenyl)-*1H*-imidazole (17b)

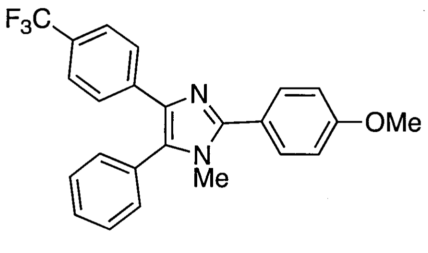


Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

80% yield, white solid, mp 192-193 °C, Rf = 0.45 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3071, 2999, 2965, 2935, 2836, 1576, 1470, 1332, 1253 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H, NMe), 3.88 (s, 3H, OMe), 7.04 (d, *J* = 8.8 Hz, 2H, Ar), 7.19-7.25 (m, 3H, Ar), 7.51 (d, *J* = 8.4 Hz, 2H, Ar), 7.54 (d, *J* = 7.8 Hz, 2H, Ar), 7.68 (d, *J* = 8.8 Hz, 2H, Ar), 7.73 (d, *J* = 8.4 Hz, 2H, Ar).

^{13}C NMR (CDCl$_3$) δ 33.3 (NMe), 55.3 (OMe), 114.1, 123.1 (Ar), 124.1 (q, *J* = 272.1 Hz, C̲F$_3$), 125.9 (q, *J* = 3.3 Hz, C̲=C-CF$_3$), 126.7, 127.3, 128.3, 128.6 (Ar), 130.1 (q, *J* = 32.3 Hz, C̲-CF$_3$), 130.5, 131.1, 134.3, 135.1, 138.6, 148.8, 160.3 (Ar). ^{19}F NMR (CDCl$_3$) δ -63.0 (CF$_3$).MS (EI) *m*/*z*: 408 (M$^+$). HRMS (EI): Exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M$^+$); 408.1449. Found: 408.1457.

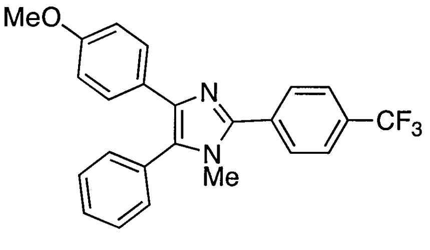
1-Methyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenyl-*1H*-imidazole (17c)



Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

84% yield, white solid, mp 196-197 °C, Rf = 0.45 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 2938, 2840, 1616, 1578, 1322, 1251 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.49 (s, 3H, NMe), 3.88 (s, 3H, OMe), 7.04 (d, *J* = 8.8 Hz, 2H, Ar), 7.41-7.52 (m, 7H, Ar), 7.64-7.69 (m, 4H, Ar). ^{13}C NMR (CDCl$_3$) δ 33.0 (NMe), 55.3 (OMe), 114.1, 123.1 (Ar), 124.5 (q, *J* = 272.1 Hz, C̲F$_3$), 125.0 (q, *J* = 4.1 Hz, C̲=C-CF$_3$), 126.7 (Ar), 128.9 (q, *J* = 32.3 Hz, C̲-CF$_3$), 129.0, 129.3, 130.5, 130.8, 130.9, 131.4, 136.1, 138.3, 148.3, 160.3 (Ar). ^{19}F NMR (CDCl$_3$) δ -58.0 (CF$_3$). MS (EI) *m*/*z*: 408 (M$^+$). HRMS (EI): Exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M$^+$); 408.1449. Found: 408.1459.

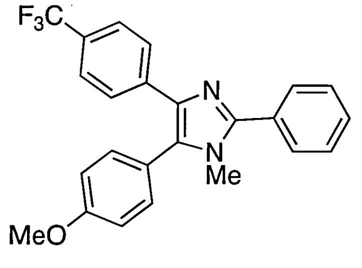
1-Methyl-2-(4-trifluoromethylphenyl)-4-(4-methoxyphenyl)-5-phenyl-*1H*-imidazole (17d)



Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

97% yield, white solid, mp 162-165 °C, Rf = 0.60 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 2937, 2841, 1617, 1578, 1322, 1251 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.54 (s, 3H, NMe), 3.77 (s, 3H, OMe), 6.79 (d, *J* = 9.0 Hz, 2H, Ar), 7.40-7.50 (m, 7H, Ar), 7.76 (d, *J* = 8.2 Hz, 2H, Ar), 7.90 (d, *J* = 8.2 Hz, 2H, Ar). ^{13}C NMR (CDCl$_3$) δ 33.2 (NMe), 55.1 (OMe), 113.6 (Ar), 123.7 (q, *J* = 272.1 Hz, C̲F$_3$), 125.5 (q, *J* = 3.3 Hz, C̲=C-CF$_3$), 127.1, 128.1, 128.7, 129.1, 129.1, 130.4 (Ar), 130.5 (q, *J* = 33.1 Hz, C̲-CF$_3$), 130.9, 131.0, 134.5, 138.2, 146.2, 158.5 (Ar). ^{19}F NMR (CDCl$_3$) δ -63.0 (CF$_3$). MS (EI) *m*/*z*: 408 (M$^+$). HRMS (EI): Exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M$^+$); 408.1449. Found: 408.1447.

1-Methyl-2-phenyl-4-(4-trifluoromethylphenyl)-5-(4-methoxyphenyl)-*1H*-imidazole (17e)

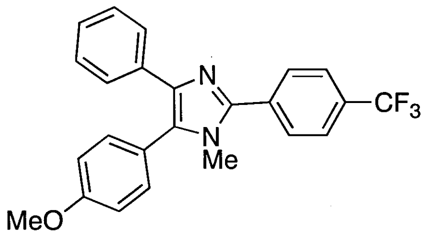


Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

79% yield, white solid, mp 167-169 °C, Rf = 0.45 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3070, 3009, 2962, 2938, 1616, 1562, 1322, 1251 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.50 (s, 3H, NMe), 3.90 (s, 3H, OMe), 7.05 (d, *J* = 8.8 Hz, 2H, Ar), 7.34 (d, J =8.3 Hz, 2H, Ar), 7.44-7.53 (m, 5H, Ar), 7.70 (d, *J* = 8.3 Hz, 2H, Ar), 7.73 (d, *J* = 7.3 Hz, 2H, Ar). ^{13}C NMR (CDCl$_3$) δ 32.9 (NMe), 55.3 (OMe), 114.8, 122.8 (Ar), 124.5 (q, *J* = 272.1 Hz, C̲F$_3$), 125.0 (q, *J* = 3.3

Hz, C=C-CF_3), 126.0 (Ar), 127.7 (q, *J* = 32.3 Hz, C-CF_3), 128.7, 129.0, 129.0, 130.8, 131.5, 132.1, 136.2, 138.4, 148.1, 160.2 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.6 (CF_3). MS (EI) *m/z* (relative intensity, %): 408 (100, M^+). HRMS (EI): Exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1442.

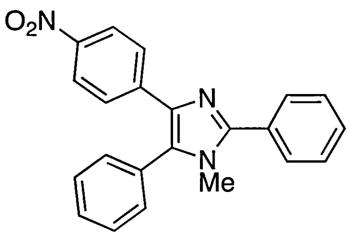
1-Methyl-2-(4-trifluoromethylphenyl)-4-phenyl-5-(4-methoxyphenyl)-*1H*-imidazole (17f)



Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

92% yield, white solid, mp 146-147 °C, Rf = 0.45 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3070, 3020, 2938, 2841, 2938, 2841, 1613, 1600, 1572, 1326, 1251 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.54 (s, 3H, NMe), 3.90 (s, 3H, OMe), 7.04 (d, *J* = 8.8 Hz, 2H, Ar), 7.18 (t, *J* = 7.3 Hz, 1H, Ar), 7.25 (t, *J* = 7.3 Hz, 2H, Ar), 7.35 (d, *J* = 8.8 Hz, 2H, Ar), 7.59 (d, *J* = 7.3 Hz, 2H, Ar), 7.77 (d, *J* = 8.3 Hz, 2H, Ar), 7.91 (d, *J* = 8.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.1 (NMe), 55.3 (OMe), 114.6, 122.9 (Ar), 124.1 (q, *J* = 272.1 Hz, CF_3), 125.6 (q, *J* = 3.3 Hz, C=C-CF_3), 126.5, 126.8, 128.2, 129.1 (Ar), 130.3 (q, *J* = 32.3 Hz, C-CF_3), 131.1, 132.1, 134.5, 134.6, 138.3, 146.1, 160.0 (Ar). ^{19}F NMR ($CDCl_3$) δ -63.0 (CF_3). MS (EI) *m/z*: 408 (M^+). HRMS (EI): Exact mass calcd for $C_{24}H_{19}F_3N_2O$ (M^+); 408.1449. Found: 408.1442.

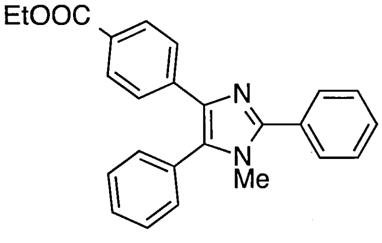
1-Methyl-2,5-diphenyl-4-(4-nitrophenyl)-*1H*-imidazole (17g)



Chemical Formula: $C_{22}H_{17}N_3O_2$
Exact Mass: 355.1321
Molecular Weight: 355.3893

75% yield, yellow solid, mp 207-209 °C, Rf = 0.20 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3057, 2950, 1594, 1558, 1508, 1382, 1321, 853 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H, NMe), 7.40-7.54 (m, 8H, Ar), 7.69 (d, *J* = 8.8 Hz, 2H, Ar), 7.74 (d, *J* = 6.8 Hz, 2H, Ar), 8.05 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.1 (s, NMe), 123.5, 126.7, 128.7, 129.0, 129.2, 129.3, 129.4, 130.3, 130.4, 130.6, 132.9, 135.5, 141.3, 145.8, 148.6 (Ar). MS (EI) *m/z* 355 (M^+); HRMS (EI) Calcd for $C_{22}H_{17}N_3O_2$ (M^+); 355.1321. Found: 355.1334.

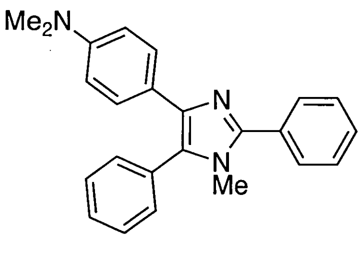
1-Methyl-2,5-diphenyl-4-(4-ethoxycarbonylphenyl)-*1H*-imidazole (17h)



Chemical Formula: $C_{25}H_{22}N_2O_2$
Exact Mass: 382.1681
Molecular Weight: 382.4544

56% yield, yellow solid, mp 122-122.5 °C, Rf = 0.25 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 3058, 2979, 1709, 1508, 1474, 1323, 1270, 1097, 859 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* = 7.3 Hz, 3H, Me), 3.50 (s, 3H, NMe), 4.34 (q, *J* = 7.3 Hz, 2H, CH_2), 7.39-7.52 (m, 8H, Ar), 7.62 (d, *J* = 8.8 Hz, 2H, Ar), 7.74 (d, *J* = 6.8 Hz, 2H, Ar), 7.89 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.3 (Me), 33.1 (NMe), 60.6 (CH_2), 126.1, 127.6, 128.3, 128.4, 128.7, 128.9, 128.9, 129.1, 130.4, 130.4, 130.5, 131.4, 136.4, 138.9, 147.9 (Ar), 166.4 (C=O). MS (EI) *m*/*z* 382 (M^+); HRMS (EI) Calcd for $C_{25}H_{22}N_2O_2$ (M^+); 382.1681. Found: 368.1689.

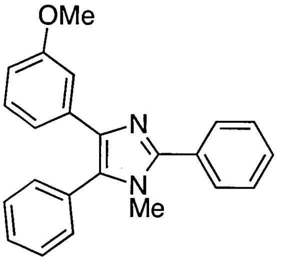
1-Methyl-2,5-diphenyl-4-(4-N,N-dimethylaminophenyl)-*1H*-imidazole (17i)



Chemical Formula: $C_{24}H_{23}N_3$
Exact Mass: 353.1892
Molecular Weight: 353.4595

84% yield, white solid, mp 144-145 °C, Rf = 0.13 (*n*-Hex : EtOAc = 4 : 1). IR (KBr) 3056, 2923, 2798, 1615, 1514, 1348, 1194 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.84 (s, 6H, NMe_2), 3.43 (s, 3H, NMe), 6.55 (d, *J* = 8.8 Hz, 2H, Ar), 7.35-7.44 (m, 10 H, Ar), 7.68 (d, *J* = 7.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 30.0 (NMe), 40.5 (NMe_2), 112.3, 127.8, 128.3, 128.5, 128.6, 128.8, 128.9, 128.9, 129.1, 129.3, 131.1, 131.7, 138.1, 147.5, 149.2 (Ar). MS (EI) *m*/*z* 353 (M^+); HRMS (EI) Calcd for $C_{24}H_{23}N_3$ (M^+); 353.1892. Found: 353.1900.

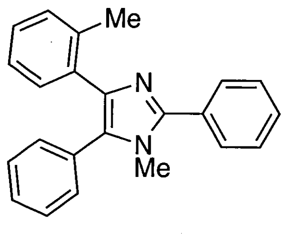
1-Methyl-2,5-diphenyl-4-(3-methoxyphenyl)-*1H*-imidazole (17j)



Chemical Formula: $C_{23}H_{20}N_2O$
Exact Mass: 340.1576
Molecular Weight: 340.4177

66% yield, colorless sticky oil, Rf = 0.25 (*n*-Hex : EtOAc = 1 : 1). IR (neat) 3056, 2932, 2832, 1601, 1238, 1043 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.51 (s, 3H, NMe), 3.66 (s. 3H, OMe), 6.73 (ddd, J = 7.8, 2.7, 1.5 Hz, 1H, Ar), 7.11-7.18 (m, 3H, Ar), 7.43-7.53 (m, 8H, A), 7.77 (d, *J* = 6.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 33.0 (NMe), 54.9 (OMe), 114.5, 112.9, 119.4, 128.5, 128.6, 128.6, 128.8, 129.0, 129.1, 130.6, 130.8, 130.9, 131.2, 135.9, 137.5, 147.8, 159.4 (Ar). MS (EI) *m*/*z* 340 (M^+); HRMS (EI) Calcd for $C_{23}H_{20}N_2O$ (M^+); 340.1576. Found: 340.1570.

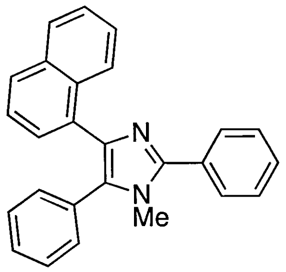
1-Methyl-2,5-diphenyl-4-(2-methylphenyl)-*1H*-imidazole (17k)



Chemical Formula: $C_{23}H_{20}N_2$
Exact Mass: 324.1626
Molecular Weight: 324.4183

56% yield, white solid, mp 50-51 °C, Rf = 0.39 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 2921, 1601, 1498, 1469, 1377, 1073 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.21 (S, 3H, Me), 3.72 (s, 3H, Me), 7.12-7.18 (m, 2H, Ar), 7.30-7.55 (m, 10H, Ar), 7.83 (d, *J* = 7.3 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 20.3 (Me), 33.9 (NMe), 125.2, 127.1, 127.4, 127.6, 128.4, 128.6, 128.9, 129.9, 130.1, 130.7, 130.8, 130.9, 131.5, 134.4, 137.0, 139.1, 147.8 (Ar). MS (EI) *m*/*z* 324 (M^+); HRMS (EI) Calcd for $C_{23}H_{20}N_2$ (M^+); 324.1626. Found: 324.1624.

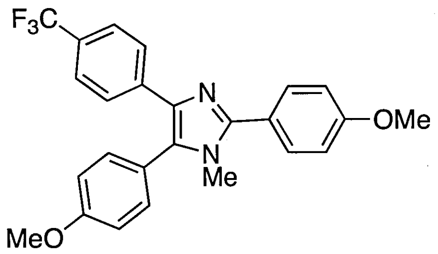
1-Methyl-2,5-diphenyl-4-(1-naphtyl)-*1H*-imidazole (17l)



Chemical Formula: $C_{26}H_{20}N_2$
Exact Mass: 360.1626
Molecular Weight: 360.4504

78% yield, white solid, mp 95-96 °C, Rf = 0.25 (*n*-Hex : EtOAc = 4 : 1). IR (KBr) 3053, 2952, 1470, 1374, 1314, 771, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H, NMe), 7.26-7.52 (m, 12H, Ar), 7.74-7.84 (m, 4H, Ar), 8.30 (d, *J* = 8.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 34.0 (NMe), 125.1, 125.4, 125.7, 126.7, 127.5, 127.8, 127.9, 128.4, 128.5, 128.5, 128.7, 129.0, 129.1, 130.1, 139.3, 130.9, 132.4, 132.6, 133.9, 138.1, 148.0 (Ar). MS (EI) *m*/*z* 360 (M^+); HRMS (EI) Calcd for $C_{26}H_{20}N_2$ (M^+); 360.1626. Found: 360.1615.

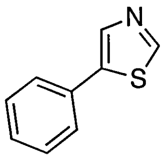
1-Methyl-2,5-bis(4-methoxyphenyl)- 4-(4-trifluoromethylphenyl)-*1H*-imidazole (17m)



Chemical Formula: $C_{25}H_{21}F_3N_2O_2$
Exact Mass: 438.1555
Molecular Weight: 438.4416

86% yield, white solid, mp 65-66 °C, Rf = 0.43 (*n*-Hex : EtOAc = 1 : 1). IR (KBr) 2932, 1616, 1495, 1324, 1250 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H, NMe), 3.87 (s, 3H, OMe), 3.88 (s, 3H, OMe), 7.01-7.04 (m, 4H, Ar), 7.31 (d, *J* = 8.8 Hz, 2H, Ar), 7.47 (d, *J* = 8.3 Hz, 2H, Ar), 7.65-7.69 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.3 (NMe), 54.9 (OMe), 55.0 (OMe), 113.8, 114.4, 122.5, 122.9 (Ar), 124.2 (q, *J* = 271.3 Hz, $\underline{C}F_3$), 124.7 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 126.2, (Ar), 127.7 (q, *J* = 32.3 Hz, $\underline{C}$-CF_3), 130.1, 130.9, 131.7, 135.6, 138.2, 147.7, 159.8, 159.9 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.6 (CF_3). MS (EI) *m*/z: 438 (M^+). HRMS (EI): Exact mass calcd for $C_{25}H_{21}F_3N_2O_2$ (M^+); 438.1555. Found: 438.1553.

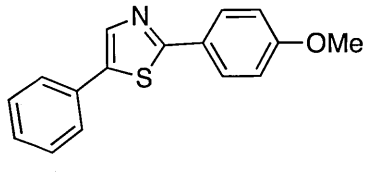
5-Phenylthiazole (18)[28]



Chemical Formula: C_9H_7NS
Exact Mass: 161.0299
Molecular Weight: 161.2236

53% yield, yellow solid, Rf = 0.22 (*n*-Hex : EtOAc = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 7.35-7.44 (m, 3H, Ar), 7.59 (d, *J* = 9.3 Hz, 2H, Ar), 8.09 (s, 1H, Ar), 8.76 (s, 1H, Ar).

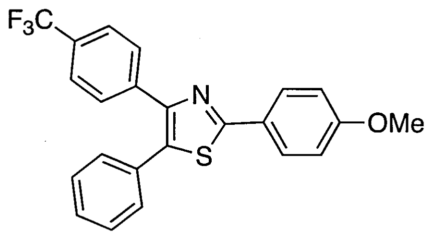
2-(4-Methoxyphenyl)-5-phenylthiazole (19)[6] (Method I)



Chemical Formula: $C_{16}H_{13}NOS$
Exact Mass: 267.0718
Molecular Weight: 267.3455

88% yield, white solid, Rf = 0.50 (*n*-Hex : EtOAc = 3 : 1).^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H, OMe), 6.98 (d, *J* = 8.8 Hz, 2H, Ar), 7.32 (t, *J* = 7.3 Hz, 1H, Ar), 7.42 (dd, *J* = 7.8, 7.3 Hz, 2H, Ar), 7.60 (d, *J* = 7.8 Hz, 2H, Ar), 7.92 (d, *J* = 8.8 Hz, 2H, Ar), 7.98 (s, 1H, Ar).

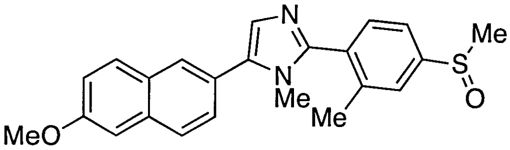
2-(4-Methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenylthiazole (20)



Chemical Formula: $C_{23}H_{16}F_3NOS$
Exact Mass: 411.0905
Molecular Weight: 411.4394

62% yield, white solid, mp 95-97 °C, Rf = 0.50 (*n*-Hex : EtOAc = 10 : 1). IR (KBr) 3027, 2937, 2835, 1607, 1575, 1324, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H, OMe), 7.00 (d, *J* = 9.3 Hz, 2H, Ar), 7.36-7.40 (m, 5H, Ar), 7.56 (d, *J* = 8.3 Hz, 2H, Ar), 7.73 (d, *J* = 8.3 Hz, 2H, Ar), 7.96 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe), 113.6 (Ar), 124.1 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 125.2 (q, *J* = 3.3 Hz, $\underline{C}$=C-CF_3), 126.4, 128.0, 128.5, 129.0, 129.3 (Ar), 129.6 (q, *J* = 32.7 Hz, $\underline{C}$-CF_3), 129.7, 131.7, 133.7, 138.6, 148.9, 161.4, 166.0 (Ar). ^{19}F NMR ($CDCl_3$) δ -62.9 (CF_3). MS (EI) *m*/*z*: 438 (M^+). HRMS (EI) *m*/*z*: Exact mass calcd for $C_{23}H_{16}F_3NOS$ (M^+); 411.0905. Found: 411.0905.

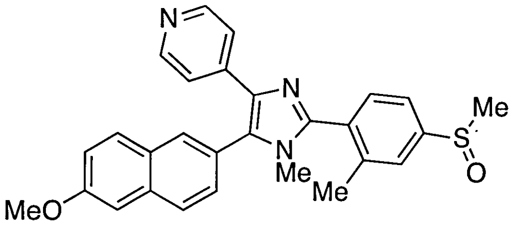
1-Methyl-2-(4-methanesulfinyl-2-methylphenyl)-5-(6-methoxynaphthalen-2-yl)-*1H*-imidazole (25)



Chemical Formula: $C_{23}H_{22}N_2O_2S$
Exact Mass: 390.1402
Molecular Weight: 390.4980

58% yield, white solid. mp 190.5-191.5 °C, Rf = 0.05 (DCM : MeOH = 100 : 1). IR (KBr) 2926, 2865, 1733, 1632, 1507, 1456, 1352, 1251, 1135, 1011, 903 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, Me), 2.78 (s, 3H, Me), 3.52 (s, 3H, Me), 3.95 (s, 3H, Me), 7.18-7.19 (m, 1H, Ar), 7.21 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H, Ar), 7.31 (s, 1H, Ar), 7.54 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar), 7.56-7.58 (m, 2H, Ar), 7.66 (s, 1H, Ar), 7.79 (d, *J* = 8.8 Hz, 1H, Ar), 7.82-7.85 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ 20.0, 32.6, 43.8, 55.3 (Me), 105.6, 119.5, 120.7, 125.0, 125.2, 126.9, 127.2, 127.3, 127.3, 128.6, 129.4, 131.4, 133.5, 133.9, 134.4, 140.1, 146.5, 147.2, 158.1 (Ar). MS (EI) *m*/*z*: 390 (M^+). HRMS (EI): Exact mass calcd for $C_{23}H_{22}N_2O_2S$ (M^+); 390.1402. Found: 390.1404.

1-Methyl-2-(4-methanesulfinyl-2-methylphenyl)-4-(4-pyridyl)-5-(6-methoxynaphthalen-2-yl)-*1H*-imidazole (23)[4c]



Chemical Formula: $C_{28}H_{25}N_3O_2S$
Exact Mass: 467.1667
Molecular Weight: 467.5820

64% yield, yellow solid, Rf = 0.35 (MeOH : hexane = 1 : 10). ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H, Me), 2.77 (s, 3H, Me), 3.32 (s, 3H, Me), 3.98 (s, 3H, Me), 7.24-7.27 (m, 2H, Ar), 7.44-7.46 (m, 3H, Ar), 7.58 (d, *J* = 8.3 Hz, 1H, Ar), 7.63 (d, *J* = 7.8 Hz, 1H, Ar), 7.68 (s, 1H, Ar), 7.79 (d, *J* = 9.8 Hz, 1H, Ar), 7.86 (s, 1H, Ar), 7.91 (d, *J* = 8.3 Hz, 1H, Ar), 8.36 (d, *J* = 5.9 Hz, 2H, Ar).

References and notes

(1) (a) Sohda, K.; Hiramoto, M.; Suzumura, K.; Takebayashi, Y.; Suzuki, K.; Tanaka, A. *J. Antibiot.* **2004**, *58*, 32. (b) Sohda, K.; Nagai, K.; Yamori, T.; Suzuki, K.; Tanaka, A. *J. Antibiot.* **2005**, *58*, 27. (c) Cummings, G. C.; Ross, T. N.; Katt, P. W.; Hamilton, D. A. *Org. Lett.* **2009**, *11*, 25. (d) Lefranc, D.; Ciufolini, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4198. (e) Demirbas, A.; Sahin, D.; Demirbas, N.; Karaoglu, A. S. *Eur. J. Med. Chem.* **2009**, *44*, 2896. (f) Sarojini, K. B.; Krishna, B. G.; Darshanraj, C. G.; Bharath, R. B.; Manjunatha, H. *Eur. J. Med. Chem.* **2010**, *45*, 3490.

(2) Champagne, B.; Kirtman, B. in *Handbook of Advanced Electronic and Photonic Materials and Devices*, Nalwa, S. N. Eds., Nonlinear Optical Materials, vol. 9, Academic Press, San Diego, 2001.

(3) (a) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron*, **2003**, *59*, 5685. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200.

(4) (a) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K.; *J. Org. Chem.* **2009**, *74*, 1826. (b) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3276. (c) Campeau, L.-C.; Stuart, R. D.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

(5) Joo, J. M.; Tour, B. B.; Sames, D. *J. Org. Chem.* **2010**, *75*, 4911.

(6) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Comm.* **2010**, *46*, 2471.

(7) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (b) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622.

(8) Roy, D.; Mom, A.; Beaupérin, M.; Doucet, H.; Hierso, J.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 6459.

(9) For recent reviews: (a) Meijere, D. A.; Diederich, F. *Metal-catalyzed Cross-coupling Reactions*, 2nd Ed. Wiley-VCH, Weinheim, 2004. (b) Fairlamb, J. S. I. *Chem. Soc. Rev.* **2007**, *36*, 1036.

(10) Vedejs, E.; Luchetta, M. L. *J. Org. Chem.* **1999**, *64*, 1011.

(11) (a) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (b) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362.

(12) Campeau, L.-C.; Bertrand-Laperle, L.-C.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276.

(13) Bellila, F.; Cauteruccio, S.; Di Fiore, A.; Rossi, R. *Eur. J. Org. Chem.* **2008**, 5436.

(14) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011.

(15) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578.

(16) For a review, see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(17) For example, addition of aryl radicals that are generated by using an appropriate radical initiator or one-electron transfer to aryl iodides, to benzene derivatives followed by elimination of a hydrogen radical give the biaryl compounds. For a recent review see: (a) Bowman, W. R.; Storey, J. M. D.

Chem. Soc. Rev. **2007**, *36*, 1803. Also, it is well-known that palladium complexes afford radical species such as $\mathrm{Pd}^{\cdot 1+}$ and $\mathrm{Pd}^{\cdot 3+}$, and those are participated in living radical polymerizations and oxidation reactions, see: (b) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921. (c) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689. (d) Boisvert, L.; Denney, M. C.; Hanson, S. K.; Goldberg, K. I. *J. Am. Chem. Soc.* **2009**, *131*, 15802. In addition, generation of Pd(III) species via one-electron oxidation was reported, see: (e) Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 15618.

(18) Very recently, direct arylations of unactivated arenes via a radical pathway were reported, see: (a) Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, 132, 1514. (b) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (c) Shirakawa, E.; Itoh, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537 (d) Sun, C.-L.; Li, Hu L.; Yu D.-G.; Yu, M.; Zhou X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi Z.-J. *Nat. Chem.* **2010**, *2*, 1044.

(19) The reaction via a Heck type carbopalladation–β-elminination pathway can also be considered, but no evidence for the pathway with the present catalytic system was obtained thus far. For a recent example for this reaction pathway, see: Wang J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett*, **2008**, *10*, 2923.

(20) Albéniz, A. C.; Espinet, P.; López-Feenández, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 11278.

(21) For example: Mitsudo, K.; Shiraga, T.; Kagen, D.; Shi, D.; Becker, J. Y.; Tanaka, H. *Tetrahedron* **2009**, *65*, 8384.

(22) (a) van Helden, R.; Verberg, G. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1263. (b) Mousseau, J. J.; Vallée, F. V.; Lorion, M. M.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 14412.

(23) Champagne, B.; Kirtman, B. in *Handbook of Advanced Electronic and Photonic Materials and Devices*, Nalwa, S. N. Eds., Nonlinear Optical Materials, vol. 9, Academic Press, San Diego, 2001.

(24) Izumi, Y.; Satoh, Y.; Kondoh H. Urabe, K. *J. Mol. Catal.*, **1992**, *72,* 37.

(25) Subhasis S.; Ganesh C. N.; Pallavi S.; Singh, M.S. *Tetrahedron* **2009**, *65*, 10155.

(26) Tony, H.; Stepan, C.; Natalia, C.; Vladimir, G.; Valery, V. F. *J. Am. Chem. Soc.* **2008**, *130*, 14974.

(27) Gemma, L. T.; James, A. M.; Michael, F. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996.

(28) Pavlik, J. W.; Tongcharoensirikul, P.; Bird, N. P.; Day, A. C.; Barltrop, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 2292.

List of Publications

Parts of the present thesis have been, or are to be, published in the following journals.

(1) "Synthesis of 1,3-diarylated imidazo[1,5-a]pyridines with a combinatorial approach: metal-catalyzed cross-coupling reactions of 1-halo-3-arylimidazo-[1,5-a]pyridines with arylmetal reagents"
Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron,* **2009**, *65*, 5062-5073.

(2) "Direct multiple C–H bond arylation reaction of heteroarenes catalyzed by cationic palladium complex bearing 1,10-phenanthroline"
Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471-2473.

(3) "Direct arylation of simple azoles catalyzed by 1,10-phenanthroline containing palladium complexes: An investigation of C4 arylation of azoles and synthesis of triarylated azoles by sequential arylation"
Shibahara, F.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2011**, *in press.*

Following publications are not included in this thesis.

(1) "Synthesis of 2-azaindolizines by using an iodine-mediated oxidative desulfurization promoted cyclization of *N*-2-pyridylmethyl thioamides and investigation of their photophysical properties"
Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621-5624

(2) "Synthesis of fluorescent 1,3-diarylated imidazo[1,5-*a*]pyridines: oxidative condensation–cyclization of aryl-2-pyridylmethylamines and aldehydes with elemental sulfur as an oxidant"
Shibahara, F.; Sugiura, R.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566-3568.

Acknowledgements

This study has been performed by the author under the guidance of Professor *Toshiaki Murai* at Department of Chemistry, Faculty of Engineering, Gifu University for the period from 2005 to 2011.

The author wishes to express his deepest gratitude to Assistant Professor *Fumitoshi Shibahara* for his guidance, helpful suggestions in the accomplishment of this work.

The author is grateful to Professor *Toshiaki Murai* for their constant advices.

Furthermore, the author wishes to thank *Ms. Asumi Sano* (nee *Sano*), *Ms. Aiko Sano* (nee *Suenami*), *Ms. Rie Yamaguchi* (nee *Toshio*), *Mr. Daichi Matsuoka, Ms. Noriko Mizuhata, Mr. Shinsuke Inaji, Mr. Nao Endo, Mr. Sho Nogawa, Ms. Kozue Nakagai* (nee *Fukushima*), *Ms. Akika Yamada* (nee *Yamada*) and *Atsunori Yoshida* for their instructive suggestions and be grateful to *Mr. Fumio Asai, Mr. Akio Imai, Mr. Touru Takenaka and Ms. Hiromi Tsuji* for their friendship.

His gratitude is extended to all the members of the Toshiaki Murai research group for their kind supports and hearty cooperation with him. Especially, the author thanks *Ms. Rie Sugiura, Mr. Shunsuke Tahara, Mr. Shunichiro Kobayashi Ms. Rumi Hori* and *Mr. Takafumi Kanai* for their technical assistance.

Finally, the author would like to express his thanks to his father, brother, sister and grandparents for their personal support.

March 2011

Eiji Yamaguchi