Synthesis of Multi-Substituted Heteroarenes via Palladium-Catalyzed C-H Bond Cleavage and Decarboxylation

Mitsuru Miyasaka

Osaka University

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Preface

The study in this thesis has been carried out under the direction of Professor Masahiro Miura at the Department of Applied Chemistry, Fuculty of Engineering, Osaka University from April 2008 to March 2011.

The thesis is concerned with the synthesis of multi-substituted heteroarenes via palladium-catalyzed C-H bond cleavage and decarboxylation.

Department of Applied Chemistry

Graduate School of Engineering, Osaka University

Suita, Osaka, Japan

March, 2011

Mitsru Miyasaka

Contents

General Introduction

Development of C-C bond formation reaction is one of the most important subjects in modern organic chemistry. The palladium-catalyzed cross-couplings are now recognized to be powerful synthetic tools for C–C bond formation because they can form various types of C-C bonds with high efficiency and selectivity (Scheme 1).[1]

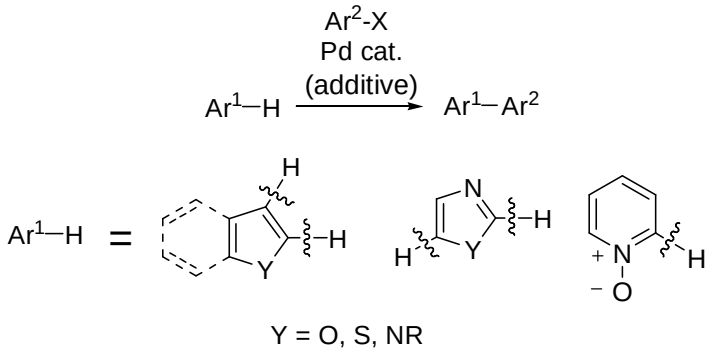
$$R{-}m \;+\; R'{-}X \xrightarrow[(addtive)]{\text{Pd cat.}} R{-}R' \;+\; Xm \qquad (1)$$

X = I, Br, Cl, TfO, • • • m = Mg, B, Si, Sn, Zn • • •

R = R' = aryl, alkenyl, alkyl, • • •

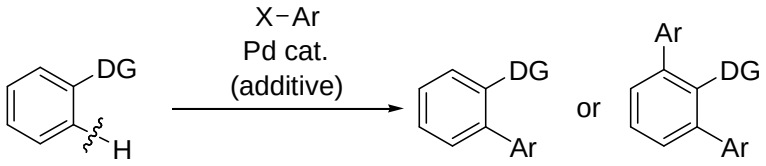
SCHEME 1. Cross-Coupling Reaction

Recently, not only the above traditional cross-couplings with organometallic reagents but also direct couplings via C-H bond cleavage have attracted much attention since they require no prefunctionalization step of the starting materials and provide a potentially more efficient alternative to the conventional methodologies.[2] In particular, various Pd-catalyzed direct arylations of electron-rich and -deficient heteroarenes have been widely explored (Scheme 2).[3] The reactions of electron-rich heteroarenes are mostly considered to proceed via S_E type mechanism, while those of electron-deficient ones may involve concerted metallation-deprotonation (CMD) mechanism.[2]



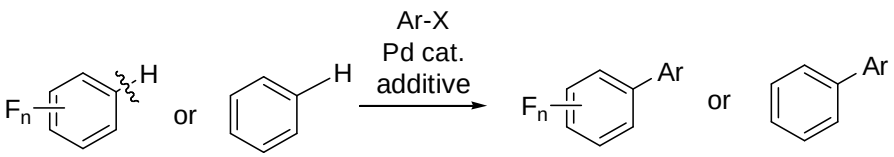
SCHEME 2. Direct C-H Arylation of Electron-Rich and -Deficient Heteroarenes

The direct arylation of benzene rings also proceeds with the aid of directing groups[2] such as phenolic hydroxyl group,[4] amide,[5] 2-pyridyl,[6] and carbamate.[7] The reaction gives the corresponding *ortho*-arylated product with high regioselectivity via proximal C-H bond cleavage (Scheme 3).



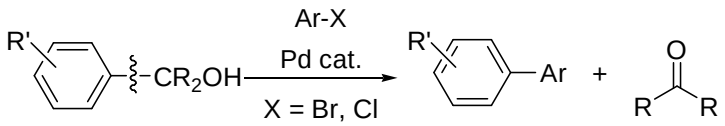
SCHEME 3. Direct C-H Arylation of Arenes Having a Directing Group

In addition, recent efforts have enabled the direct arylation of electron-deficient fluoroaromatics and benzene itself without the above chelation assistance (Scheme 4).[8] Moreover, direct dehydrogenative coupling reactions have also been developed.[9]



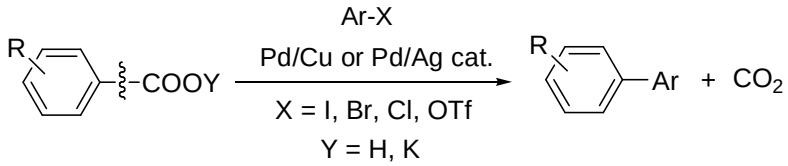
SCHEME 4. Direct C-H Arylation of Electron-Deficient Fluoroaromatics or Simple Benzenes

On the other hand, cross-coupling via cleavage of C-C bond as well as C-H bond has also received great interest.[10] For example, Miura and co-workers reported the arylation of α,α-disubstituted arylmethanols with aryl halides via cleavage of the sp^2C-sp^3C bond with the liberation of a ketones (β-carbon elimination) to give the corresponding biaryls (Scheme 5).[11]



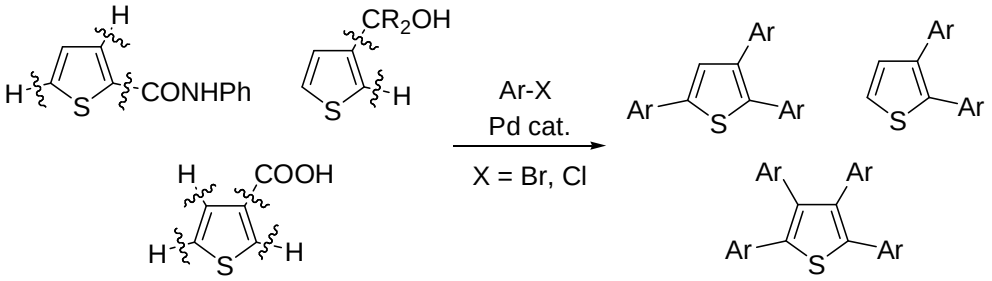
SCHEME 5. Cross-Coupling via β-Carbon Elimination

Goossen et al. developed the Pd/Cu or Pd/Ag co-catalyzed decarboxylative arylation of *ortho*-substituted benzoic acids with aryl halides (Scheme 6).[12] The analogous reaction of potassium carboxylates with aryl triflates was found to accommodate *meta*- and *para*-substituted patterns.[13]



SCHEME 6. Decarboxylative Arylation

These carbon functional groups work as not only a leaving group but also a directing group. Miura and co-workers reported the multi-arylation of thiophenes bearing an amide, an α,α-disubstituted methanol, or a carboxyl group via successive C-H and C-C bond cleavages (Scheme 7).[14]



SCHEME 7. Multi-Arylation of Thiophenes Having Carbon Functional Groups via C-H and C-C bond Cleavages

Meanwhile, multi-substituted heteroarenes are found in a large number of biologically active natural and unnatural compounds, and functional materials. Therefore, the development of efficient and selective methods for the construction of these compounds is of considerable importance in organic synthesis.

The purpose of this study is to develop methods for the synthesis of multi-substituted heteroarenes via C-H bond cleavage and decarboxylation using palladium catalysts. This thesis consists of the following three chapters.

Chapter 1 describes the synthesis of 2,3-diarylindoles via C-H bond cleavage and decarboxylation.

Chapter 2 describes the synthesis of multi-substituted benzothiophenes via decarboxylative arylation as the key synthetic process.

Chapter 3 refers to the synthesis of 5-alkenylazoles via direct alkenylation, so-called Fujiwara-Moritani reaction.

Finally, this work is summarized in the conclusion section.

References

(1) a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., eds.; Wiley-VCH: Weinheim, 2004. b) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004. c) *Cross-Coupling Reactions*; Miyaura, N., Ed.; *Top. Curr. Chem. 219*; Springer: Berlin, 2002.

(2) For recent reviews of C-H activation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (g) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (h) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (j) Lapointe, D; Fagnou, K. *Chem. Lett.* **2010**, 1118

(3) Selected examples: (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (c) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685. (d) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Let*t. **2003**, *5*, 301. (e) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (f) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083. (g) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (h) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, M. *Org. Lett.* **2005**, *7*, 5083. (i) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (j) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (k) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (l) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888. (m) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (n) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc*. **2008**, *130*, 3276. (o) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (p) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060. (q) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (r) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383. (s) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (t) Campeau, L.-C.; Stuart, D. R.; 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. (u) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. (v) Ackermann, L.; Barfuβer, S. *Synlett* **2009**, 808. (w) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (x) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946.

(4) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (b) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.

(5) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655.

(6) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.

(7) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

(8) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (c) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (d) Rene, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.
(9) (a) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (c) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (d) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (f) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (g) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (h) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850. (i) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (j) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (k) Brasche, G.; Garcı´a-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (l) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (m) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837.
(10) For recent reviews of C-C activation: (a) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022. (b) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (c) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (d) Bonesi, S. M.; Fagnoni, M. *Chem. Eur. J.* **2010**, *16*, 13572. (e) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395.
(11) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.
(12) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Goossen, L. J.; Rodoriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (c) Goosen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (d) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945. (e) Shang, R.; Fu, Y.; Li, J. B.; Zhang, S. L.; Guo, Q. X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738. (f) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, 48, 9350. (g) Goossen, L. J.; Lange, P. P.; Rodriguez, N.; Linder, C. *Chem. Eur. J.* **2010**, *16*, 3906.
(13) (a) Goosen, L. J.; Rodríguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (b) Goossen, L. J.; Linder, C.; Rodríguez, N.; Lange P. P. *Chem. Eur. J.* **2009**, *15*, 9336.
(14) (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (b) Nakano, M.; Satoh, T.; Miura, M. *J. Org. Chem.* **2006**, *71*, 8309. (c) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851.

Chapter 1

Synthesis of 2,3-Diarylindoles via C-H Bond Cleavage and Decarboxylation

1.1 Introduction

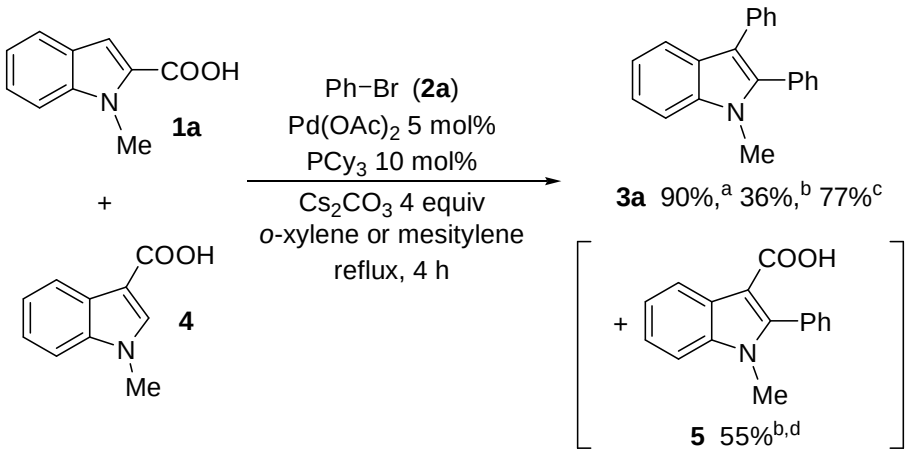
The indole nucleus is found in a large number of biologically active natural and unnatural compounds, and the synthesis of its derivatives is of considerable importance in organic chemistry.[1] In addition, as tryptophan is an intrinsic fluorescent probe in proteins, indole derivatives are known to display fascinating photophysical properties.[2] Thus, suitably arylated indoles may be considered to exhibit fluorescence, and the wavelength and intensity may depend on the nature of the aryl substituents. A literature search indicates that some 2,3-diarylindoles, for example 2,3-bis(4-methoxy and hydroxyphenyl)indoles, show not only interesting biological activities,[3a-g] but also fluorescence[3e-h] in the blue region, whereas very little is known about their fluorescent efficiency. Accordingly, because the development of efficient blue emitters is currently one of the important subjects in materials chemistry,[4,5] the synthesis of various related compounds is of particular interest in terms of their physical features and their biological behavior.

Transition-metal-catalyzed biaryl cross-coupling with aryl halides and aryl metal reagents is one of the most reliable methods for the synthesis of indoles having a variety of aryl functionalities, and recent advances in the metal-mediated direct C-H arylation reactions of heteroarenes provide an efficient access to C2- or C3-monoarylated indoles.[6,7] However, the 2,3-diarylation reactions on an indole scaffold are quite rare.[8] Thus, efficient methods for installing identical and different aryl groups at the 2- and 3-positions are required.[10] The present synthetic strategy involves sequential *ortho*- and *ipso*-arylations, and gratifyingly, it has been successfully utilized in carboxyindole systems.[12-14] Herein, the author reports the palladium-catalyzed 2,3-diarylation of carboxyindole derivatives with aryl bromides, as well as a

practical route to 2,3-diarylindoles having different aryl substituents by performing ester hydrolysis in the sequence. As result of these studies, the author has found a highly fluorescent 2,3-diarylindoles among the products, and their photoluminescent properties are described.

1.2 Results and Discussion

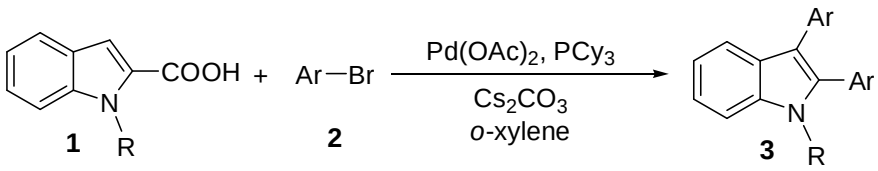
In a typical synthesis, treatment of 1-methyl-1*H*-indole-2-carboxylic acid (**1a**) with bromobenzene (**2a**) (3 equiv) in the presence of $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), and Cs_2CO_3 (4 equiv) in refluxing *o*-xylene for 4 h afforded 1-methyl-2,3-diphenyl-1*H*-indole (**3a**) in 90% yield (Scheme 1). In the reaction of 1-methyl-1*H*-indole-3-carboxylic acid (**4**) in place of **1a** under the same conditions, formation of the 2-monophenylated product, 1-methyl-2-phenyl-1*H*-indole-3-carboxylic acid (**5a**) (55%) was observed together with **3a** (36%). Thus, the second *ipso*-phenylation at the 3-position appears to be a relatively slower process. The reaction of **4** at a higher temperature using mesitylene as a solvent, however, gave **3a** in an acceptable yield (77%).

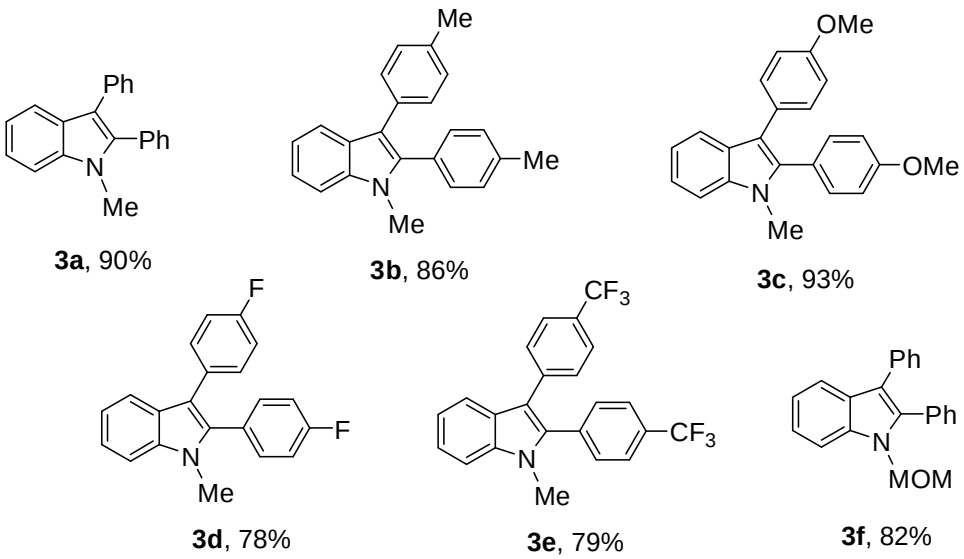


SCHEME 1. [a] Reaction of **1a** in *o*-xylene. [b] Reaction of **4** in *o*-xylene. [c] Reaction of **4** in mesitylene with addition of MS 4A (150 mg). [d] Determined by GC as its methyl ester **7a** after methylation with MeI.

Various aryl bromides having an electron-donating or -withdrawing group could be employed for the diarylation reaction of **1a** (Table 1). The reaction using other 2-carboxyindoles was also undertaken. Under the standard reaction conditions, *N*-methoxymethyl-protection was tolerated, and thus, carboxyindole **1b** coupled with **2a** to give the expected products **3f**.

TABLE 1. Reaction of 2-Carboxyindoles **1** with Aryl Bromides **2**.[a,b]



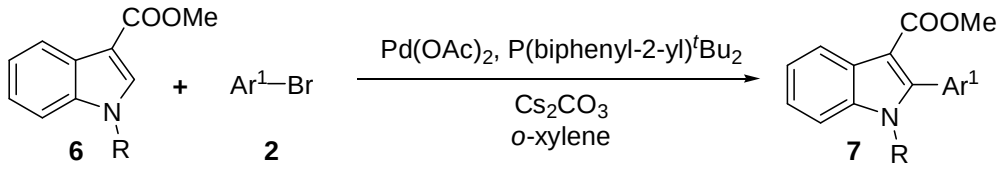


[a] A mixture of **1** (0.50 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol), and Cs_2CO_3 (1.5mmol) was stirred in refluxing *o*-xylene (2.5 mL) for 4 h under N_2. [b] Isolated yield.

To achieve the selective synthesis of indoles having different aryl groups at the 2- and 3-positions, we examined a stepwise diarylation with methyl esters of **1a** and **4** as the starting materials, since an ester function was found to be inert under the present conditions. The latter ester, methyl 1-methyl-1*H*-indole-3-carboxylate (**6a**) was effectively monoarylated with **2a**, **2c**, and **2d** using P(biphenyl-2-yl)^{t}Bu$_2$ as a ligand to give the corresponding 2-arylated products **7a**–**c**

in good yields (Table 2, entries 1–3), whereas the former ester did not react at all. The ligand PCy_3 was less effective in this case (entry 4). MOM-protected indole **6b** was also available for use (entry 5).

TABLE 2. Reaction of 3-(Methoxycarbonyl)indoles **6** with Aryl Bromides **2**.[a]

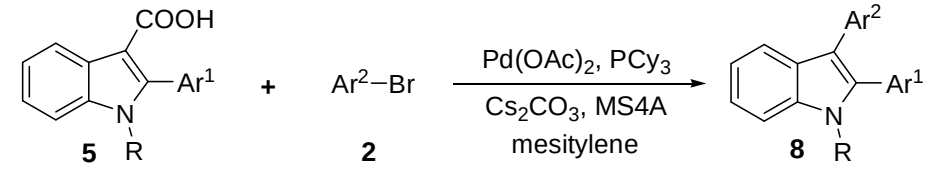


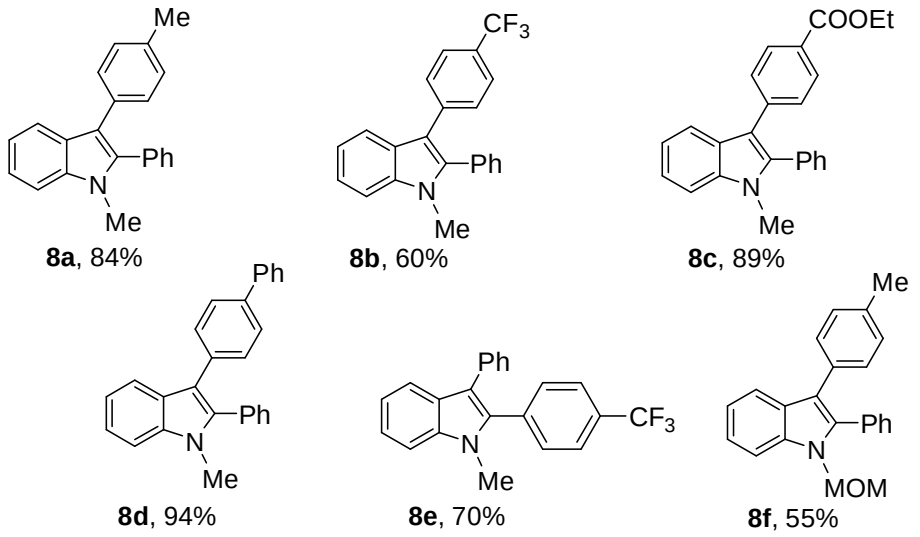
entry	**6**, R	**2**, Ar^1	**7**, Yield (%)[b]
1	**6a**, Me	**2a**,Ph	**7a**, 82
2	**6a**, Me	**2b**, 4-$MeOC_6H_4$	**7b**, 90
3	**6a**, Me	**2c**, 4-$CF_3C_6H_4$	**7c**, 79
4[c]	**6a**, Me	**2a**, Ph	**7a**, 57
5	**6b**, MOM	**2a**, Ph	**7d**, 82

[a] A mixture of **6** (0.50 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), P(biphenyl-2-yl)^tBu_2 (0.05 mmol), and Cs_2CO_3 (1.0 mmol) was stirred in refluxing *o*-xylene (2.5 mL) for 6 h under N_2. [b] Yield of isolated product. [c] PCy_3 was used as a ligand.

Then, **7a**, **7c**, and **7d** were hydrolyzed with ethanolic KOH to quantitatively afford the corresponding carboxylic acids. Subsequently, the acids were subjected to the second arylation accompanied by decarboxylation in mesitylene, and diarylindoles **8a**–**8f** were obtained in good yields (Table 3).

TABLE 3. Decarboxylative Arylation of **5**.[a,b]



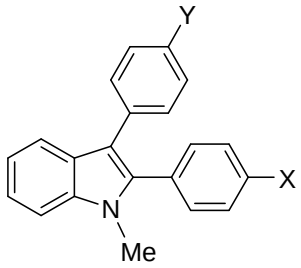


[a] A mixture of **5** (0.50 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol), and Cs_2CO_3 (1.0 mmol) was stirred in refluxing mesitylene (2.5 mL) for 6 h under N_2. [b] Isolated yield.

With the above 2,3-diarylindoles **3** and **8** in hand, a preliminary survey of their solid-state photoluminescence by using a UV lamp was carried out. It was found that 1-methyl-2,3-bis(4-trifluoromethylphenyl)-*1H*-indole (**3d**) was especially luminescent. Consequently, the photoluminescence spectra of **3d** and, to examine the substituent effects on the aryl groups, those of **3a**, **3c**, **8b**, and **8e** as well as their absorption spectra were measured for their ethanol solutions and solid powders (Table 4 and Figure 1). Accordingly, diarylindole **3d** is highly luminescent with emission maxima at 436 nm and 422 nm and with quantum yields of 0.90 and 0.97, in solution and as a solid, respectively. The quantum efficiency of the solid samples decreased in the following order: **3d**>**8e**>**3a**>**8b**>**3c**. This trend is the same as that in solution. In each case, the discrepancy between the emission maxima in solution and in the solid state is relatively small. These facts suggest that the solid-state luminescence in each case is

essentially based on the intrinsic structure and electronic conjugation of individual molecules.

TABLE 4. Optical Properties of 1-Methyl-2,3-diarylindoles.



3a; X = Y = H
3c; X = Y = MeO
3d; X = Y = CF_3
8b; X = H, Y = CF_3
8a; X = CF_3, Y = H

entry	**3** or **8**	$\lambda_{abs\text{-}sl}$ (nm)[a]	log ε	$\lambda_{em\text{-}sl}$ (nm)[b]	$\Phi_{f\text{-}sl}$[c]	$\lambda_{em\text{-}pw}$ (nm)[d]	$\Phi_{f\text{-}pw}$[e]
1	**3a**	225	4.63	418	0.51	419	0.65
		298	4.24				
2	**3c**	248	4.48	421	0.13	441	0.44
		299	4.22				
3	**3d**	225	4.80	436	0.90	422	0.97
		286	4.46				
4	**8b**	225	4.66	419	0.37	420	0.56
		296	4.30				
5	**8e**	225	4.63	438	0.64	426	0.76
		303	4.12				

[a] Absorption maximum in EtOH. [b] Emission maximum in EtOH. [c] Determined by comparison with ethanol solution of anthracene (Φ_f = 0.30) excited at 254 nm. [d] Emission maximum of solid powder excited at 350 nm. [e] Absolute quantum yield determined by an integrating sphere system.

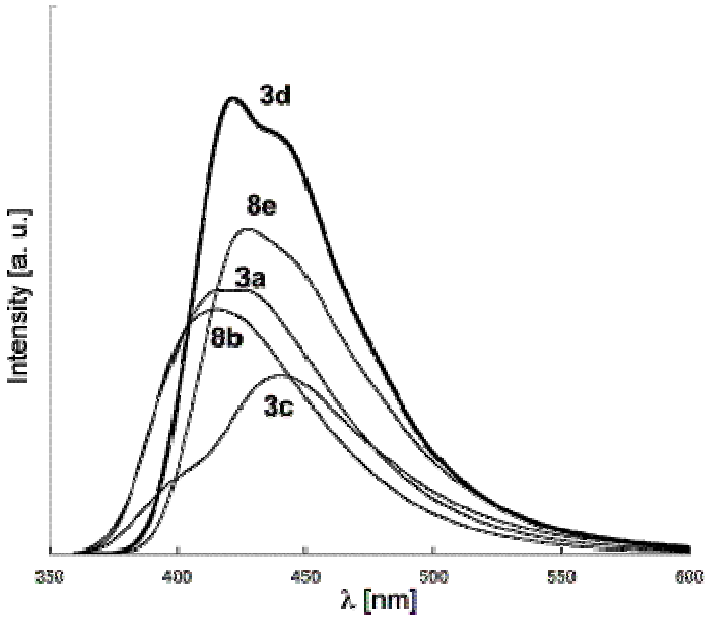


FIGURE 1. Photoluminescence Spectra of the Powders of 1-Methy-2,3-diarylindoles **3** and **8.**

This was, at least in the case of **3d**, supported by the crystal structure and packing determined by single-crystal X-ray diffraction (Figure 2). The torsion angles between the indole plane and the C2 and C3 aryl groups are 45 º and 43 º, respectively, which appear to prevent intermolecular electronic interactions. In this case, the presence of two CF_3 substituents also appears to be an important factor in allowing the almost perfect quantum yield in the solid (Table 4). However, further studies are needed to gain a better understanding of the observed remarkable effect of the substituents on the luminescent efficiency.

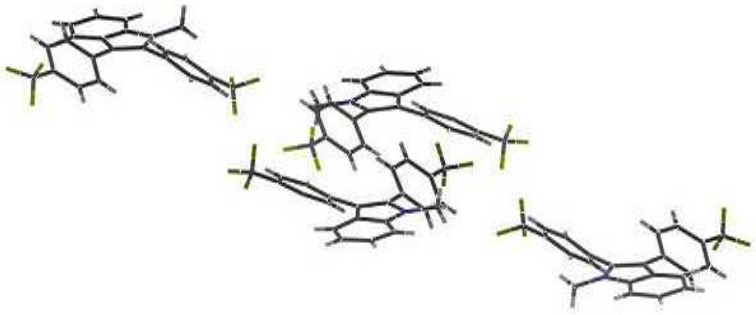


FIGURE 2. Molecular Structure of **3d** and its Packing ($P2_1/n$) within the Crystal Determined by Single-Crystal X-ray Diffraction.

1.3 Conclusion

Physically and biologically interesting 2,3-diarylindoles can be readily prepared by palladium-catalyzed direct and decarboxylative arylations using commercially available carboxyindoles. This approach has led to the discovery of a highly luminescent solid blue emitter.

1.4 Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for $CDCl_3$ solutions. MS data were obtained by EI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or a CBP-1 capillary column (i. d. 0.5 mm x 25 m). The fluorescence analysis of some products was carried out with the samples recrystallized from hexane-toluene or hexane-dichloromethane and then crashed. The absolute fluorescence quantum efficiency of the crashed crystal of **3a**, **3c**, **3d**, **8b**, and **8e** encapsulated in a quartz cell (30 x 30 x 0.3 mm) under deoxygenated conditions, was measured by using an integrating sphere unit (the excitation wavelength: 350 nm). Silica gel (Wakogel 200 mesh) was used for column chromatography. All reactions were carried out under nitrogen atmospheres.

Materials. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. *o*-Xylene and mesitylene were distilled from CaH. $Pd(OAc)_2$ was purchased from Wako. PCy_3 and P(biphenyl-2-yl)$^{t}Bu_2$ were obtained from Strem. Indolecarboxylate esters **6a**[13a] and **6b**[13b] were prepared by the methods reported previously.

Experimental Procedure

Palladium-Catalyzed Reaction of 1-Methyl-1*H*-indole-2-carboxylic Acid (1a) with Bromobenzene (2a). In a 20 mL two-necked flask were added bromobenzene (**2a**) (2 mmol,

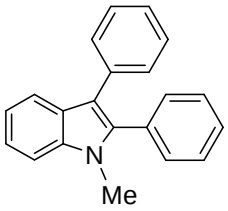
374 mg), 2-carboxyindole **1a** (0.5 mmol, 87 mg), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), PCy_3 (0.05 mmol, 14 mg), Cs_2CO_3 (2 mmol, 652 mg), 1-methylnaphthalene (ca. 50 mg) as internal standard, and *o*-xylene (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 170 ºC (bath temperature) for 4 h. After cooling, analysis of the mixture by GC confirmed the formation of compound **3a** (quantitatively). The product (127 mg, 90%) was also isolated by filtration of the mixture through a filter paper with ether as an eluent, evaporation of the solvents, and chromatography on silca gel using hexane-ethyl acetate (98:2, v/v).

Palladium-Catalyzed Reaction of Methyl 1-Methyl-1*H*-indole-3-carboxylate (6a) with Bromobenzene (2a). In a 20 mL two-necked flask were added bromobenzene (**2a**) (1 mmol, 157 mg), methyl 1-methyl-1*H*-indole-2-carboxylate (**6a**) (0.5 mmol, 94mg), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), P(biphenyl-2-yl)^{t}Bu$_2$ (0.05 mmol, 15 mg), Cs_2CO_3 (1 mmol, 325 mg), 1-methylnaphthalene (ca. 50 mg) as internal standard, and *o*-xylene (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 150 ºC (bath temperature) for 6 h. After cooling, analysis of the mixture by GC confirmed the formation of compound **7a** (quantitatively). The product (108 mg, 82%) was also isolated by filtration of the mixture through a filter paper with ether, evaporation of the solvents, and chromatography on silca gel using hexane-ethyl acetate (95:5, v/v)

Hydrolysis of Methyl 1-Methyl-2-phenyl-1*H*-indole-3-carboxylate (7a). In a 100mL flask were added methyl 1-methyl-2-pheny-1*H*-lindole-3-carboxylate (**7a**) (4.7 mmol, 1.2 g), potassium hydroxide (1.7 g, 30 mmol), water (24 mL), and ethanol (12 mL). The mixture was heated at 80 ºC (bath temperature) for 8 h under N_2. After cooling and acidification with aq. HCl (2 M), white precipitate was collected, washed with water, and dried under vaccum to afford carboxylic acid **5a** (1.12 g, 95%).

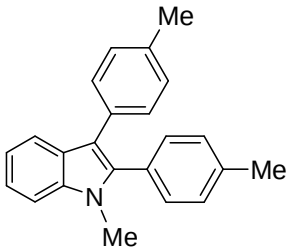
Palladium-Catalyzed Reaction of 1-Methyl-2-phenyl-1*H*-indole-3-carboxlic Acid (5a) with 4-bromotoluene (2b). In a 20 mL two-necked flask were added 4-bromotoluene (**2b**) (1 mmol, 171 mg), 1-Methyl-2-phenyl-1*H*-indole-3-carboxlic acid (**5a**) (0.5 mmol, 125mg), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), PCy_3 (0.05 mmol, 14 mg), Cs_2CO_3 (1 mmol, 325 mg), MS4A (150 mg), 1-methylnaphthalene (ca. 50 mg) as internal standard, and mesitylene (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 170 ºC (bath temperature) for 6 h. The product **8a** (125 mg, 84%) was isolated by filtration of the mixture through a filter paper with ether, evaporation of the solvents, and chromatography on silca gel using hexane-ethyl acetate (98:2, v/v)

Characterization Data of Products.

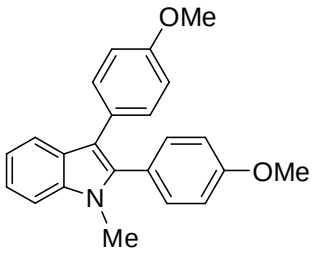


1-Methyl-2,3-diphenyl-1*H*-indole (3a)

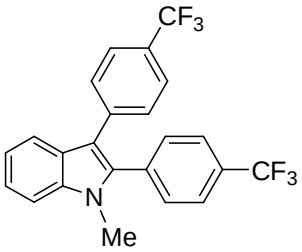
m.p. 137-139 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 7.14-7.42 (m, 13H), 7.79 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 109.8, 115.3, 119.8, 120.4, 122.4, 125.7, 127.2, 128.2, 128.4, 128.6, 130.1, 131.4, 132.1, 135.4, 137.5, 137.9; Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.73; H, 6.05; N, 4.87.



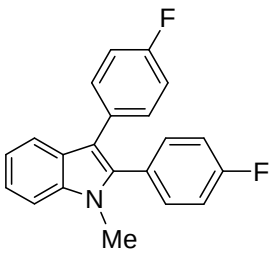
1-Methyl-2,3-bis(4-methylphenyl)-1*H*-indole (3b) m.p. 124-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.38 (s, 3H), 3.65 (s, 3H), 7.08 (d, J = 7.7 Hz, 2H), 7.14-7.23 (m, 7H), 7.28 (dd, J = 7.8 Hz, 7.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.6, 31.1, 109.7, 119.8, 120.2, 122.2, 128.6, 128.7, 129.1, 129.28, 129.32, 129.9, 131.2, 132.6, 135.1, 137.5, 137.9, 138.0; HRMS *m/z* (M^+) calcd for $C_{23}H_{21}N$: 311.1682, found: 311.1674.



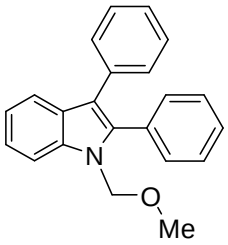
2,3-Bis(4-methoxyphenyl)-1-methyl-1*H*–indole (3c) m.p. 114-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 6.83 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.14-7.29 (m, 6H), 7.38 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 55.38, 55.46, 109.6, 114.0, 114.1, 114.4, 119.7, 120.2, 122.1, 124.5, 127,4, 128.0, 131.1, 132.5, 137.4, 137.5, 157.8, 159.6; HRMS *m/z* (M^+) calcd for $C_{23}H_{21}NO_2$: 343.1567, found: 343.1572.



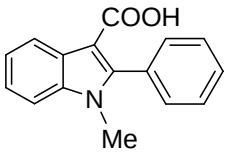
1-Methyl-2,3-bis(4-trifluoromethylphenyl)-1*H*-indole (3d) m.p. 170-172 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 7.23 (t, J = 6.6 Hz, 1H), 7.34-7.38 (m, 3H), 7.44 (d, J = 7.3 Hz, 3H), 7.53 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 109.9, 114.8, 119.5, 121.0, 123.1, 124.0 (q, J = 270 Hz), 124.4 (q, J = 270 Hz), 125.3 (q, J = 3.8 Hz), 125.6 (q, J = 3.8 Hz), 126.6, 127.8 (q, J = 32 Hz), 130.4, 129.5 (q, J = 32 Hz), 131.4, 135.2, 136.6, 137.7, 138.6; Anal. Calcd for $C_{23}H_{15}F_6N$: C, 65.87; H, 3.61; N, 3.34. Found: C, 65.60; H, 3.59; N, 3.36.



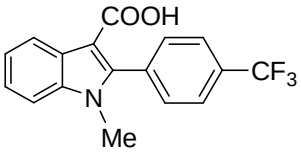
2,3-Bis(4-fluorophenyl)-1-methyl-1*H*–indole (3e) m.p. 147-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 6.97 (dd, J = 8.8Hz, 8.8Hz, 2H), 7.09 (dd, J = 8.8 Hz, 8.8 Hz, 2H), 7.17-7.33 (m, 6H), 7.41 (d, 1H), 7.71 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 109.8, 115.4 (d, J = 21 Hz), 115.9 (d, J = 21 Hz), 119.6, 120.6, 122.7, 127.1, 128.0, 131.17, 131.20, 131.5 (d, J = 7.5 Hz), 133.1 (d, J = 8.4 Hz), 136.8, 137.5, 161.4 (d, J = 243 Hz), 162.9 (d, J = 247 Hz); HRMS *m/z* (M^+) calcd for $C_{21}H_{15}F_2N$: 319.1171, found: 319.1173.



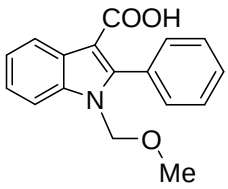
1-Methoxymethyl-2,3-diphenyl-1*H*-indole (3f) m.p. 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 3H), 5.37 (s, 2H), 7.16-7.40 (m, 12H), 7.57 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 55.9, 74.7, 110.2, 116.6, 119.73, 119.76, 121.0, 122.8, 125.8, 127.7, 128.2, 130.0, 131.37, 131.43, 134.7, 137.2, 137.6; Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.02; H, 6.04; N, 4.41.



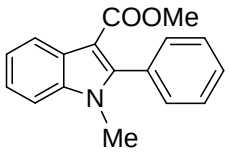
1-Methyl-2-phenyl-1*H*-indole-3-carboxylic acid (5a) m.p. 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3H), 7.28-7.50 (m, 8H), 8.30-8.32(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 104.3, 109.7, 122.3, 122.4, 123.0, 127.1, 128.1, 129.0, 130.3, 131.2, 136.9, 147.6, 170.1. HRMS m/z (M^+) Calcd for $C_{16}H_{13}NO_2$: 251.0946. Found: 251.0948.



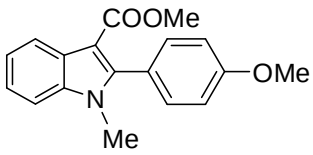
1-Methyl-2-(4-trifluoromethylphenyl)-1*H*-indole-3-carboxylic acid (5b) m.p. 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H), 7.32-7.39 (m, 3H), 7.55 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H), 8.29-8.31, (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 104.9, 109.8, 122.4, 122.7, 123.5, 124.0 (q, J = 271 Hz), 125.1 (q, J = 3.8 Hz), 126.8, 130.9, 131.2 (q, J = 33 Hz), 134.9, 137.1, 145.8, 170.1. HRMS m/z (M^+) Calcd for $C_{17}H_{12}F_3NO_2$: 319.0820. Found: 319.0819.



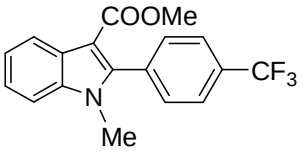
1-Methoxymethy-2-phenyl-1*H*-indole-3-carboxylic acid (5c) m.p. 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3H), 5.25 (s, 2H), 7.32-7.35 (m, 2H), 7.45-7.55 (m, 6H), 8.29-8.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 74.7, 105.9 110.6, 122.3, 122.9, 123.5, 127.2, 128.1, 129.3, 130.6, 130.7, 136.5, 147.6, 170.0. HRMS m/z (M^+) Calcd for $C_{17}H_{15}NO_3$: 281.1052. Found: 281.1048.



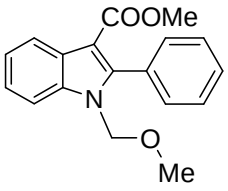
Methyl 1-methyl-2-phenyl-1*H*-indole-3-carboxylate (7a) m.p. 120-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 3H), 3.76 (s, 3H), 7.31-7.51 (m, 8H), 8.22-8.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 50.6, 105.0, 109.7, 122.0, 122.1, 122.8, 126.6, 128.0, 128.9, 130.3, 131.5, 136.8, 146.9, 165.5; Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.70; H, 5.78; N, 5.24.



Methyl 2-(4-methoxyphenyl)-1-methyl-1*H*-indole-3-carboxylate (7b) m.p. 147-148 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 3H), 3.77 (s, 3H), 3.88 (s, 3H), 7.00-7.04 (m, 2H), 7.28-7.38(m, 5H), 8.20-8.22(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 50.6, 55.3, 104.9, 109.7, 113.6, 121.9, 122.0, 122.7, 123.4, 126.6, 131.7, 136.8, 147.0, 160.1, 165.7; Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.81; H, 5.84; N, 4.69.

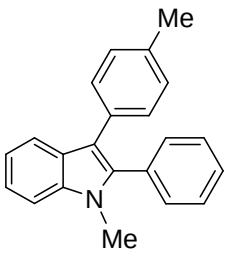


Methyl 1-methyl-2-(4-trifluoromethylphenyl)-1*H*-indole-3-carboxylate (7c) m.p. 142-144 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 3H), 3.76 (s, 3H), 7.33-7.41 (m, 3H), 7.55 (d, J = 8.0Hz, 2H), 7.76 (d, J = 8.0Hz, 2H), 8.22-8.24(m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 50.8, 105.6, 109.8, 122.1, 122.4, 123.3, 124.0 (q, J = 270 Hz), 125.1 (q, J = 3.8 Hz), 126.3, 130.8, 131.0 (q, J = 32 Hz), 135.2, 137.0, 144.9, 165.3; HRMS m/z (M^+) Anal. Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; N, 4.20. Found: C, 64.68; H, 4.35; N, 4.10.

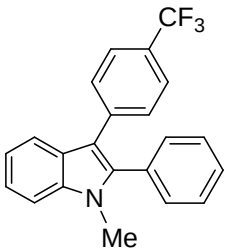


Methyl 1-methoxymethyl-2-phenyl-1*H*-indole-3-carboxylate (7d) m.p. 76-78 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 3H), 3.75 (s, 3H), 5.27 (s, 2H), 7.32-7.34 (m, 2H), 7.43-7.59(m, 6H), 8.22-8.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.8, 56.0, 74.7, 106.6, 110.6, 122.0, 122.6, 123.4, 126.7, 128.0, 129.1,

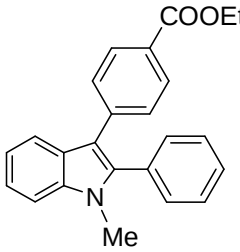
130.6, 130.9, 136.4, 146.8, 165.4; HRMS m/z (M^+) Calcd for $C_{18}H_{17}NO_3$: 295.1208. Found: 295.1220.



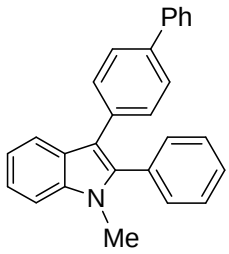
1-Methyl-3-(4-methylphenyl)-2-phenyl-1*H*-indole (8a) m.p. 155-156 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.66 (s, 3H), 7.07 (d, J = 8.1 Hz, 2H), 7.15-7.40 (m, 10H), 7.78 (d, J = 7.7 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 30.9, 109.5, 115.1, 119.7, 120.0, 122.0, 127.1, 127.9, 128.3, 128.9, 129.7, 131.1, 132.1, 132.2, 134.9, 137.3, 137.5; HRMS *m/z* (M^+) calcd for $C_{22}H_{19}N$: 297.1517, found: 297.1522.



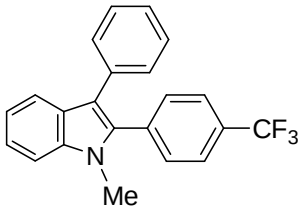
1-Methyl-2-phenyl-3-(4-trifluoromethylphenyl)-1*H*-indole (8b) m.p. 134-136 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 7.24 (t, J = 7.0 Hz, 1H), 7.30-7.45 (m, 9H), 7.50 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.0 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 109.8, 113.8, 119.2, 120.7, 122.5, 124.5 (q, J = 270 Hz), 125.1 (q, J = 3.8 Hz), 126.8, 127.3 (q, J = 32 Hz), 128.4, 128.6, 129.7, 130.6, 131.5, 137.4, 138.5, 139.2; HRMS *m/z* (M^+) calcd for $C_{22}H_{16}F_3N$: 351.1235, found: 351.1241.



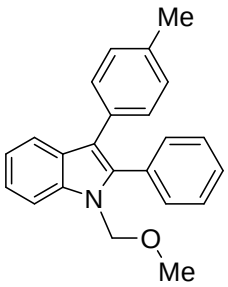
Ethyl 4-(1-methyl-2-phenyl-1*H*-indole-3-yl)benzoate (8c) m.p. 131-133 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.3 Hz, 3H), 3.68 (s, 3H), 4.35 (q, J = 7.3 Hz, 2H), 7.19-7.42 (m, 10H), 7.81 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 30.9, 60.7, 109.7, 114.3, 119.4, 120.6, 122.5, 126.7, 127.3, 128.4, 128.6, 129.4, 129.5, 131.1, 131.6, 137.5, 138.5, 140.4, 166.8; Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.96. Found: C, 80.89; H, 5.96; N, 3.94.



3-(4-Biphenylyl)-1-methyl-2-phenyl-1*H*-indole (8d) m.p. 132-134 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 7.21 (t, J = 7.7 Hz, 1H), 7.29-7.44 (m, 12H), 7.50-7.52 (m, 2H), 7.59-7.61 (m, 2H), 7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 109.6, 114.7, 120.0, 120.3, 122.2, 126.82, 126.86, 126.94, 126.99, 128.1, 128.4, 128.7, 130.1, 131.2, 132.0, 134.4, 137.4, 137.9, 138.0, 141.0; HRMS *m/z* (M^+) calcd for $C_{27}H_{21}N$: 359.1674, found: 359.1671.



1-Methyl-3-phenyl-2-(4-trifluoromethylphenyl)-1*H*-indole (8e) m.p. 139-141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 7.19-7.22 (m, 2H), 7.28-7.35 (m, 5H), 7.43 (m, 3H), 7.63 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 109.7, 116.3, 119.9, 120.5, 122.8, 124.1, (q, J = 271 Hz), 125.3 (q, J = 3.8 Hz), 125.9, 127.0, 128.4, 129.95 (q, J = 32 Hz), 129.96, 131.4, 134.6, 135.7, 135.9, 137.7; HRMS *m/z* (M^+) calcd for $C_{22}H_{16}F_3N$: 351.1235, found: 351.1233.



1-Methoxymethy-3-(4-methylphenyl)-2-phenyl-1*H*-indole (8f) m.p. 113-115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.24 (s, 3H), 5.37 (s, 2H), 7.15-7.32 (m, 11H), 7.39 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 55.9, 74.7, 110.2, 116.6, 119.8, 120.9, 122.7, 127.8, 128.1, 128.3, 129.0, 129.8, 131.4, 131.6, 131.7, 135.4, 137.2, 137.4; Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.09; H, 6.40; N, 4.17.

Crystal dada for compound 3d (CCDC No. 713262) MF $C_{23}H_{15}F_6N$, MW 419.37, Crystal Dimensions 0.58 x 0.27 x 0.10 mm, monoclinic, space group $P2_1/n$, a = 8.006(3) Å, b = 10.620(3) Å, c = 22.036(7) Å, β = 95.280(8)^{o}, V = 1865.7(10) Å^3, Z = 4, D_{calc} 1.493 g/cm^3,

μ(MoKα) 1.290 cm^{-1}, 21158 reflections easured, R1 = 0.15, R = 0.29, wR2 = 0.47.

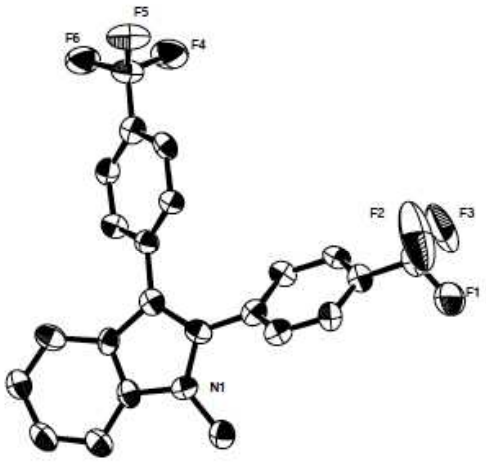


FIGURE 3 An ORTEP Drawing of Compound **3d**.

1.5 References and Notes

(1) For selected reviews: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (b) Gribble, G. W. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (e) Ackermann, L. *Synlett* **2007**, 507.

(2) (a) Medina, F.; Poyato, J. M. L.; Pardo, A.; Rodriguez, J. G. *J. Photochem. Photobiol. A.: Chem.* **1992**, *67*, 301. (b) Chen, Y.; Liu, B.; Yu, H.-T.; Barkley, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 9271.

(3) (a) Chesworth, R.; Wessel, M. D.; Heyden, L.; Mangano, F. M.; Zawistoski, M.; Genas, L.: Galluzo, D.: Lefker, B.; Cameron, K. O.; Tickner, J.; Lu, B.; Castleberry, T. A.; Petersen, D. N.; Brault, A.; Perry, P.; Ng, O.; Owen, T. A.; Pan, L.; Ke, H.-Z.; Brown, T. A.; Thompson, D. D.; DaSilva-Jardine, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5562. (b) Sutherland, A. G.; Alvarez, J.; Ding, W.; Foreman, K. W.; Kenny, C. H.; Labthavikul, P.; Mosyak, L.; Petersen, P. J.; Rush III, T. S.; Ruzin, A.; Tsao, D. H. H.; Wheless, K. L. *Org. Biomol. Chem.* **2003**, *1*, 4138. (c) Hu, W.; Guo, Z.; Yi, X.; Guo, C.; Chu, F.; Cheng, G. *Bioorg. Med. Chem.* **2003**, *11*, 5539. (d) Hu, W.; Guo, Z.; Chu, F.; Bai, A.; Yi, X.; Cheng, G.; Li, J. *Bioorg. Med. Chem.* **2003**, *11*, 1153. (e) Kasiotis, K. M. S.; Haroutounian, A. *Bioorg. Chem.* **2006**, *34*, 1. (f) Koulocheri, S. D.; Haroutounian, S. A. *Eur. J. Org. Chem.* **2001**, 1723. (g) Kaiser, D. G.; Bowman, B. J.; Forist, A. A. *Anal. Chem.* **1966**, *38*, 977. (h) Harrocks, D. L. *J. Chem. Phys.* **1969**, *50*, 4151.

(4) (a) Mitschke, U.; Buerle, P. *J. Mater. Chem.* **2000**, *10*, 1471. (b) Organic Light-Emitting Devices—Synthesis Properties and Applications (Eds.: K. Müllen, U. Scherf), Wiley-VCH, Weinheim, 2006.

(5) Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9760, and references therein.
(6) Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477.
(7) Recent work: (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 3994. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, 316, 1172. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (d) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R.; *Tetrahedron Lett.* **2007**, *48*, 2415. (e) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (f) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (g) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888. (h) Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428. (i) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (j) Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 1045. (k) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050.
(8) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607.
(9) (a) Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348*, 715. (b) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (c) Bellina, F.; Benelli, F.; Rossi, R.; *J. Org. Chem.* **2008**, *73*, 5529. (d) Cusati, G.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 2499. (e) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62.
(10) (a) Nakano, M.; Satoh, T.; Miura, M. *J. Org. Chem.* **2006**, *71*, 8309. (b) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851. (b) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.
(11) The *ortho*-arylation of benzoic acids: (a) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, Saunders, S. P. L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.
(12) Decarboxylative *ipso*-arylation: (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C. Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (c) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (d) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007,** *9*, 1781. (e) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (f) Goossen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (g) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022.
(13) (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*. 8146. (b) Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Process Res. Dev.* **2001**, *5*, 604.

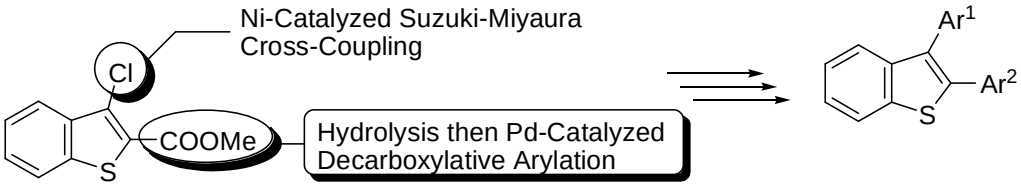
Chapter 2

Synthesis of 2,3-Disubstituted Benzothiophenes via Decarboxylative Arylation

2.1 Introduction

The benzo[*b*]thiophene nucleus is ubiquitous in biologically active compounds and functional materials.[1] In particular, 2,3-diarylbenzo[*b*]thiophenes and their 3-carbonyl- or heteroatom-inserted analogues are known to work as selective estrogen receptor modulator,[2] stubulin-binding agents,[3] multidrug resistanceassociated protein (MRP1) inhibitors,[4] angiogenesis inhibitors,[5] site-directed thrombin inhibitors,[6] anti-inflammatory agents,[7] and antifungal agents.[8] On the other hand, multiply arylated benzo[*b*]thiophenes[9] and further π-extended benzo[1,2-*b*;4,5-*b*']dithiophenes as well as their condensed aromatics[10] have recently aroused considerable interest in the field of organic electronics including light-emitting diodes (LEDs) and field-effect transistors (FETs).[11] Therefore, the development of efficient and selective methods for the construction of these arylated benzothiophenes and benzodithiophenes is of considerable importance in organic synthesis.

Here the author reports an efficient, convergent protocol for the synthesis of various 2,3-diarylbenzo[*b*]thiophenes and 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*']dithiophenes. As outlined in Scheme 1, the present synthetic approach relies on the sequential Suzuki–Miyaura cross-coupling reaction and decarboxylative arylation of 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene. The benzothiophene scaffold is easily prepared from cinnamic acid and thionyl chloride.[12] The use of commercially available 1,4-phenylenediacrylic acid instead of cinnamic acid as the starting material also allows the concise synthesis of the benzodithiophene system. The decarboxylative arylation with aryl halides under palladium catalysis has very recently emerged as one of the potential cross-coupling methods.[13,14]

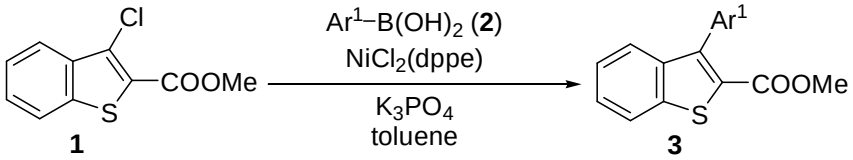


SCHEME 1. Synthetic Approach

2.2 Results and Discussion

Initially, the author carried out the first arylation of 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene (**1**) through nickel-catalyzed Suzuki–Miyaura cross-coupling reaction with arylboronic acids **2** (Table 1). The nickel based method induced efficient activation of the C-Cl bond.[15] Thus, benzothiophene **1** coupled with phenylboronic acid (**2a**) effectively in the presence of 5 mol% of $NiCl_2$(dppe) and 2.0 equivalents of K_3PO_4 in a boiling toluene to furnish **3a** in 91% isolated yield (entry 1). Electron-rich and electron-deficient aryl groups as well as the sterically demanding naphthalene motif could be introduced to the benzothiophene core without any difficulties (entries 2–5).

TABLE 1. Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction of 3-Chloro-2-methoxycarbonylbenzo[*b*]thiophene (**1**) with Arylboronic Acids **2**.[a]

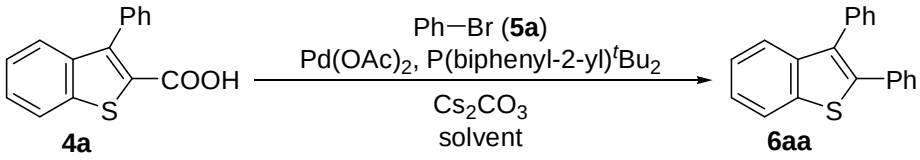


entry	**2**, Ar^1	Yield (%)[b]
1	**2a**, Ph	**3a**, 93
2	**2b**, 4-MeC_6H_4	**3b**, 83
3	**2c**, 4-$MeOC_6H_4$	**3c**, 97
4	**2d**, 4-$CF_3C_6H_4$	**3d**, 93
5	**2e**, 1-nap	**3e**, 93

[a] A mixture of **1** (3.0 mmol), **2** (4.5 mmol), $NiCl_2$(dppe) (0.15 mmol), and K_3PO_4 (6.0 mmol) was stirred in a boiling toluene (10 mL) for 6 h at 120 °C under N_2. [b] Isolated yield.

The monoarylated benzothiophenes **3** obtained above were readily hydrolyzed upon treatment with ethanolic KOH to afford the corresponding carboxylic acids **4a–e** quantitatively. Subsequently, the author selected **4a** and bromobenzene (**5a**) as model substrates and performed the palladium-catalyzed second arylation accompanied by decarboxylation [13,14] (Table 2). It was found that **4a** was transformed to **6aa** in 37% yield in *o*-xylene (entry 1). The addition of CuI had no positive effect on the yield (entry 2).[13a,c-f] On the other hand, a choice of solvent dramatically affected the reaction efficiency (entries 3–6). While the reaction proceeded sluggishly in DMSO, the use of amide solvents improved the yield of **6aa**, with DMAc proving to be optimal. Although the author tested MS4A and PCy_3 as a dehydrating reagent and ligand, respectively, based on our previous findings,[14b] the yield was decreased (entries 7 and 8). Finally, with 3.0 equivalents of **5a** and a prolonged reaction period (48 h), the desired product **6aa** was obtained in 94% isolated yield (entry 10).[16]

TABLE 2. Optimization for Palladium-catalyzed Decarboxylative Arylation of 3-Phenylbenzo[*b*]thiophene-2-carboxylic Acid (**4a**) with Bromobenzene (**5a**).[a]



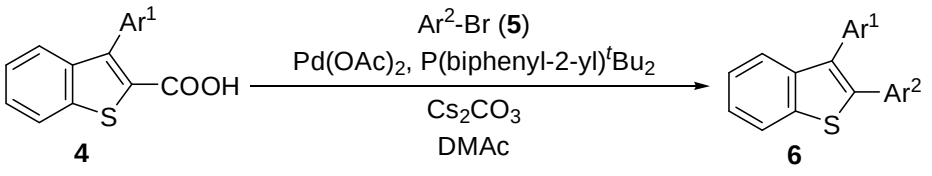
4a **6aa**

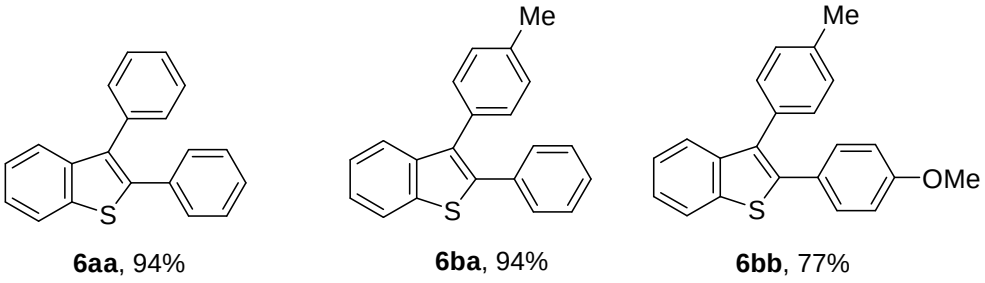
entry	**5a**, X	Solvent	**6aa**, GC Yield (%)[b]
1	2.0	o-xylene	37
2[c]	2.0	o-xylene	10
3	2.0	DMAc	76
4	2.0	DMF	67
5	2.0	NMP	62
6	2.0	DMSO	10
7[d]	2.0	DMAc	49
8[e]	2.0	DMAc	24
9	3.0	DMAc	84
10[f]	3.0	DMAc	98

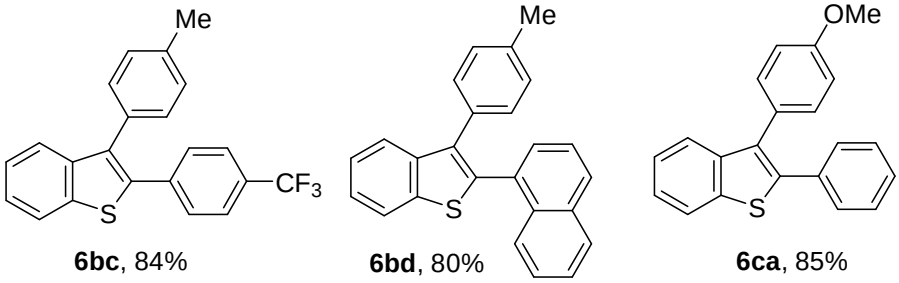
[a] A mixture of **4a** (0.50 mmol), **5a**, $Pd(OAc)_2$ (0.050 mmol), P(biphenyl-2-yl)^{t}Bu$_2$ (0.10 mmol), and Cs_2CO_3 (2.0 mmol) was stirred in solvent (2.5 mL) for 24 h at 160 ^{o}C under N_2. [b] GC yield. [c] With CuI (0.50 mmol). [d] With MS4A (400 mg). [e] With PCy_3 instead of P(biphenyl-2-yl)^{t}Bu$_2$. [f] 48 h.

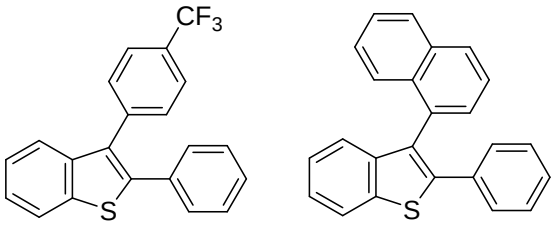
By employing the optimized conditions, the author examined the decarboxylative arylation of **4a**–**e** with various aryl bromides **5**. The results are illustrated in Table 3. As observed in the first arylation, electron-donating and electron-withdrawing groups as well as the bulky naphthyl core were tolerant toward the reaction.

TABLE 3. Palladium-Catalyzed Decarboxylative Arylation of **4a**–**e** with Various Aryl Bromides **5**.[a, b]





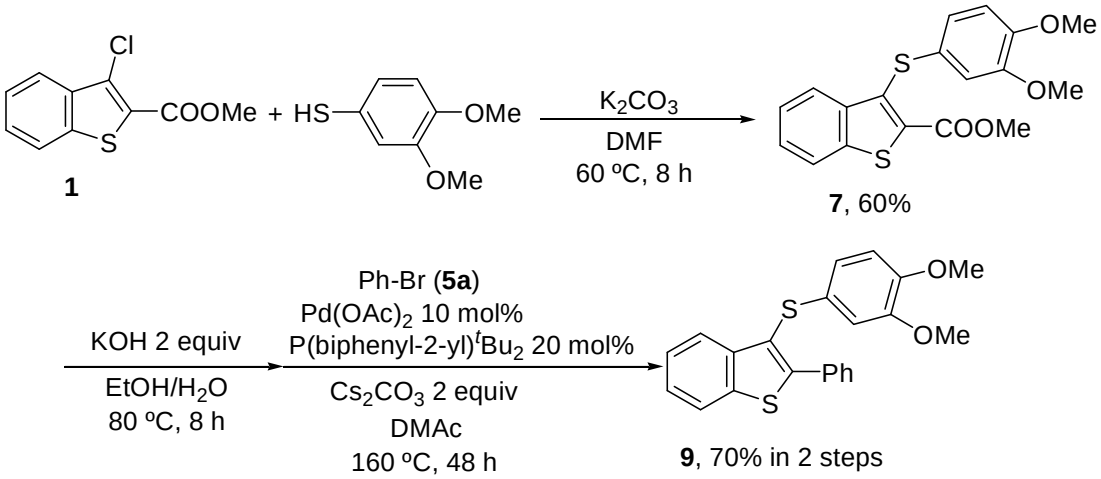




[a] A mixture of **4** (0.50 mmol), **5** (1.5 mmol), $Pd(OAc)_2$ (0.050 mmol), P(biphenyl-2-yl)^{t}Bu$_2$ (0.10 mmol), and Cs_2CO_3 (2.0 mmol) was stirred in DMAc (2.5 mL) for 48 h at 160 ºC under N_2. Ar-Br **5**: Ar = Ph; **5a**, Ar = 4-$MeOC_6H_4$; **5b**, Ar = 4-$CF_3C_6H_4$; **5c,** and Ar = 1-naphthyl; **5d**. [b] Isolated yield.

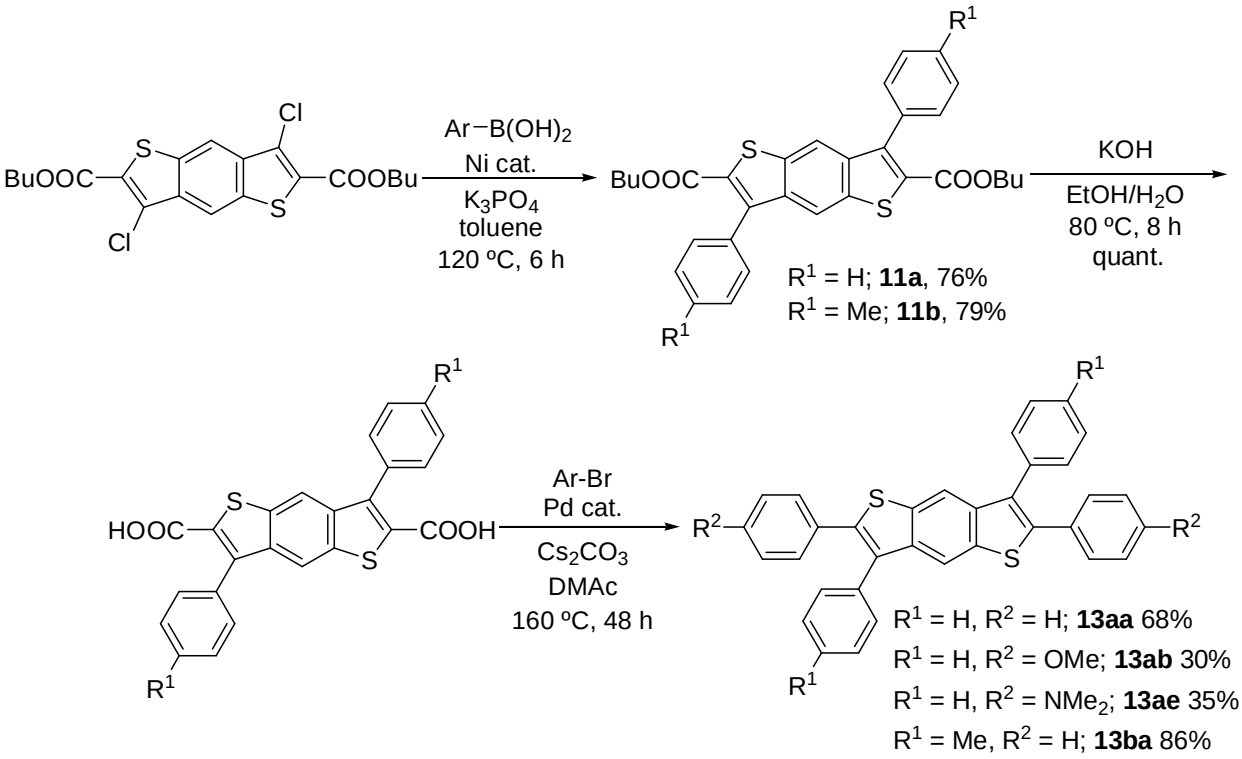
3-Chloro-2-methoxycarbonylbenzo[*b*]thiophene (**1**) may also be a useful building block for the synthesis of 3-heteroatom-substituted 2-arylbenzothiophenes of high pharmaceutical value (Scheme 2).[17] The carbon-chlorine bond in **1** is activated toward the nucleophilic substitution reaction with the aid of the electron-withdrawing nature of the proximal methoxycarbonyl group

so that the coupling with thiols is possible through an S_NAr reaction even in the absence of transition metal catalysts. Thus, the reaction of **1** with 3,4-dimethoxybenzenethiol (**7**) gave the expected product **8** and subsequent hydrolysis followed by palladium-catalyzed arylation under the same conditions as in Table 3 produced compound **9** in a good yield.



SCHEME 2. Synthesis of 2-Phenyl-3-sulfanylbenzo[*b*]thiophene **9**.

Next, the author applied the strategy to the construction of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*']dithiophenes. The readily accessible 2,6-bis(butoxycarbonyl)-3,7-dichlorobenzo[*b*]thiophene (**10**) from 1,4-phenylenediacrylic acid[12c] was employed as a platform, and the Suzuki–Miyaura coupling/ester hydrolysis/decarboxylative arylation sequence led to the facile preparation of tetraarylbenzodithiophenes **13** (Scheme 3). It is noted that the corresponding dimethyl ester as the starting material was sparingly soluble in common organic solvents so that the author employed the dibutyl ester **10**.



SCHEME 3. Synthesis of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*']dithiophenes **13**.

With the above benzodithiophenes **13**, the investigation into their optical properties in $CHCl_3$ solution was conducted. The results are summarized in Table 4, and the spectra are shown in Figures 1 and 2. The absorption and emission spectra of tetraphenyl derivative **13aa** exhibited the major bands with maximum absorption λ_{abs} and emission λ_{em} at 344 and 412 nm, respectively (entry 1). By the installation of the strongly electron-donating dimethylamino group to the benzene ring at the 2- and 6-positions, these peaks were red-shifted by about 35 nm to 378 and 447 nm, respectively (entry 3). The methoxy substituent caused similar shifts, although the effects were relatively small (entry 2). In accordance with the trend, the optical band gap E_{00} decreased in the order **13aa**>**13ab**>**13ae**. On the other hand, the modification at the 3- and 7-positions with the 4-tolyl substituted that may enhance the solubility gave only a minor change in the optical properties of the parent structure of **13aa** (entry 4).

TABLE 4. Optical Properties of 2,3,6,7-Tetraarylbenzo[1,2-*b*;4,5-*b*']dithiophenes **13**.

entry	**13**	$\lambda_{abs\text{-}sl}$ (nm)[a]	log ε	$\lambda_{em\text{-}sl}$ (nm)[b]	$\Phi_{f\text{-}sl}$[c]	E_{00} (eV)[d]
1	**13aa**	344	4.31	412	0.30	3.29
2	**13ab**	349	4.41	421	0.51	3.21
3	**13ae**	378	4.60	447	0.35	2.94
4	**13ba**	345	4.35	412	0.31	3.26

[a] Absorption maximum in $CHCl_3$ (5.0×5^{-10} M). [b] Emission maximum in $CHCl_3$ (5.0×5^{-10} M). [c] Determined by comparison with $CHCl_3$ solution (5.0×6^{-10} M) of quinine sulfate ($\Phi_f = 0.55$) exited at 366 nm. [d] Optical band gap.

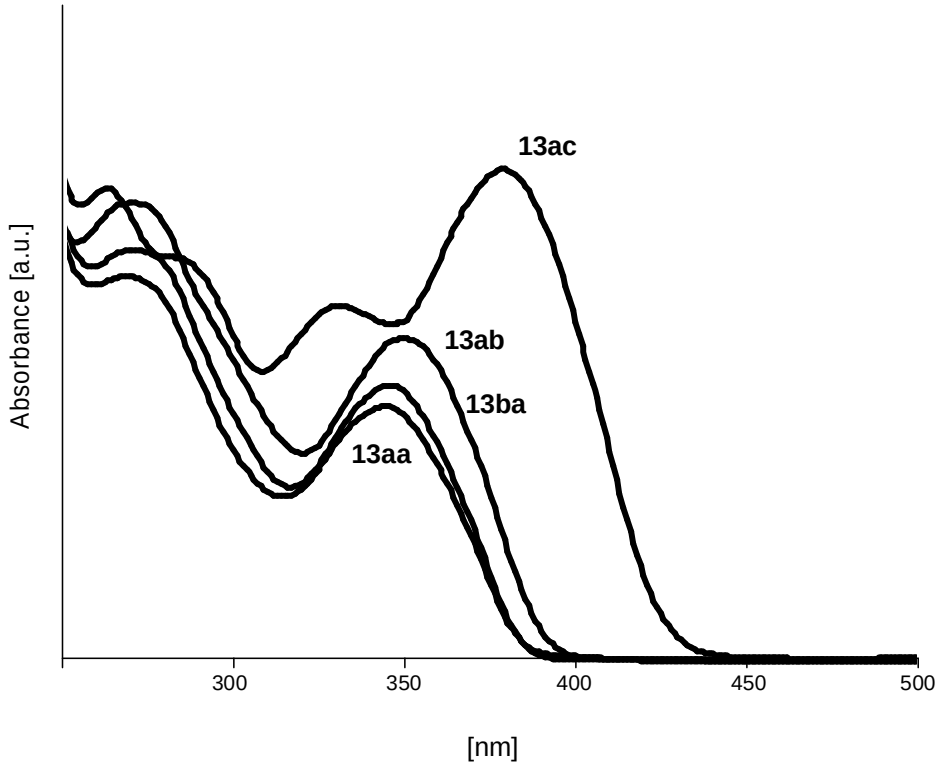


FIGURE 1. Absorption Spectra of the $CHCl_3$ Solution of **13**.

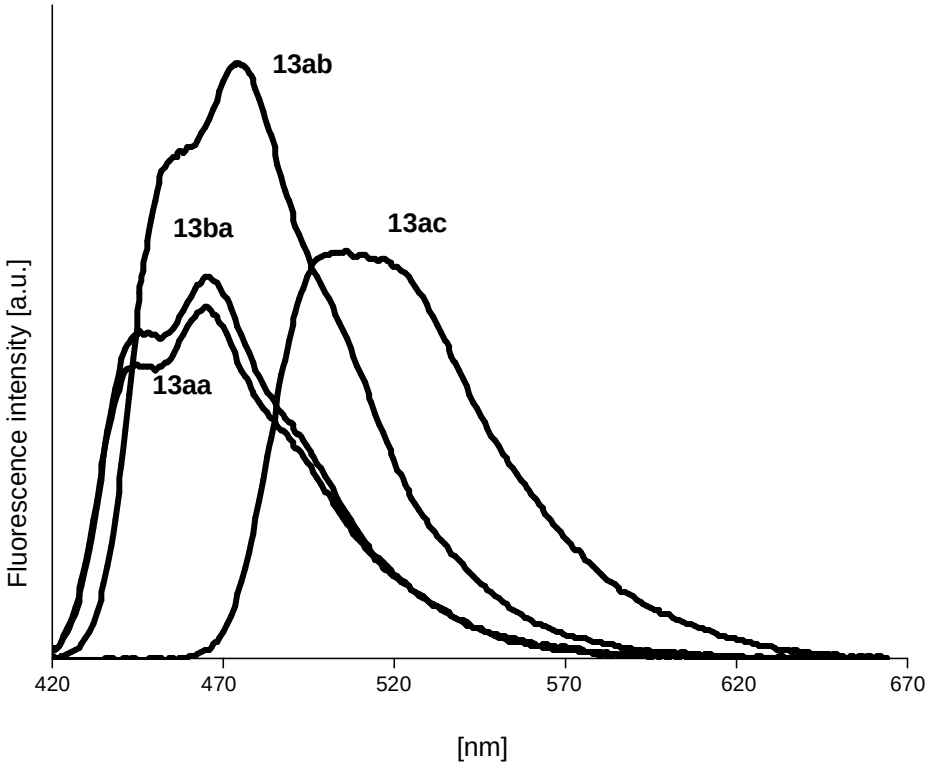


FIGURE 2. Photoluminescence spectra of the $CHCl_3$ solution of **13**.

2.3 Conclusion

In summary, the author has developed an effective method for the concise and convergent synthesis of 2,3-diarylbenzo[*b*]thiophenes from 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene via nickel-catalyzed Suzuki–Miyaura cross-coupling and palladium-catalyzed decarboxylative arylation as the key transformations. Its application to the construction of 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*']dithiophene π systems appears to demonstrate the high synthetic utility of this methodology.

2.4 Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for $CDCl_3$ or DMSO-d_6 solutions. MS data were obtained by EI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or a CBP-1 capillary column (i.

d. 0.5 mm x 25 m). Silica gel (Wakogel 200 mesh) was used for column chromatography. All reactions were carried out under nitrogen atmospheres.

Materials. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and *N*,*N*-dimethylacetamide (DMAc) were freshly distilled from CaH_2 prior to use. $Pd(OAc)_2$ was purchased from Wako. P(biphenyl-2-yl)^{t}Bu$_2$ obtained from Strem. $NiCl_2$(dppe) was synthesized from $NiCl_2$ and dppe.[18] Methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (**1**)[12a] and 3,7-dichlorobenzo[1,2-*b*;4,5-*b*']dithiophene-2,6-dicarbonyl dichloride[12c] were prepared by the methods reported previously.

Experimental Procedure

Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction of 3-Chloro-2-methoxycarbonylbenzo[*b*]thiophene (1) with Phenylboronic Acid (2a) In a 20-mL two-necked flask were added methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (**1**) (3.0 mmol, 680 mg), phenylboronic acid (**2a**) (4.5 mmol, 549 mg), $NiCl_2$(dppe) (0.15 mmol, 79 mg), K_3PO_4 (6.0 mmol, 1.3 g), and toluene (10 mL). The resulting mixture was stirred under N_2 (balloon) at 120 ºC (bath temperature) for 10 h. The product **3a** (yield: 732 mg, 2.7 mmol, 91%) was isolated by filtration of the mixture through a filter paper with diethyl ether as an eluent, evaporation of the solvents, and column chromatography on silica gel using hexane-ethyl acetate (98:2, v/v)

Hydrolysis of Methyl 3-Phenylbenzo[*b*]thiophene-2-carboxylate (3a) In a 100-mL flask were added methyl 3-phenylbenzo[*b*]thiophene-2-carboxylate (**3a**) (2.0 mmol, 536 mg), potassium hydroxide (12 mmol, 673 mg), water (4.0 mL), and ethanol (8.0 mL). The mixture was heated at 80 ºC (bath temperature) for 8 h under N_2. After cooling and acidification with aqueous HCl (2.0 M), a white precipitate was collected, washed with water, and dried under

vacuum to afford carboxylic acid **4a.**

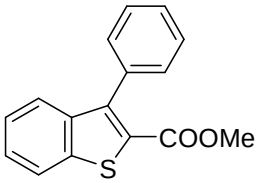
Palladium-Catalyzed Decarboxylative Arylation of 3-Phenylbenzo[*b*]thiophene-2-carboxylic Acid (4a) with Bromobenzene (5a) In a 20-mL two-necked flask were added 3-phenylbenzo[*b*]thiophene-2-carboxylic acid (**4a**) (0.50 mmol, 127 mg), bromobenzene (**5a**) (1.5 mmol, 235 mg), $Pd(OAc)_2$ (0.050 mmol, 11 mg), P(biphenyl-2-yl)^{t}Bu$_2$ (0.10 mmol, 30 mg), Cs_2CO_3 (1.0 mmol, 325 mg), 1-methylnaphthalene (ca. 50 mg) as an internal standard, and DMAc (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 160 ºC (bath temperature) for 48 h. Analysis of the mixture by GC confirmed the formation of compound **6aa** (yield: 140 mg, 98%). After cooling, the reaction mixture was poured into diluted aqueous HCl, extracted with diethyl ether, and dried over Na_2SO_4. The product **6aa** (yield: 135 mg, 0.47 mmol, 94%) was isolated by column chromatography on silica gel using hexane as an eluent.

Reaction of Methyl 3-Chlorobenzo[*b*]thiophene-2-carboxylate (1a) with 3,4-Dimethoxybenzenethiol (7) In a 100-mL two-necked flask were added 3-chlorobenzo[*b*]thiophene-2-carboxylate (**1a**) (3.0 mmol, 680 mg), 3,4-dimethoxybenzenethiol (**7**) (3.6 mmol, 612 mg), K_2CO_3 (6.0 mmol, 829 mg), and DMF (20 mL). The resulting mixture was stirred under N_2 (balloon) at 80 ºC (bath temperature) for 6 h. After cooling, the reaction mixture was poured into diluted aqueous HCl, extracted with diethyl ether, and dried over Na_2SO_4. The product **8** (yield: 623 mg, 1.8 mmol, 60%) was isolated by column chromatography on silica gel using hexane-ethyl acetate as eluents (90:10, v/v)

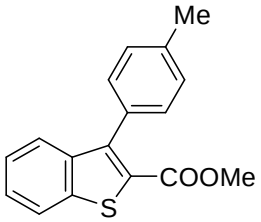
Preparation of 2,6-Bis(butoxycarbonyl)-3,7-dichlorobenzo[1,2-*b*;4,5-*b*']dithiophene (10) In a 100-mL two-necked flask were added 3,7-dichlorobenzo[1,2-*b*;4,5-*b*']-dithiophene-2,6-dicarbonyl dichloride (5.0 mmol, 1.9 g), butanol (20 mmol, 1.8 mL), pyridine

(20 mmol, 1.6 mL), and chlorobenzene (10 mL). The resulting mixture was stirred under N_2 (balloon) at 100 ºC (bath temperature) for 6 h. After cooling, the reaction mixture was filtered through a filter paper with diethyl ether as an eluent followed by evaporation of the solvent. The resulting solid was washed with water, and dried under vacuum. The diester **10** (yield: 1.9 g, 4.2 mmol, 83%) was isolated by recrystallization from toluene/hexane.

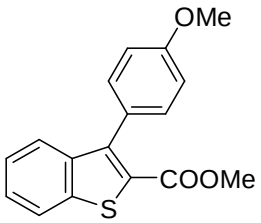
Characterization Data of Products.



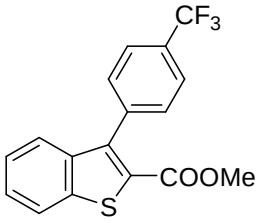
Methyl 3-phenylbenzo[*b*]thiophene-2-carboxylate (3a) m.p. 154-155 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 7.32-7.55 (m, 8H), 7.88 (d, J = 8.1 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 52.2, 122.5, 124.8, 125.3, 127.2, 127.8, 128.0, 128.1, 129.6, 134.5, 140.1, 140.4, 144.2, 162.9; HRMS *m/z* = 268.0557 (M^+), calcd. for $C_{16}H_{12}O_2S$: 268.0558.



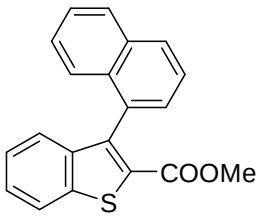
Methyl 3-(4-methylphenyl)benzo[*b*]thiophene-2-carboxylate (3b) m.p. 95-97 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.79 (s, 3H), 7.29-7.36 (m, 5H), 7.47 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 52.1, 122.4, 124.7, 125.4, 127.2, 128.8, 129.5, 131.4, 133.6, 137.8, 140.1, 140.4, 144.4, 162.9; HRMS *m/z* = 282.0712 (M^+), calcd. for $C_{17}H_{14}O_2S$: 282.0715.



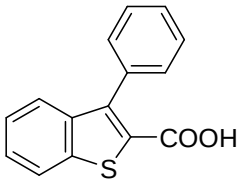
Methyl 3-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxylate (3c) m.p. 164-166 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.89 (s, 3H), 7.01-7.05 (m, 2H), 7.33-7.38 (m, 3H), 7.47 (m, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 55.3, 113.5, 122.5, 124.7, 125.4, 126.5, 127.2, 127.4, 131.0, 140.2, 140.4, 144.1, 159.5, 163.0; HRMS *m/z* = 298.0660 (M^+), calcd. for $C_{17}H_{14}O_3S$: 298.0664.



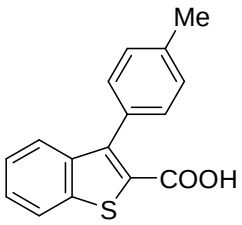
Methyl 3-(4-trifluoromethylphenyl)benzo[*b*]thiophene-2-carboxylate (3d) m.p. 127-129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H), 7.23-7.49 (m, 5H), 7.76 (d, J = 8.0 Hz, 2H), 7.91-7.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.3, 122.6, 124.2 (q, J = 273.3 Hz), 124.9, 125.0 (q, J = 3.8 Hz), 125.1, 127.5, 128.5, 130.1, 130.2 (q, J = 32.9 Hz), 138.4, 139.6, 140.5, 142.4, 162.7; HRMS *m/z* = 336.0423 (M^+), calcd. for $C_{17}H_{11}F_3O_2S$: 336.0432.



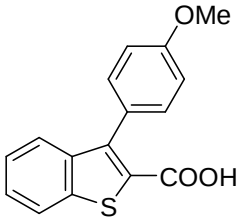
Methyl 3-(1-naphthyl)benzo[*b*]thiophene-2-carboxylate (3e) m.p. 135-136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 7.22-7.49 (m, 7H), 7.56-7.60 (m, 1H), 7.91-7.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1, 122.5, 124.8, 125.2, 125.47, 125.50, 125.8, 126.1, 127.2, 127.3, 128.3, 128.5, 129.5, 132.2, 132.6, 133.5, 140.4, 140.6, 142.5, 162.7; HRMS *m/z* = 318.0721 (M^+), calcd. for $C_{20}H_{14}O_2S$: 318.0714.



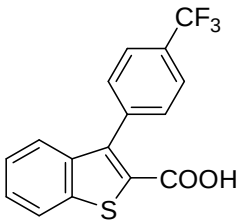
3-Phenylbenzo[*b*]thiophene-2-carboxylic acid (4a) m.p. 188-191 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38-7.56 (m, 8H), 8.08 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 122.9, 124.6, 125.2, 127.3, 127.9, 128.0, 129.69, 129.72, 134.3, 139.4, 139.8, 142.3, 163.3; HRMS *m/z* = 254.0399 (M^+), calcd. for $C_{15}H_{10}O_2S$: 254.0402.



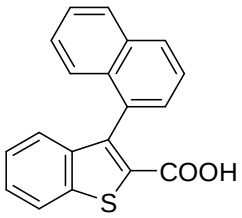
3-(4-Methylphenyl)benzo[*b*]thiophene-2-carboxylic acid (4b) m.p. 229-230 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 7.29 (s, 4H), 7.37-7.44 (m, 2H), 7.51 (m, 1H), 8.05 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9, 122.9, 124.6, 125.1, 127.1, 128.6, 129.7, 130.2, 131.4, 137.1, 139.4, 139.9, 142.0, 163.5; HRMS *m/z* = 268.0562 (M^+), calcd. for $C_{16}H_{12}O_2S$: 268.0558.



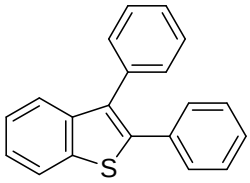
3-(4-Methoxyphenyl)benzo[*b*]thiophene-2-carboxylic acid (4c) m.p. 233-235 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 7.04 (d, J = 8.2 Hz, 2H), 7.33 (dt, J = 8.2 Hz, 0.5 Hz, 2H), 7.40 (m, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.50-7.55 (m, 1H), 8.05 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.1, 113.5, 122.9, 124.7, 125.1, 126.2, 127.2, 129.3, 131.1, 139.4, 139.9, 142.2, 159.0, 163.5; HRMS: *m/z* = 284.0508 (M^+), calcd. for $C_{16}H_{12}O_3S$: 284.0507.



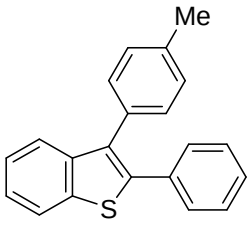
3-(4-Trifluoromethylphenyl)benzo[*b*]thiophene-2-carboxylic acid (4d) m.p. 266-268 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37-7.43 (m, 2H), 7.53-7.57 (m, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 8.08-8.11 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.0, 124.36, 124.37 (q, J = 270.8 Hz), 124.9 (q, J = 3.8 Hz), 125.4, 127.5, 129.4 (q, J = 32.4 Hz), 130.6, 130.7 138.8, 139.3, 139.5, 140.7, 163.1; HRMS *m/z* = 322.0272 (M^+), calcd. for $C_{16}H_9F_3O_2S$: 322.0275.



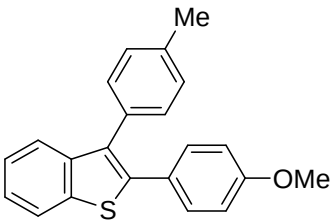
3-(1-Naphthyl)benzo[*b*]thiophene-2-carboxylic acid (4e) m.p. 213-214 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.03 (d, J = 8.2 Hz, 1H), 7.29 (m, 2H), 7.35 (m, 1H), 7.44-7.54 (m, 3H), 7.60-7.65 (m, 1H), 8.02 (dd, J = 7.8 Hz, 8.3 Hz, 2H), 8.14 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.0, 124.6, 125.1, 125.2, 125.5, 125.9, 126.3, 127.3, 127.4, 128.2, 128.3, 131.4, 131.8, 132.5, 133.1, 139.5, 140.4, 140.6, 163.2; HRMS *m/z* = 304.0559 (M^+), calcd. for $C_{19}H_{12}O_2S$: 304.0558.



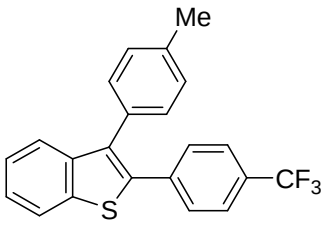
2,3-Diphenylbenzo[*b*]thiophene (6aa) m.p. 115-117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.27 (m, 3H), 7.30-7.42 (m, 9H), 7.58-7.61 (m, 1H), 7.85-7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.1, 123.4, 124.4, 124.5, 127.4, 127.7, 128.3, 128.6, 129.6, 130.4, 133.2, 134.2, 135.5, 138.8, 139.5, 140.9; HRMS *m/z* = 286.0811 (M^+), calcd. for $C_{20}H_{14}S$: 286.0816.



3-(4-Methylphenyl)-2-phenylbenzo[*b*]thiophene (6ba) m.p. 58-60 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.17-7.27 (m, 7H), 7.29-7.37 (m, 4H), 7.58-7.61 (m, 1H), 7.84-7.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 122.0, 123.4, 124.4, 124.5, 127.6, 128.3, 129.4, 129.6, 130.3, 132.4, 133.2, 134.4, 137.0, 138.8, 139.2, 141.0; HRMS *m/z* = 300.0974 (M^+), calcd for $C_{21}H_{16}S$: 300.0973.

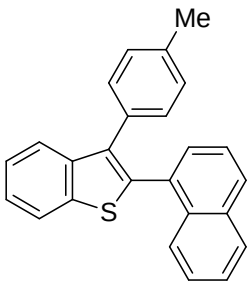


2-(4-Methoxyphenyl)-3-(4-methylphenyl)benzo[*b*]thiophene (6bb) m.p. 105-106 ºC; ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.74 (s, 3H), 6.76 (m, 2H), 7.17-7.32 (m, 8H), 7.52-7.55 (m, 1H), 7.79-7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 55.2, 113.8, 122.2, 123.2, 124.2, 124.3, 126.8, 129.4, 130.3, 130.7, 132.3, 132.6, 136.9, 138.5, 139.1, 141.1, 159.1; HRMS *m/z* = 330.1078 (M^+), calcd. for $C_{22}H_{18}OS$: 330.1078.

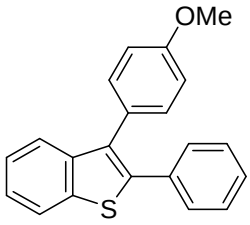


3-(4-Methylphenyl)-2-(4-trifluoromethylphenyl)benzo[*b*]thiophene (6bc) m.p. 122-123 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.18-7.23 (m, 4H), 7.35 (quint-d, *J* = 7.3 Hz, 1.8 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.49, (d, *J* = 8.0 Hz, 2H), 7.58-7.63 (m, 8.2 Hz, 1H), 7.85-7.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 122.7, 123.8, 124.1 (q, *J* = 273.3 Hz), 124.6, 125.0, 125.3 (q, *J* = 3.8 Hz), 129.4 (q, *J* = 32.9 Hz), 129.6, 129.7, 130.1, 131.9, 134.7,

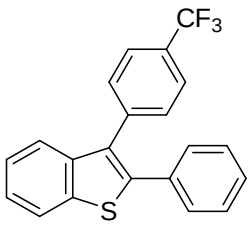
137.2, 137.5, 138.0, 139.0, 140.9; HRMS *m/z* = 368.0852 (M^+), calcd. for $C_{22}H_{15}F_3S$: 368.0847.



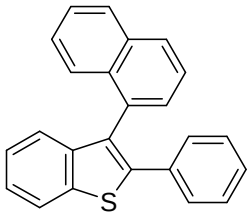
3-(4-Methylphenyl)-2-(1-naphthyl)benzo[*b*]thiophene (6bd) m.p. 130-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 6.97 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.15-7.40 (m, 10H), 7.78 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 122.1, 123.5, 124.4, 124.5, 125.0, 125.9, 126.17, 126.22, 128.1, 128.7, 128.9, 129.6, 129.7, 131.9, 132.1, 132.6, 133.4, 135.8, 136.6, 137.4, 139.8, 139.9; HRMS *m/z* 350.1130 (M^+), calcd. for $C_{25}H_{18}S$: 350.1129.



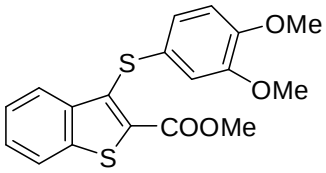
3-(4-Methoxyphenyl)-2-phenylbenzo[*b*]thiophene (6ca) m.p. 127-128 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.93 (m, 2H), 7.22-7.28 (m, 5H), 7.30-7.36 (m, 4H), 7.56-7.61 (m, 1H), 7.84-7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 114.1, 122.1, 123.4, 124.4, 124.5, 127.6, 127.7, 128.3, 129,6, 131.5, 132.9, 134.4, 138.8, 139.1, 141.1, 159.9; HRMS *m/z* = 316.0916 (M^+), calcd. for $C_{21}H_{16}OS$: 316.0922.



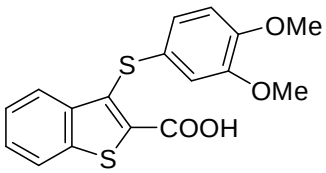
2-Phenyl-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene (6da) m.p. 89-91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.31 (m, 5H), 7.33-7.40 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.53-7.57 (m, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.87-7.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.2, 122.9, 124.2 (q, *J* = 273.4 Hz), 124.7, 124.8, 125.6 (q, *J* = 3.8 Hz), 128.1, 128.6, 129.5 (q, *J* = 32.5 Hz), 129.7, 131.8, 131.6, 133.7, 139.0, 139.4, 140.3, 140.8; HRMS *m/z* = 354.0688 (M^+), calcd. for $C_{19}H_{13}F_3S$: 354.0690.



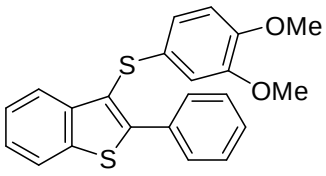
3-(1-Naphthyl)-2-Phenylbenzo[*b*]thiophene (6ea) m.p. 144-146 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06-7.40 (m, 10H), 7.43-7.49 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.0, 123.8, 124.4, 124.6, 125.8, 126.0, 126.1, 126.2, 127.7, 128.2, 128.3, 128.7, 28.8, 131.6, 132.7, 133.5, 133.8, 134.2, 138.5, 140.8, 141.9 (One signal would be overlapped by other signal.); HRMS: *m/z* = 336.0972 (M^+), calcd. for $C_{24}H_{16}S$: 336.0973.



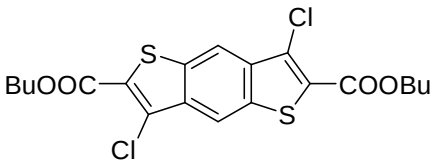
Methyl 3-(3,4-dimethoxyphenylthio)benzo[*b*]thiophene-2-carboxylate (8) m.p. 111-113 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 3.82 (s, 3H), 3.95 (s, 3H), 6.72 (d, J = 8.4 Hz, 1H), 6.83-6.90 (m, 2H), 7.29-7.33 (m, 1H), 7.42-7.46 (m, 1H), 7.78-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.5, 55.87, 55.92, 111.6, 113.3, 122.6, 122.7, 125.0, 125.5, 126.6, 127.4, 132.7, 132.9, 139.8, 139.9, 148.3, 149.2, 162.4; HRMS: *m/z* = 360.0488 (M^+), calcd. for $C_{18}H_{16}O_4S_2$: 360.0490.



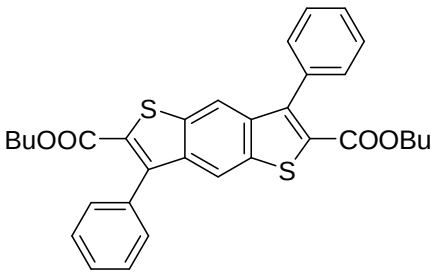
3-(3,4-Dimethoxyphenylthio)benzo[*b*]thiophene-2-carboxylic acid m.p. 172-174 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 3H), 3.69 (s, 3H), 6.71 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 7.38 (m, 1.1 Hz, 1H), 7.51 (m, 1H), 7.72 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 56.0, 112.9, 113.8, 122.6, 123.7, 125.1, 125.7, 126.3, 127.8, 130.9, 135.5, 139.4, 139.8, 148.5, 149.4, 163.1; HRMS: *m/z* = 346.0331 (M^+) calcd for $C_{17}H_{14}O_4S_2$: 346.0334.



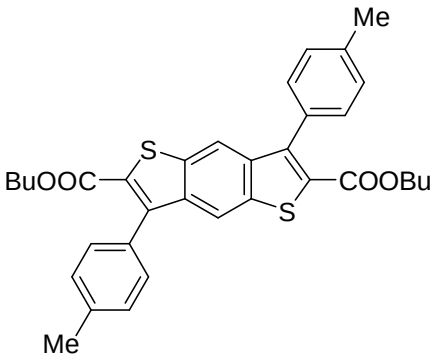
3-(3,4-Dimethoxyphenylthio)-2-phenylbenzo[*b*]thiophene (9) m.p. 97-100 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 3.68 (s, 3H), 3.77 (s, 3H), 6.57-6.67 (m, 3H), 7.34-7.46 (m, 5H), 7.72 (m, 2H), 7.82-7.89 (m, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 55.7, 55.9, 111.0, 111.8, 119.7, 119.8, 122.1, 122.9, 125.0, 125.1, 128.3, 128.4, 128.8, 129.9, 133.5, 138.3, 141.1, 147.4, 148.8, 149.2; HRMS *m/z* = 378.0743 (M^{+}), calcd. for $C_{22}H_{18}O_2S_2$: 378.0748.



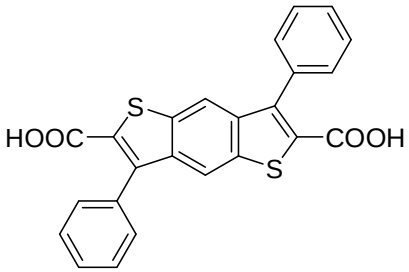
2,6-Bis(butoxycarbonyl)-3,7-dichlorobenzo[1,2-*b*;4,5-*b*']dithiophene (10) m.p. 128-129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.3 Hz, 6H), 1.48-1.57 (m, 4H), 1.76-1.84 (m, 4H), 4.40 (t, *J* = 6.6 Hz, 4H), 7.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 19.5, 30.8, 66.1, 121.4, 126.5, 128.4, 133.1, 137.3, 161.0; HRMS: *m/z* = 458.0172 (M^{+}), calcd. for $C_{20}H_{20}Cl_2O_4S_2$: 458.0180.



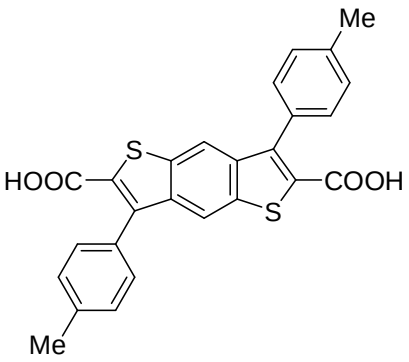
3,7-Diphenyl-2,6-bis(butoxycarbonyl)benzo[1,2-*b*;4,5-*b*']dithiophene (11a) m.p. 100-103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 6H), 1.22-1.32 (m, 4H), 1.52-1.59 (m, 4H), 4.21 (t, *J* = 6.6 Hz, 4H), 7.37-7.51 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 19.1, 30.5, 65.4, 122.1, 128.1, 128.2, 128.6, 129.7, 134.4, 134.5, 139.5, 144.5, 162.4; HRMS: *m/z* = 542.1578 (M^{+}), calcd. for $C_{32}H_{30}O_4S_2$: 542.1586.



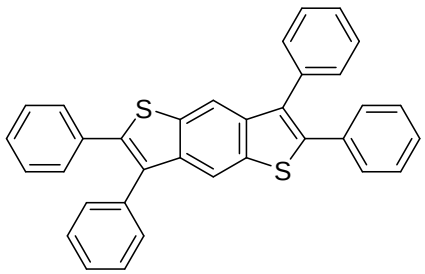
2,6-Bis(butoxycarbonyl)-3,7-bis(4-methylphenyl)benzo[1,2-*b*;4,5-*b*']dithiophene (11b) m.p. 110-111 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.4 Hz, 6H), 1.24-1.34 (m, 4H), 1.51-1.62 (m, 4H), 2.44 (s, 6H), 4.21 (t, J = 6.7 Hz, 4H), 7.29 (s, 8H), 7.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 19.1, 21.4, 30.5, 65.3, 122.1, 128.2, 128.8, 129.6, 131.5, 134.4, 138.0, 139.5, 144.8, 162.4; HRMS: *m/z* = 570.1893 (M^+), calcd. for $C_{34}H_{34}O_4S_2$: 570.1899.



3,7-Diphenylbenzo[1,2-*b*;4,5-*b*']dithiophene-2,6-dicarboxylic acid (12a) m.p. >300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (s, 2H), 7.41-7.52 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 122.0, 128.0, 128.1, 129.5, 129.6, 133.0, 133.9, 139.0, 143.3, 162.7; HRMS: *m/z* = 430.0329 (M^+), calcd. for $C_{24}H_{14}O_4S_2$: 430.0334.

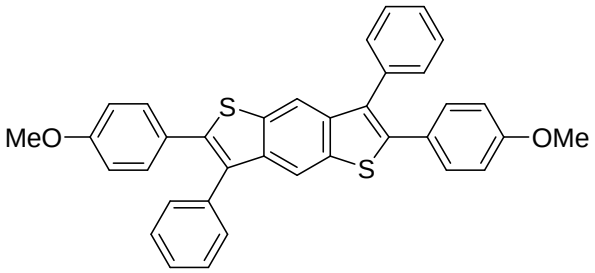


3,7-Bis(4-methylphenyl)benzo[1,2-*b*;4,5-*b*']dithiophene-2,6-dicarboxylic acid (12b) m.p. >300 ºC; 1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 6H), 7.28-7.31 (m, 8H), 7.34-7.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.7, 122.8, 129.5, 130.1, 130.4, 131.8, 133.8, 138.2, 139.9, 144.2, 163.6; HRMS: *m/z* = 458.0655 (M^+), calcd. for $C_{26}H_{18}O_4S_2$: 458.0647.

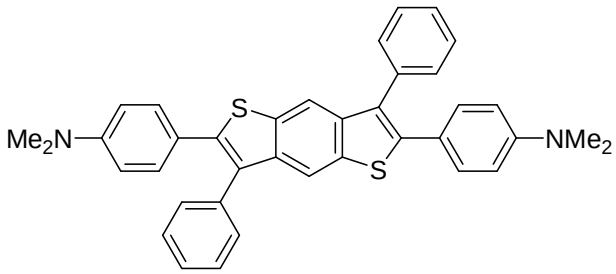


2,3,6,7-Tetraphenylbenzo[1,2-*b*;4,5-*b*']dithiophene (13aa) m.p. 262-265 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.29 (m, 6H), 7.34-7.44 (m, 14H), 7.48 (s, 2H); ^{13}C NMR (100 MHz,

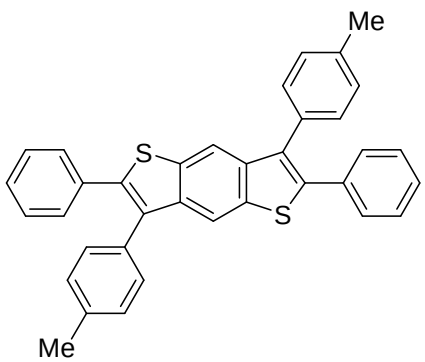
$CDCl_3$) δ 120.4, 127.5, 127.7, 128.4, 128.7, 129.6, 130.5, 132.2, 134.1, 134.2, 135.7, 138.0, 138.6; HRMS *m/z* (M^+) calcd for $C_{34}H_{22}S_2$: 494.1163, found: 494.1160.



2,6-Bis(4-methoxyphenyl)-3,7-diphenylbenzo[1,2-*b*;4,5-*b*']dithiophene (13ab) m.p. 220-224 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 6H), 6.78-6.82 (m, 4H), 7.25-7.30 (m, 4H), 7.34-7.44 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 113.9, 120.1, 126.6, 127.4, 128.7, 130.5, 130.7, 131.8, 133.3, 135.9, 137.8, 138.5, 159.2; HRMS: *m/z* = 554.1370 (M^+), calcd. for $C_{36}H_{26}O_2S_2$: 554.1374.



2,6-Bis(4-dimethylaminophenyl)-3,7-diphenylbenzo[1,2-*b*;4,5-*b*']dithiophene (13ac) m.p. 279-282 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 12H), 6.58 (d, *J* = 8.8 Hz, 4H), 7.21-7.25 (m, 4H), 7.34-7.44 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2, 112.0, 119.7, 122.0, 127.1, 128.6, 130.2, 130.6, 131.5, 132.0, 136.5, 138.6, 149.8 (One signal would be overlapped by other signal.); HRMS: *m/z* = 580.2003 (M^+), calcd. for $C_{38}H_{32}N_2S_2$: 580.2007.



3,7-Bis(4-methylphenyl)-2,6-diphenylbenzo[1,2-*b*;4,5-*b*']dithiophene (13ba) m.p. 224-225 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 6H), 7.20-7.29 (m, 14H), 7.35-7.40 (m, 4H), 7.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 124.0, 127.6, 128.4, 129.4, 129.6, 130.3, 132.2, 132.7, 134.2, 134.3, 137.2, 137.6, 138.6; HRMS: *m/z* = 522.1469 (M^+), calcd. for $C_{36}H_{26}S_2$: 522.1476.

2.5 References and Notes

(1) (a) Campaigne, E. Comprehensive Heterocyclic Chemistry, (Eds.: Katritzky, A. R.; Rees C. W.), Pergamon Press, Oxford, 1984, Vol. 4, pp 863–934. (b) Russell, R. K.; Press, J. B. in: Comprehensive Heterocyclic Chemistry II, (Eds.: Katritzky, A. R.; Rees, C. W;. Scriven, E. F. V.), Pergamon Press, Oxford, 1996, Vol. 2, pp 679–729. (c) Tony, Y. Z.; O'Toole, J.; Proctor, C. R.; *Sulfur Rep*. 1999, *22*, 1.

(2) (a) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057. (b) Magarian, R. A.; Overacre, L. B.; Singh, S.; Meyer, K. L. *Curr. Med. Chem.* 1994, *1*, 61. (c) Palkowitz, A. D.; Glasebrook, A. L.; Thrasher, K. J.; Hauser, K. L.; Short, L. L.; Phillips, D. L.; Muehl, B. S.; Sato, M.; Shetler, P. K.G.; Cullinan, J.; Pell, T. R.; Bryant, H. U. *J. Med. Chem.* **1997**, *40*, 1407. (d) Schopfer, U.; Schoeffter, P.; Bischoff, S. F.; Nozulak, J.; Feuerbach, D.; Floersheim, P. *J. Med. Chem.* **2002**, *45*, 1399.

(3) (a) Pinney, K. G.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081. (b) Zhang, S.-X.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Mauger, A.; Narayanan, V. L.; Lee, K.-H. *J. Med. Chem.* **1999**, *42*, 4081. (c) Chen, Z.; Mocharla, V. P.; Farmer, J. M.; Pettit, G. R.; Hamel, E.; Pinney, K. G. *J. Org. Chem.* **2000**, *65*, 8811. (d) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (e) Brown, T.; Holt, Jr. H.; Lee, M. *Top. Heterocycl. Chem.* **2006**, *2*, 1.

(4) Norman, B. H.; Dantzig, A. H.; Kroin, J. S.; Law, K. L.; Tabas, L. B.; Shepard, R. L.; Palkowitz, A. D.; Hauser, K. L.; Winter, M. A.; Sluka, J. P.; Starling, J. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3381.

(5) (a) Boschelli, D. H.; Kramer, J. B.; Connor, D. T.; Lesch, M. E.; Schrier, D. J.; Ferin, M. A.; Wright, C. D. *J. Med. Chem.* **1994**, *37*, 717. (b) Cobb, R. R.; Felts, K. A.; McKenzie, T. C.; Parry, G. C. N.; Mackman, N. *FEBS Lett.* **1996**, *382*, 323. (c) Gualberto, A.; Marquez, G.; Garballo, M.; Youngblood, G. L.; Hunt III, S. W.; Baldwin, A. S.; Sobrino, F. *J. Biol. Chem.* **1998**, 273, 7088.

(6) (a) Sall, D. J.; Bastian, J. A.; Briggs, S. L.; Buben, J. A.; Chirgadze, N. Y.; Clawson, D. K.; Denney, M. L.; Giera, D. D.; Gifford-Moore, D. S.; Harper, R. W.; Hauser, K. L.; Klimkowski, V. J. T.; Kohn, J.; Lin, H.; McCowan, J. R.; Palkowitz, A. D.; Smith, G. F.; Taleuchi, K.; Thrasher, K. J.; Tinsley, J. M.; Utterback, B. G.; Yan, S. B.; Zhang, M. *J. Med. Chem.* **1997**, *40*, 3489. (b) Takeuchi, K.; Kohn, T. J.; Bastian, J. A.; Chirgadze, N. Y.; Denney, M. L.; Harper, R. W.; Lin, H.; Mccowan, J. R.; Gifford-Moore, D. S.; Richett, M. E.; Sall, D. J.; Smith, G. F.; Zhang, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 759.

(7) (a) Wright, C. D.; Stewart, S. F.; Kuipers, P. J.; Hoffman, M. D.; Devall, L. J.; Kennedy, J. A.; Ferin, M. A.; Theuson, D. O.; Conroy, M. C. *J. Leukocyte Biol.* **1994**, *55*, 443. (b) Bleavins, M. R.; de La Igelsia, F. A.; McCay, J. A.; White Jr, L.; Kimber, L.; Munson, A. E. *Toxicology* **1995**, *98*, 111.

(8) Pinto, E.; Queiroz, M. R. P.; Vale-Silva, L. A.; Oliveira, J. F.; Begouin, A.; Begouin, J.-M.;

Kirsch, G. *Bioorg. Med. Chem.* **2008**, *16*, 8172.
(9) (a) Barbarella, G.; Favaretto, L.; Zanelli, A.; Gigli, G.; Mazzeo, M.; Anni, M.; Bongini, A. *Adv. Funct. Mater.* **2005**, *15*, 664. (b) Kim, M.-S.; Choi, B.-K.; Lee, T.-W.; Shin, D.; Kang, S. K.; Kim, J. M.; Tamura, S.; Noh, T. *Appl. Phys. Lett.* **2007**, *91*, 251111.
(10) (a) Takimiya, K.; Kunugi, Y.; Konda, Y.; Niihara, N.; Otsubo, T. *J. Am. Chem. Soc.* **2004**, *126*, 5084. (b) Wang, C.-H.; Hu, R.-R.; Liang, S.; Chen, J.-H.; Yang, Z.; Pei, J. *Tetrahedron Lett.* **2005**, *46*, 8153. (c) Zhou, Y.; Liu, W.-J.; Ma, Y.; Wang, H.; Qi, L.; Cao, Y.; Wang, J.; Pei, J.; *J. Am. Chem. Soc.* **2007**, *129*, 12386. (d) Zhou, Y.; Wang, L.; Wang, J.; Pei, J.; Cao, Y. *Adv. Mater.* **2008**, *20*, 3745.
(11) Recently, their O- and N-analogues, that is, 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*']difurans and 2,3,6,7-tetraarylbenzo[1,2-*b*;4,5-*b*']dipyrroles have been applied to thecomponents of an OLED system. (a) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902. (b) Tsuji, H.; Yokoi, Y.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *Chem. Asian J.* **2009**, *4*, 655.
(12) (a) Higa, T.; Krubsack, A. J. *J. Org. Chem.* **1975**, *40*, 3037. (b) Ried, W.; Oremek, G.; Ocakcioglu, B. *Liebigs Ann. Chem.* **1980**, 1424. (c) Maleševic', M.; Karminsky-Zamola, G.; Bajic', M.; Boykin, D. W. *Heterocycles* **1995**, *41*, 2691.
(13) Dearboxylative *ipso*-arylation: (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (c) Goossen, L. J.; Rodoriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (d) Goosen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (e) Goosen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (f) Goosen, L. J.; Rodríguez, N.; Linder, C.; *J. Am. Chem. Soc.* **2008**, *130*, 15248.
(14) (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (b) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851.
(15) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.
(16) The excess of bromo-derivatives was essential for the full conversion of **4a**. The protodebromination would be competitive under the reaction conditions.
(17) Related palladium-catalyzed amination of 3-bromo- or 3-chlorobenzothiophenes; (a) ref. (8). (b) Queiroz, M.-J. R. P.; Begouin, A.; Ferreira, I. C. F. R.; Kirsch, G.; Calhelha, R. C.; Barbosa, S.; Estevinho, L. M. *Eur. J. Org. Chem.* **2004**, 3679. (c) Lamanna, G.; Menichetti, S. *Adv. Synth. Catal.* **2007**, *349*, 2188.
(18) Browning, M. C.; Davies, R. F. B.; Morgan, D. J.; Sutton, L. E.; Venanzi, L. M. *J. Chem. Soc.* **1961**, 4816.

Chapter 3

Synthesis of 5-Alkenylazoles via Fujiwara-Moritani Reaction

3.1 Introduction

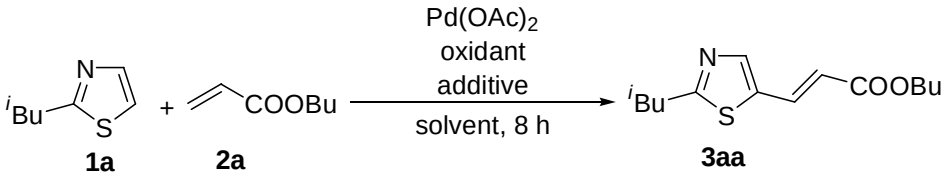
The palladium-catalyzed oxidative cross-coupling of arenes and alkenes via C-H bond cleavage of each substance, so-called Fujiwara-Moritani reaction, is quite attractive from the viewpoint of step economy and enables a rapid increase of molecular complexity in various arenes and heteroarenes.[1] For example, the reactions of six-membered arenes having a directing group[2] such as benzoic acid, anilide, and benzylamine, and electron-rich heteroarenes[3] including indole, thiophene, furan, and indolizine have been developed. In addition, the direct alkenylation of unactivated electron-deficient arenes like pyridine *N*-oxide and perfluoroarene has been achieved.[5] However, less attention has so far been focused on azoles, which are useful heteroaromatic cores in pharmaceutical and material chemistry.[6] Most direct alkenylations of azoles still rely on the use of the corresponding alkenyl halides[7] due to the problematic homocoupling under the oxidative conditions.[8] Herein, the author reports an efficient palladium-based catalyst system for the direct C-H alkenylation of azoles with a number of alkenes.

3.2 Results and Discussion

As an initial attempt, treatment of isobutylthiazole (**1a**) with butyl acrylate (**2a**) in the presence of 10 mol% of $Pd(OAc)_2$ and 3.0 equiv of AgOAc as an oxidant in mesitylene (2.5 mL) at 120 ˚C for 8 h afforded the corresponding 5-alkenylated product **3aa** albeit in 29% yield (Table 1, entry 1). While an acidic additive, PivOH, was found to accelerate the direct alkenylation, a small but significant amount of alkenylated mesitylene was also detected as a byproduct (entry 2). Thus, nonaromatic solvents were tested. Aprotic polar solvents such as DMAc and

DMSO were ineffective (entries 3 and 4). On the other hand, the reaction in PivOH itself gave **3aa** in high yield, and no byproduct was formed (entry 5). EtCOOH further improved the yield of **3aa** (entry 6). The use of $Cu(OAc)_2$ in place of AgOAc or lower temperature decreased the reaction efficiency (entries 7 and 8). The lower catalyst loading had no negative influence on the yield (entry 9).

TABLE 1. Optimization for Palladium-Catalyzed Reaction of Isobutylthiazole (**1a**) with Butyl Acrylate (**2a**). [a]



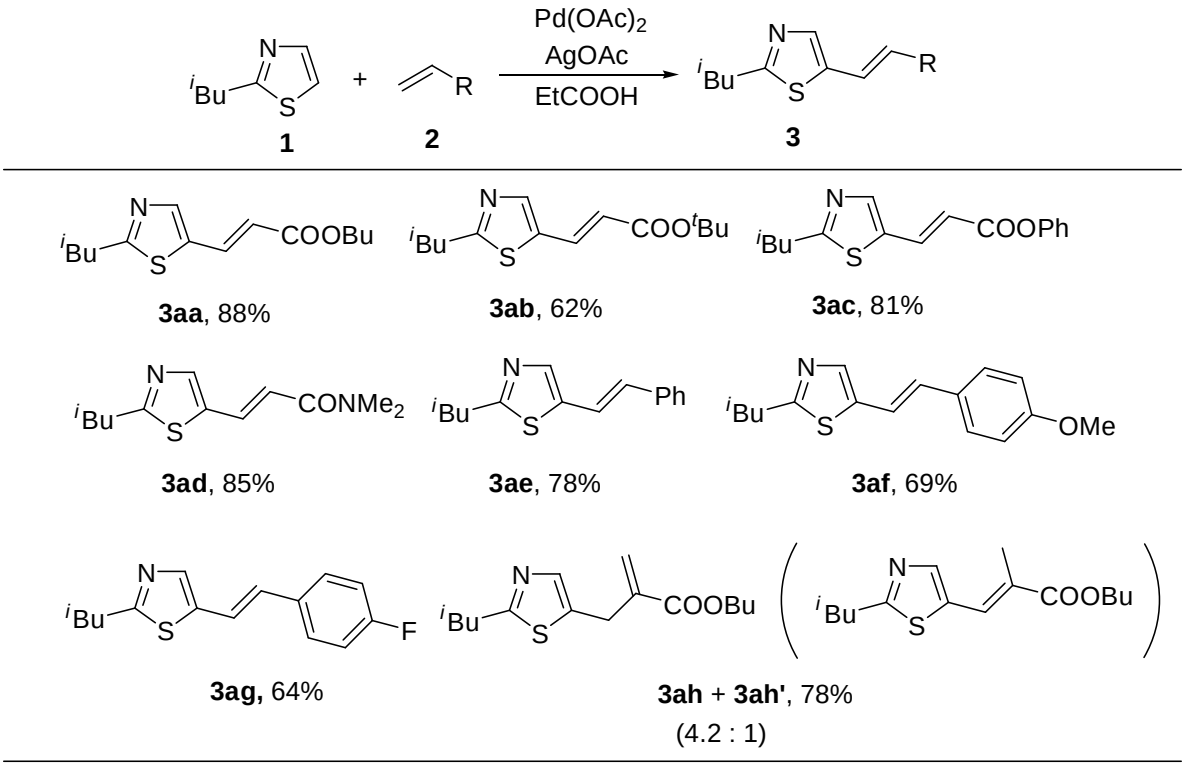
entry	oxidant	additive	solvent	temp (°C)	yield (%)[b]
1	AgOAc	-	mesitylene	120	29
2	AgOAc	PivOH	mesitylene	120	88
3	AgOAc	PivOH	DMSO	120	15
4	AgOAc	PivOH	DMAc	120	49
5	AgOAc	-	PivOH	120	88
6	AgOAc	-	EtCOOH	120	93
7	$Cu(OAc)_2$	-	EtCOOH	120	54
8	AgOAc	-	EtCOOH	90	30
9[c]	AgOAc	-	EtCOOH	120	93

a) A mixture of **1a** (0.2 mol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), additive (0.2 mmol), and oxidant (0.6 mmol) was stirred in solvent (1 mL) for 8 h. b) GC yield. c) $Pd(OAc)_2$ (0.01 mmol) was used.

With the optimized reaction conditions in hand (Table 1, entry 9), a variety of alkenes were tested for the direct alkenylation of **1a** (Table 2). Acrylate esters bearing bulky *t*-butyl **2b** and aromatic phenyl groups **2c** resulted in the formation of **3ab** and **3ac** in 62% and 81% yields, respectively. Acrylamide **2d** showed a similar reactivity. Styrenes also could be employed for the oxidative coupling. Not only simple styrene (**2e**) but also electron-rich and -deficient styrenes **2f** and **2g** reacted with **1a** smoothly to furnish **3ae**-**ag** in good yields. Interestingly,

methacrylate ester **2h** provided the unconjugated (to azole) product **3ah** as the major product (**3ah** : **3ah'** = 4.2 : 1). In contrast, internal alkenes such as methyl cinnamate and 1-hexene gave the corresponding 5-alkenylated products in low yields (ca. <10%).

TABLE 2. Palladium-Catalyzed Alkenylation of 2-Isobuylthiazole (**1a**) with Various Alkenes **2a**. **a, b**

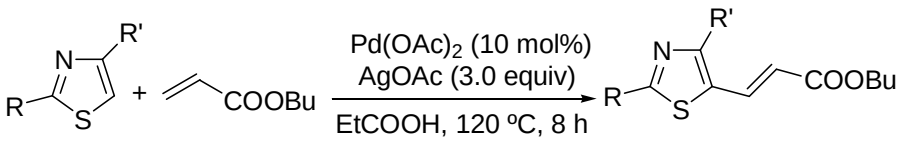


[a] A mixture of **1a** (0.50 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), and AgOAc (1.5 mmol) was stirred in EtCOOH (2.5 mL) at 120 ˚C for 8 h. Key: **2a**, R = COOBu; **2b**, R = COO^{t}Bu; **2c**, R = COOPh; **2d**, R = $CONMe_2$; **2e**, R = Ph; **2f**, R = 4-$MeOC_6H_4$; **2g**, R = 4-FC_6H_4. [b] Isolated yield. [c] Butyl methacrylate was used as an alkene.

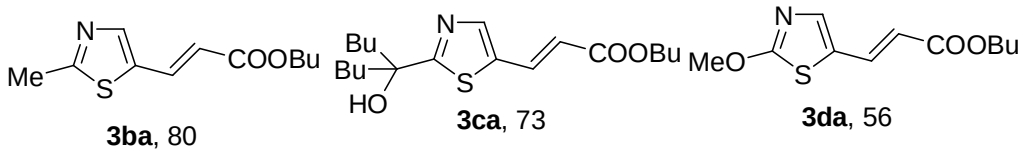
The oxidative coupling reaction was further extended to various thiazoles **1** as shown in Table 3. A smaller methyl-substituted thiazole **1b** also afforded the desired product **3ba** in 80% yield. Thiazole having a free hydroxyl group **1c** reacted with **2a** without any difficulties. Moreover, thiazoles bearing heteroatom substituents at the 2-poition **1d-f** gave **3da**, **3ea**, and **3fa** in moderate to good yields. On the other hand, 2-phenylthiazole showed less activity toward the

reaction. This is probably because of the catalyst deactivation arising from a competitive cyclopalladation on benzene ring.[9] Therefore, the author tested 2-(2,6-dimethylphenyl)thiazole (**1h**) as the reactant to suppress the unfavorable palladation mentioned above. As expected, **1h** could be transformed to **3ha** in 71% yield. Notably, an introduction of a methyl group to the 4-potition of thiazole significantly accelerated the reaction despite the presence of a phenyl substituent at the 2-potion (**3ja**).[10] Furthermore, the coupling of 2,4-dimethylthiazole (**1j**) proceeded smoothly under the standard conditions.

TABLE 3. Palladium-Catalyzed Alkenylation of Various Thiazoles **1** with n-Butyl Acrylate (**2a**).[a]



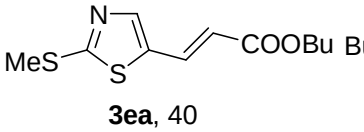
1 **2a** **3**



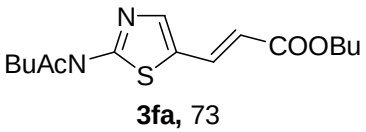
3ba, 80

3ca, 73

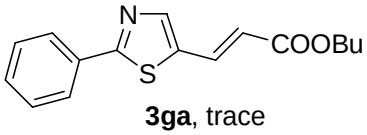
3da, 56



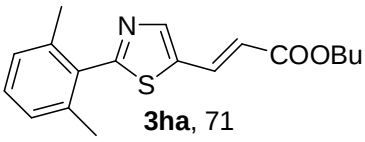
3ea, 40



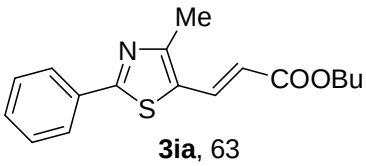
3fa, 73



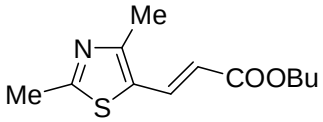
3ga, trace



3ha, 71



3ia, 63

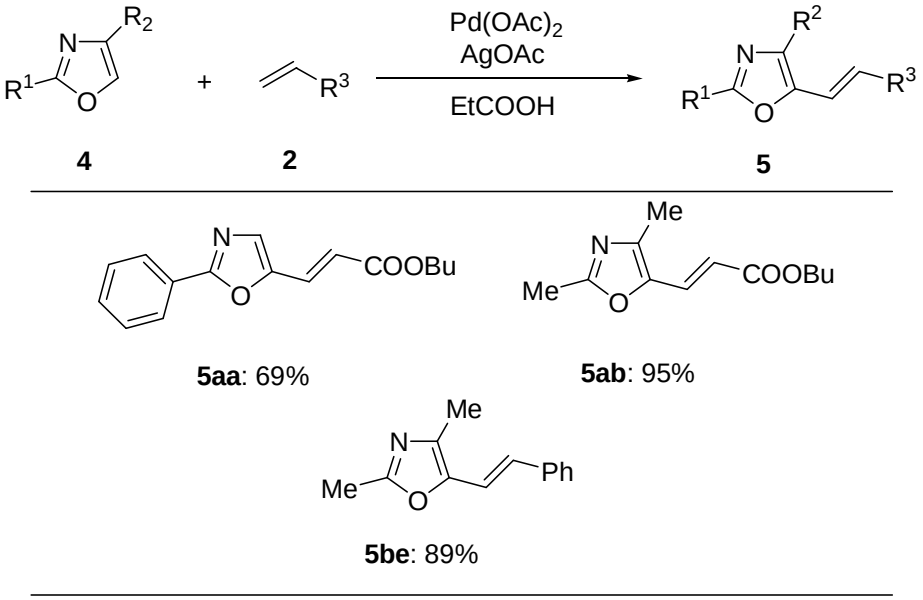


3ja, 75

[a] A mixture of **1** (0.50 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), and AgOAc (1.5 mmol) was stirred in EtCOOH (2.5 mL) at 120 ˚C for 8 h. Key: **1b**, R = Me, R' = H; **1c**, R = Bu_2COH, R' = H; **1d**, R = MeO, R' = H; **1e**, R = MeS, R' = H; **1f**, R = NBuAc, R' = H; **1g**, R = Ph, R' = H; **1h**, R = 2,6-$Me_2C_6H_3$, R' = H; **1i**, R = Ph, R' = Me; **1j**, R, R' = Me. [b] Isolated yield.

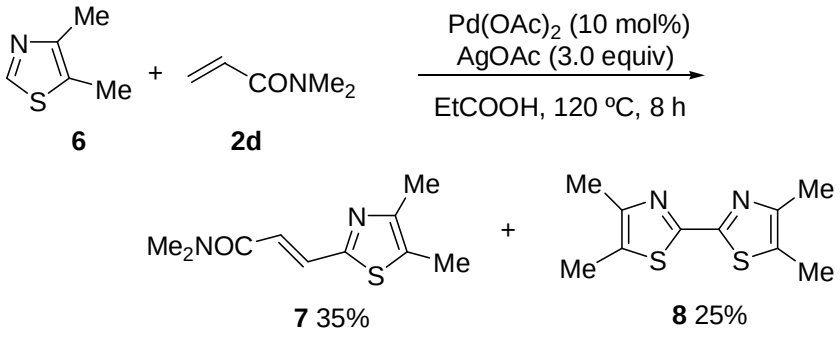
2-Substituted oxazoles instead of thiazoles **1** were also available for use (Table 4). Interestingly, 2-phenyloxazole (**4a**) gave 5-alkenyled product **5a** in 69% yield, which is in marked contrast to the trend of thiazole (Table 2, **3ga**). 2,4-Dimethyloxazole (**4b**) also reacted with **2a** and **2e** smoothly to afford excellent yields of **5ab** and **5be**, respectively.

TABLE 4. Palladium-Catalyzed Alkenylation of Oxazoles **4** with Alkenes **2**.



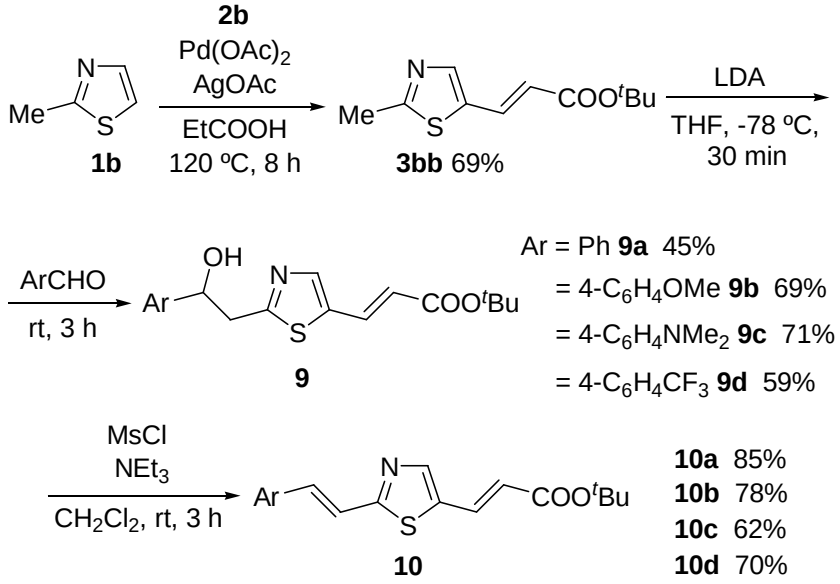
[a] A mixture of **1** (0.50 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), and AgOAc (1.5 mmol) was stirred in EtCOOH (2.5 mL) at 120 ˚C for 8 h. Key: **4a**, R^1 = Ph, R^2 = H; **4b**, R^1, R^2 = Me; [b] Isolated yield.

Next, the author attempted the direct C2 alkenylation of 4,5-dimethylthiazole (**6**) (Scheme 1). Under the standard conditions, the desired **7** was obtained albeit in 35% yield, contaminated with the conceivable homocoupling product **8**.



SCHEME 1. Palladium-Catalyzed Alkenylation of 4,5-Dimethylthiazole (**6**) with **2d**

π-Extended 2,5-disubstituted thiazoles are known to show unique optical properties.[11] Inspired by the literature, the author synthesized some 2,5-dialkenylated thiazoles **10** and investigated their fluorescence in the solid state (Scheme 2). The mono-alkenylated thiazole **3bb** was first prepared by the palladium-catalyzed direct alkenylation of 2-methylthiazole (**1b**). The deprotonation of **3bb** with LDA at -78 ºC in THF and addition of the resultant lithium reagent to aromatic aldehydes at room temperature gave aldol-type products **9a-d**. Finally, the author obtained the desired 2,5-dialkenylthiazoles **10** by dehydration of **9** upon treatment with mesyl chloride and triethylamine.



SCHEME 2. Synthesis of 2,5-Dialkenylthizoles **10**.

Dialkenylthiazoles **10** except for **10d** showed solid-state fluorescence (Figure 1). The emission spectra of styryl-substituted **10a** exhibited the major band with maximum emission λ_{em} at 492 nm. By the installation of the strongly electron-donating dimethylamino group to the benzene ring, this peak was red-shifted by 78 nm (**10c**). The methoxy substituent caused a similar shift, although the effect was considerably small (**10b**). These compounds exhibited similar or relatively strong emissions compared to a typical emitter, tris(8-hydroxyquinolinato)aluminum (Alq_3).

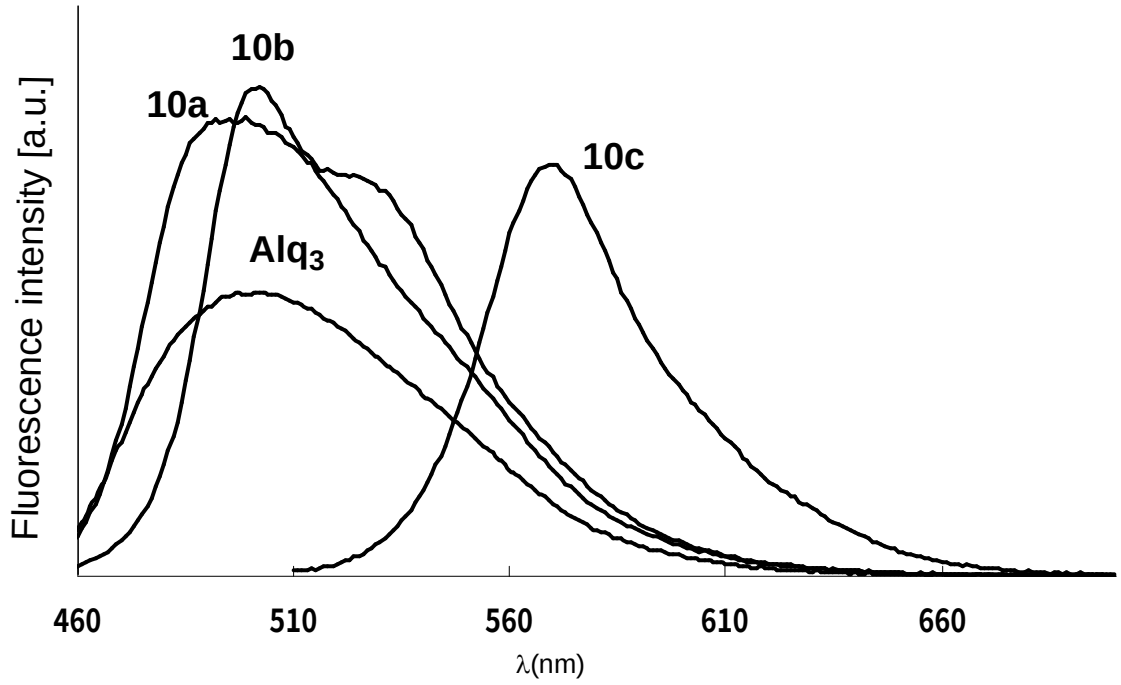


FIGURE 1. Fluorescence Spectra of **10a**,[a] **10b**,[a] **10c**,[b] and Alq_3[c] in the Solid State. [a] Exited at 430 nm.[b] Exited at 500 nm. [c] Exited at 380 nm.

3.3 Conclusion

In summary, the author has described an effective palladium catalyst system for the direct alkenylation of thiazoles and oxazoles with alkenes.[12] In addition, with the catalysis as the key transformation, the author succeeded in the efficient synthesis of π-conjugated 2,5-dialkenylated

thiazoles with interesting optical properties.

3.4 Experimental Section

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for $CDCl_3$ solutions. MS data were obtained by EI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or a CBP-1 capillary column (i. d. 0.5 mm x 25 m). Silica gel (Wakogel 200 mesh) was used for column chromatography.

Materials. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $Pd(OAc)_2$ and AgOAc were purchased from Wako. 2-Phenylthiazole (**2g**)[13] and 2-phenyloxazole (**4a**)[14] were prepared by the methods reported previously.

Experimental Procedure

Synthesis of 5-(thiazol-2-yl)nonan-5-ol (1c). In a 20 mL two-necked flask were added 2-bromothiazole (3 mmol, 492 mg) and Et_2O (2.5 mL) under nitrogen. $^{n}BuMgBr$ (3.6 mmol, 4.2 mL, 0.85 M, Et_2O solution) were added dropwise, and the resulting mixture was then stirred at 40 ºC (bath temperature) for 1 h. The reaction mixture was cooled to room temperature, and 5-nonanone (512 mg, 3.6 mmol) was added. The mixture was stirred overnight, poured into saturated aq. NH_4Cl, and extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product **1c** (2.24 mmol, 509 mg, 75%) was isolated by chromatography on silca gel using hexane-ethyl acetate (9:1, v/v).

Synthesis of 2-(2,6-dimethylphenyl)thiazole (1h). In a 20 mL two-necked flask were added 2-bromothiazole (2 mmol, 325 mg), 2,6-dimethylphenylboronic acid (2 mmol, 300 mg), $Pd(PPh_3)_4$ (0.2 mmol, 231 mg), 2 M aq. Na_2CO_3 (2.4 mL), toluene (2.4 mL) and EtOH (1 mL). The resulting mixture was stirred under nitrogen at 90 ºC (bath temperature) overnight. After

cooling, the reaction mixture was poured into H_2O, extracted with Et_2O, and dried over Na_2SO_4. The product **1h** (0.55 mmol, 104 mg, 28%) was isolated by chromatography on silca gel using hexane-ethyl acetate (95:5, v/v).

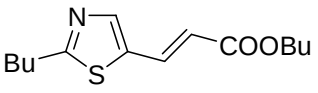
Typical Procedure for Palladium-Catalyzed Alkenylation of Azoles 1 or 4 with Alkenes 2. In a 20 mL two-necked flask were added 2-isobutylthiazole (**1a**, 0.5 mmol, 71 mg), butyl acrylate (**2a**, 1 mmol, 128 mg), $Pd(OAc)_2$ (0.03 mmol, 5.6 mg), AgOAc (1.5 mmol, 250 mg), dibenzyl (ca. 50 mg) as internal standard, and propionic acid (2.5 mL). The resulting mixture was stirred under nitrogen at 120 ºC (bath temperature) for 8 h. After the suspension was allowed to cool to room temperature, analysis of the mixture by GC confirmed the formation of the desired compound. The reaction mixture was poured into saturated aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product **3aa** (0.44 mmol, 118 mg, 88%) was also isolated by chromatography on silica gel using hexane-ethyl acetate (95:5, v/v).

Aldol-Type Reaction of 3bb with Benzaldehyde. In a 20 mL two-necked flask were added diisopropylamine (1 mmol, 145 μL) and THF (1 mL) under nitrogen. BuLi (1 mmol, 625 μL, 1.6 M hexane solution) was added dropwise at 0 ºC, and the solution was stirred for 1 h at the same temperature. The reaction mixture was cooled to -78 ºC and **3bb** (225 mg, 1 mmol) in THF (1 mL) was added. After 1 h, benzaldehyde (127 mg, 1.2 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was poured into saturated aq. NH_4Cl and extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product **9a** (146 mg, 0.45 mmol, 45%) was also isolated by chromatography on silca gel using hexane-ethyl acetate (8:2, v/v).

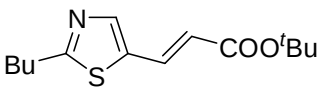
Dehydration of 9a. In a 20 mL two-necked flask were added **9a** (0.4 mmol, 132 mg), MsCl

(0.48 mmol, 37 μL) and CH_2Cl_2 (2 mL). Triethylamine (0.96 mmol, 136 μL) was added at 0 ºC. The mixture was stirred at room temperature under air overnight and then poured into H_2O. The organic layer was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. The product **10a** (0.34 mmol, 106 mg, 85%) was also isolated by chromatography on silca gel using hexane-ethyl acetate (9:1, v/v).

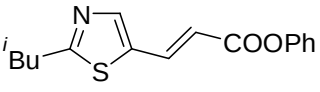
Characterization Data of Products.



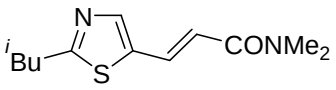
(*E*)-Butyl 3-(2-isobutylthiazol-5-yl)acrylate (3aa) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.00 (d, J = 6.9 Hz, 6H), 1.39-1.45 (m, 2H), 1.64-1.69 (m, 2H), 2.09-2.16 (m, 1H), 2.87 (d, J = 7.0 Hz, 2H), 4.19 (t, J = 7.0 Hz, 2H), 6.13 (d, J = 15.7 Hz, 1H), 7.74 (d, J = 15.7 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.1, 22.2, 29.7, 30.7, 42.7, 64.5, 119.6, 134.0, 134.3, 145.4, 166.3, 172.8; HRMS *m/z* (M^+) calcd for $C_{14}H_{21}NO_2S$: 267.1293, found: 267.1297.



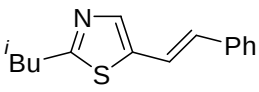
(*E*)-*tert*-Butyl 3-(2-isobutylthiazol-5-yl)acrylate (3ab) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 6H), 1.52 (s, 9H), 2.08-2.15 (m, 1H), 2.86 (d, J = 7.3 Hz, 2H), 6.06 (d, J = 15.7 Hz, 1H), 7.63 (d, J = 15.7 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 28.1, 29.7, 42.7, 80.8, 121.7, 133.1, 134.5, 145.1, 165.5, 172.5; HRMS *m/z* (M^+) calcd for $C_{14}H_{21}NO_2S$: 267.1293, found: 267.1291.



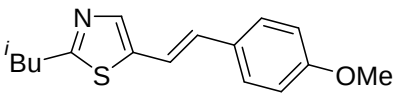
(*E*)-Phenyl 3-(2-isobutylthiazol-5-yl)acrylate (3ac) m.p. 81-82 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.6 Hz, 6H), 2.11-2.18 (m, 1H), 2.90 (d, J = 7.3 Hz, 2H), 6.32 (d, J = 15.8 Hz, 1H), 7.15 (d, J = 7.7 Hz, 2H), 7.22-7.26 (m, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.83(s, 1H), 7.93 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 29.8, 42.8, 118.6, 121.5, 125.8, 129.4, 134.1, 136.0, 146.2, 150.7, 164.7, 173.6; HRMS *m/z* (M^+) calcd for $C_{16}H_{17}NO_2S$: 287.0980, found: 287.0983.



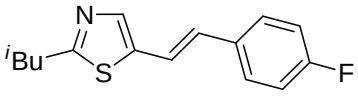
(*E*)-3-(2-Isobutylthiazol-5-yl)-*N*,*N*-dimethylacrylamide (3ad) m.p. 73-75 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.6 Hz, 6H), 2.09-2.16 (m, 1H), 2.86 (d, J = 7.3 Hz, 2H), 3.06 (s, 3H), 3.14 (s, 3H), 6.18 (d, J = 15.0 Hz, 1H), 7.72 (s, 1H) 7.74 (d, J = 15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 29.7, 35.9, 37.2, 42.7, 118.8, 132.1, 135.1, 144.6, 165.8, 171.6; HRMS *m/z* (M^+) calcd for $C_{12}H_{18}N_2OS$: 238.1140, found: 238.1141.



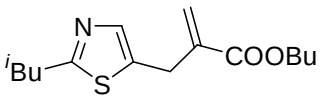
(*E*)-2-Isobutyl-5-styrylthiazole (3ae) m.p. 64-66 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.6 Hz, 6H), 2.09-2.16 (m, 1H), 2.85 (d, J = 7.0 Hz, 2H), 6.80 (d, J = 16.2 Hz, 1H), 7.16 (d, J = 16.2 Hz, 1H), 7.23-7.27 (m, 1H), 7.32-7.36 (m, 2H), 7.43-7.45 (m, 2H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 29.7, 42.7, 118.7, 126.3, 127.9, 128.7, 130.9, 136.6, 137.3, 140.8, 169.1; HRMS *m/z* (M^+) calcd for $C_{15}H_{17}NS$: 243.1082, found: 243.1078.



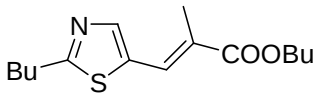
(*E*)-2-Isobutyl-5-(4-methoxystyryl)thiazole (3af) m.p. 59-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.6 Hz, 6H), 2.08-2.15 (m, 1H), 2.85 (d, J = 7.3 Hz, 2H), 3.83 (s, 3H), 6.76 (d, J = 16.1 Hz, 1H), 6.87-6.90 (m, 2H), 7.03 (d, J = 16.1 Hz, 1H), 7.37-7.40 (m, 2H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 29.7, 42.7, 55.3, 114.2, 116.6, 127.6, 129.4, 130.5, 137.7, 140.1, 159.5, 168.6; HRMS *m/z* (M^+) calcd for $C_{16}H_{19}NOS$: 273.1187, found: 273.1182.



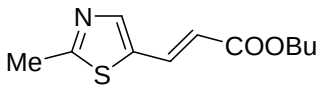
(*E*)-5-(4-Fluorostyryl)-2-isobutylthiazole (3ag) m.p. 51-52 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.6 Hz, 6H), 2.09-2.16 (m, 1H), 2.85 (d, J = 7.3 Hz, 2H), 7.76 (d, J = 16.2 Hz, 1H), 7.01-7.10 (m, 3H), 7.39-7.42 (m, 2H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 29.8, 42.7, 115.7 (d, J = 21.8 Hz), 118.5, 127.8 (d, J = 8.0 Hz), 129.6, 132.8 (d, J = 3.4 Hz), 137.1, 140.8, 162.4 (d, J = 249.3 Hz), 169.2; HRMS *m/z* (M^+) calcd for $C_{15}H_{16}FNS$: 261.0987, found: 261.0985.



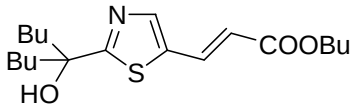
Butyl 2-[(2-isobutylthiazol-5-yl)methyl]acrylate (3ah) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 0.97 (d, J = 6.5 Hz, 6H), 1.33-1.43 (m, 2H), 1.61-1.68 (m, 2H), 2.04-2.11 (m, 1H), 2.80 (d, J = 7.3 Hz, 2H), 3.78 (s, 2H), 4.17 (t, J = 7.0 Hz, 2H), 5.59-5.60 (m, 1H), 6.22 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 22.3, 29.4, 29.7, 30.6, 42.5, 64.9, 126.4, 134.7, 139.1, 140.3, 166.4, 169.8; HRMS *m/z* (M^+) calcd for $C_{15}H_{23}NO_2S$: 281.1449, found: 281.1443.



(*E*)-Butyl 3-(2-isobutylthiazol-5-yl)-2-methylacrylate (3ah') oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.00 (d, J = 6.6 Hz, 6H), 1.39-1.47 (m, 2H), 1.66-1.73 (m, 2H), 2.11-2.18 (m, 4H), 2.90 (d, J = 7.3 Hz, 2H), 4.12 (t, J = 6.5 Hz, 2H), 7.78 (s, 1H), 7.81(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.3, 19.2, 22.3, 29.8, 30.7, 42.5, 65.0, 126.6, 128.6, 133.2, 146.0, 168.1, 178.3; HRMS *m/z* (M^+) calcd for $C_{15}H_{23}NO_2S$: 281.1449, found: 281.1444.

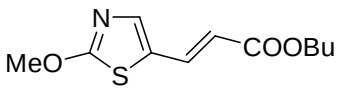


(*E*)-Butyl 3-(2-methylthiazol-5-yl)acrylate (3ba) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.7 Hz, 3H), 1.38-1.47 (m, 2H), 1.64-1.69 (m, 2H), 2.73 (s, 3H), 4.20 (t, J = 7.0 Hz, 2H), 6.12 (d, J = 15.7 Hz, 1H), 7.72, (d, J = 15.7 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 19.7, 30.7, 64.6, 119.8, 134.0, 134.8, 145.5, 166.3, 168.4; HRMS *m/z* (M^+) calcd for $C_{11}H_{15}NO_2S$: 225.0823, found: 225.0822.

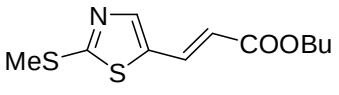


(*E*)-Butyl 3-[2-(5-hydroxynonan-5-yl)thiazol-5-yl]acrylate (3ca) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 6H), 0.96 (t, J = 7.3 Hz, 3H), 1.03-1.10 (m, 2H), 1.23-1.47 (m, 8H), 1.64-1.71 (m, 2H), 1.82-1.97 (m, 4H), 2.85 (s, 1H), 4.20 (t, J = 6.9 Hz, 2H), 6.18 (d, J = 15.6 Hz, 1H), 7.74 (d, J = 15.6 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.9, 19.1, 22.8, 25.4, 30.7, 42.2, 64.6, 78.3, 120.0, 134.1, 134.9, 145.2, 166.4, 180.5; HRMS *m/z* (M^+) calcd for $C_{19}H_{31}NO_3S$: 353.2025, found:

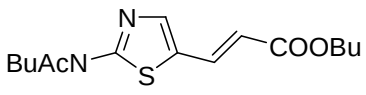
353.2019.



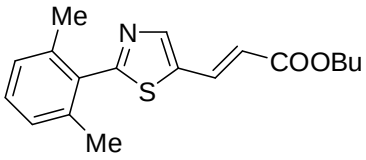
(*E*)-Butyl 3-(2-methoxythiazol-5-yl)acrylate (3da) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.42 (sex, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.3 Hz, 2H), 4.11 (s, 3H), 4.18 (t, J = 7.3 Hz, 2H), 5.94 (d, J = 15.6 Hz, 1H), 7.29 (s, 1H), 7.64 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.7, 58.6, 64.4, 117.3, 127.9, 134.9, 141.5, 166.6, 176.0; HRMS *m/z* (M^+) calcd for $C_{11}H_{15}NO_3S$: 241.0773, found: 241.0777.



(*E*)-Butyl 3-[2-(methylthio)thiazol-5-yl]acrylate (3ea) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.7 Hz, 3H), 1.42 (sex, J = 7.7 Hz, 2H), 1.63-1.70 (m, 2H), 2.72 (s, 3H), 4.19 (t, J = 6.9 Hz, 2H), 6.03 (d, J = 15.8 Hz, 1H), 7.70, (d, J = 15.8 Hz, 1H) 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 16.3, 19.1, 30.7, 64.5, 119.2, 133.4, 134.1, 145.7, 166.3, 169.7; HRMS *m/z* (M^+) calcd for $C_{11}H_{15}NO_2S_2$: 257.0544, found: 257.0543.

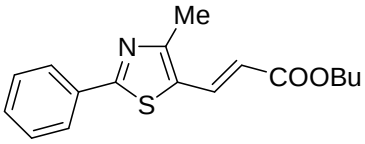


(*E*)-Butyl 3-[2-(*N*-butylacetamido)thiazol-5-yl]acrylate (3fa) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-1.01 (m, 6H), 1.40-1.46 (m, 4H), 1.64-1.78 (m, 4H), 2.43 (s, 3H), 4.12-4.20 (m, 4H), 6.15 (d, J = 15.8 Hz, 1H), 7.60 (s, 1H), 7.74 (d, J = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.71, 13.73, 19.2, 20.0, 22.6, 30.6, 30.7, 48.3, 64.4, 117.5, 129.7, 135.0, 141.3, 160.2, 166.8, 169.9; HRMS *m/z* (M^+) calcd for $C_{16}H_{24}N_2O_3S$: 324.1508, found: 324.1511.

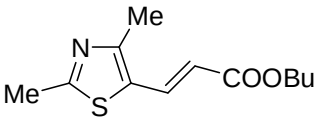


(*E*)-Butyl 3-[2-(2,6-dimethylphenyl)thiazol-5-yl]acrylate (3ha) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.44

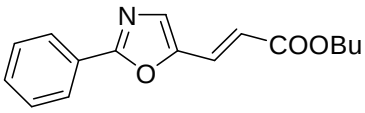
(sex, *J* = 7.3 Hz, 2H), 1.69 (quin, *J* = 7.3 Hz, 2H), 2.18 (s, 6H), 4.21 (t, *J* = 7.3 Hz, 2H), 6.23 (d, *J* = 15.1 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 15.1 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 20.2, 30.8, 64.6, 120.5, 127.7, 129.7, 132.9, 133.8, 136.3, 137.6, 145.9, 166.3, 168.7; HRMS *m/z* (M^+) calcd for $C_{18}H_{21}NO_2S$: 315.1293, found: 315.1298.



(*E*)-Butyl 3-(4-methyl-2-phenylthiazol-5-yl)acrylate (3ia) m.p. 53-55 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.7 Hz, 3H), 1.44 (sex, *J* = 7.7 Hz, 2H), 1.66-1.72 (m, 2H), 2.57 (s, 3H), 4.21 (t, *J* = 7.0 Hz, 2H), 6.13 (d, *J* = 15.4 Hz, 1H), 7.42-7.46 (m, 3H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.92-7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 15.7, 19.2, 30.7, 64.5, 118.9, 126.7, 128.5, 129.0, 130.7, 133.1, 133.8, 156.6, 166.6, 167.5; HRMS *m/z* (M^+) calcd for $C_{17}H_{19}NO_2S$: 301.1136, found: 301.1139.

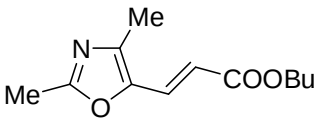


(*E*)-Butyl 3-(2,4-dimethylthiazol-5-yl)acrylate (3ja) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.43 (sex, *J* = 7.3 Hz, 2H), 1.64-1.71 (m, 2H), 2.48 (s, 3H), 2.67 (s, 3H), 4.19 (t, *J* = 6.6 Hz, 2H), 6.01 (d, *J* = 15.4 Hz, 1H), 7.74 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 15.5, 19.1, 19.6, 30.7, 64.4, 118.5, 128.2, 133.9, 155.1, 166.4, 166.7; HRMS *m/z* (M^+) calcd for $C_{12}H_{17}NO_2S$: 239.0980, found: 239.0977.

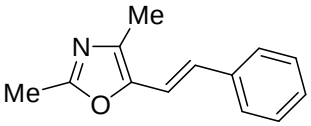


(*E*)-Butyl 3-(2-phenyloxazol-5-yl)acrylate (5aa) m.p. 83-85 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.44 (sex, *J* = 7.3 Hz, 2H), 1.66-1.73 (m, 2H), 4.20 (t, *J* = 6.6 Hz, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 7.37 (s, 1H), 7.47-7.51 (m, 4H), 8.07-8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.7, 64.6, 118.2, 126.7, 126.8, 127.6, 128.9, 131.2, 131.9, 148.0, 163.0, 166.5; HRMS *m/z* (M^+) calcd for

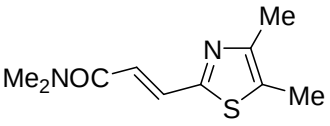
$C_{16}H_{17}NO_3$: 271.1208, found: 271.1199.



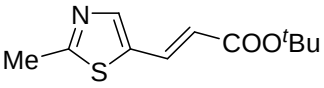
(*E*)-Butyl 3-(2,4-dimethyloxazol-5-yl)acrylate (5ba) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.43 (sex, J = 7.4 Hz, 2H), 1.64-1.71 (m, 2H), 2.24 (s, 3H), 2.46 (s, 3H), 4.20 (t, J = 6.9 Hz, 2H), 6.20 (d, J = 15.6 Hz, 1H), 7.42 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 13.7, 14.1, 19.2, 30.7, 64.4, 115.4, 127.1, 140.6, 143.4, 162.4, 167.0; HRMS *m/z* (M^+) calcd for $C_{12}H_{17}NO_3$: 233.1208, found: 233.1206.



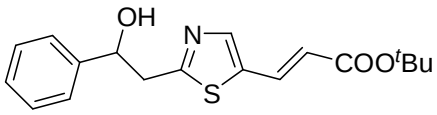
(*E*)-2,4-dimethyl-5-styryloxazole (5be) 65-67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.45 (s, 3H), 6.81 (d, J = 16.5 Hz, 1H), 6.90 (d, J = 16.5 Hz, 1H), 7.22-7.26 (m, 1H), 7.32-7.36 (m, 2H), 7.45 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 13.9, 112.6, 126.2, 126.7 127.6, 128.7, 133.8, 136.8, 145.0, 159.3; HRMS *m/z* (M^+) calcd for $C_{13}H_{13}NO$: 199.0997, found: 199.0995.



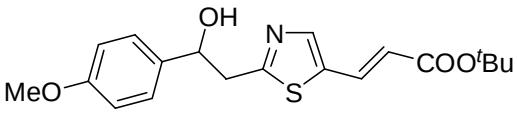
(*E*)-3-(4,5-Dimethylthiazol-2-yl)-*N*,*N*-dimethylacrylamide (7) m.p. 93-94 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.38 (s, 3H), 3.06 (s, 3H), 3.17 (s, 3H), 7.14 (d, J = 15.0 Hz, 1H), 7.60 (d, J = 15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 14.7, 35.9, 37.4, 119.9, 129.2, 133.6, 150.5, 159.2, 165.8; HRMS *m/z* (M^+) calcd for $C_{10}H_{14}N_2OS$: 210.0827, found: 210.0828.



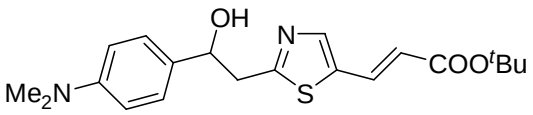
(*E*)-*tert*-Butyl 3-(2-methylthiazol-5-yl)acrylate (3bb) m.p. 58-59 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.72 (s, 3H), 6.04 (d, J = 15.7 Hz, 1H), 7.63 (d, J = 15.7 Hz, 1H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 28.1, 80.8, 121.7, 133.0, 134.9, 145.1, 165.5, 168.1; HRMS *m/z* (M^+) calcd for $C_{11}H_{15}NO_2S$: 225.0823, found: 225.0821.



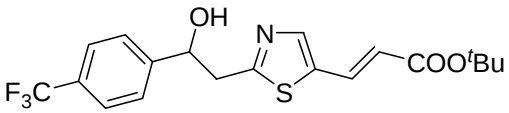
(*E*)-*tert*-Butyl 3-[2-(2-hydroxy-2-phenylethyl)thiazol-5-yl]acrylate (9a) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 3.33-3.35 (m, 2H), 3.92 (bs, 1H), 5.16-5.19 (m, 1H), 6.08 (d, J = 15.6 Hz, 1H), 7.28-7.42 (m, 5H), 7.63 (d, J = 15.6 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 42.5, 72.8, 81.0, 122.3, 125.7, 127.9, 128.6, 132.6, 134.8, 142.6, 144.7, 165.4, 169.5; HRMS *m/z* [$(M+H)^+$] calcd for $C_{18}H_{22}NO_3S$: 332.1320, found: 332.1317.



(*E*)-*tert*-Butyl 3-[2-{2-hydroxy-2-(4-methoxyphenyl)ethyl}thiazol-5-yl]acrylate (9b) m.p. 125-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.31-3.33 (m, 2H), 3.81 (s, 3H), 3.81-3.83 (m, 1H), 5.10-5.14 (m, 1H), 6.07 (d, J = 15.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 15.8 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 42.6, 55.3, 72.4, 80.9, 113.9, 122.2, 127.0, 132.7, 134.7, 134.8, 144.7, 159.2, 165.4, 169.6; HRMS *m/z* (M^+) calcd for $C_{19}H_{23}NO_4S$: 361.1348, found: 361.1341.

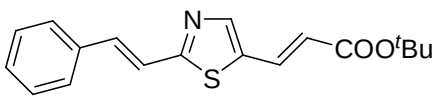


(*E*)-*tert*-Butyl 3-[2-{2-(4-dimethylaminophenyl)-2-hydroxyethyl}thiazol-5-yl]acrylate (9c) m.p. 99-100 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.95 (s, 6H), 3.28-3.40 (m, 2H), 3.49 (bs, 1H), 5.06-5.07 (m, 1H), 6.07 (d, J = 15.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 15.8 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 40.6, 42.6, 72.7, 80.9, 112.5, 122.2, 126.7, 130.4, 132.8, 134.8, 144.7 150.4, 165.5, 170.0; HRMS *m/z* (M^+) calcd for $C_{20}H_{26}N_2O_3S$: 374.1664, found: 374.1668.

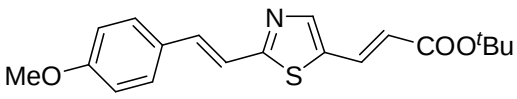


(*E*)-*tert*-Butyl 3-[2-{2-(4-trifluoromethylphenyl)-2-hydroxyethyl}thiazol-5-yl]acrylate (9d) m.p. 164-165 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H),

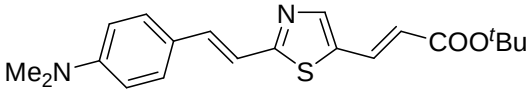
3.29-3.34 (m, 2H), 4.42 (bs, 1H), 5.24-5.26 (m, 1H), 6.08 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.63 (d, 15.6 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 42.1, 72.0, 81.0, 122.6, 124.1 (q, *J* = 270.3 Hz), 125.5 (q, *J* = 3.8 Hz), 126.0, 130.0 (q, *J* = 32.4 Hz), 132.4, 134.9, 144.6, 146.5, 165.3, 168.9; HRMS *m/z* (M^+) calcd for $C_{19}H_{20}F_3NO_3S$: 399.1114, found: 399.1111.



(*E*)-*tert*-Butyl 3-(2-styrylthiazol-5-yl)acrylate (10a) m.p. 96-97 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 6.13 (d, *J* = 15.8 Hz, 1H), 7.25 (d, *J* = 16.5 Hz, 1H), 7.34-7.40 (m, 3H), 7.42 (d, *J* = 16.5 Hz, 1H), 7.54-7.56 (m, 2H), 7.67 (d, *J* = 15.8 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 80.9, 121.2, 122.1, 127.3, 129.0, 129.4, 132.8, 134.3, 135.4, 136.1, 146.5, 165.5, 168.3; HRMS *m/z* (M^+) calcd for $C_{18}H_{19}NO_2S$: 313.1136, found: 313.1122.

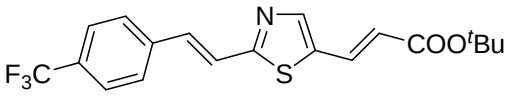


(*E*)-*tert*-Butyl 3-[2-(4-methoxystyryl)thiazol-5-yl]acrylate (10b) m.p. 128-129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.85 (s, 3H), 6.10 (d, *J* = 15.7 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 16.5 Hz, 1H), 7.41 (d, *J* = 16.5 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 15.7 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 55.4, 80.8, 114.4, 119.1, 121.7, 128.1, 128.8, 132.9, 133.8, 135.9, 146.5, 160.7, 165.5, 168.9; HRMS *m/z* (M^+) calcd for $C_{19}H_{21}NO_3S$: 343.1242, found: 343.1238.



(*E*)-*tert*-Butyl 3-[2-(4-dimethylaminostyryl)thiazol-5-yl]acrylate (10c) m.p. 150-152 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.02 (s, 6H), 6.07 (d, *J* = 15.6 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 16.0 Hz, 1H), 7.38 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 15.6 Hz, 1H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1,

40.2, 80.7, 112.0, 116.5, 121.0, 123.2, 128.9, 132.9, 133.1, 136.8, 146.6, 151.1, 165.7, 169.9; HRMS *m/z* (M^+) calcd for $C_{20}H_{24}N_2O_2S$: 356.1558, found: 356.1555.



(*E*)-*tert*-Butyl 3-[2-(4-trifluoromethylstyryl)thiazol-5-yl]acrylate

(10d) m.p. 153-155 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 6.16 (d, *J* = 15.8 Hz, 1H), 7.31 (d, *J* = 16.5 Hz, 1H), 7.47 (d, *J* = 16.0 Hz, 1H), 7.65 (m, 4H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 81.0, 122.6, 123.4, 124.0 (q, *J* = 273.3 Hz), 125.9 (q, *J* = 3.2 Hz), 127.4, 130.8 (q, *J* = 32.8 Hz), 132.5, 134.0, 135.0, 138.7, 146.6, 165.3, 167.2; HRMS *m/z* (M^+) calcd for $C_{19}H_{18}F_3NO_2S$: 381.1010, found: 381.1009.

3.5 References and Notes

(1) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399.

(2) (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211. (b) Boele, M. D. K.; van Strijdonck, G. P. J.; de Vries, A. M. H.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (c) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (d) Wang, J.-R.; Yang, C.-T.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett*. **2007**, *48*, 5449.

(3) (a) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851. (b) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (c) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. (d) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (e) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (f) Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (g) Aouf, C.; Thiery, E.; Bras, J. L.; Muzart, J. *Org. Lett.* **2009**, *11*, 4096. (h) Zhao, J.; Huang, L.; Cheng, K.; Zhang, Y. *Tetrahedron Lett.* **2009**, 50, 2758. (i) Yang, Y.; Cheng, K.; Zhang, Y. *Org. Lett.* **2009**, *11*, 5606.

(4) (a) Maehara, A.; Satoh, T.; Miura, M. *Tetrahedron* **2008**, *64*, 5982. (b) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159.

(5) (a) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (c) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang Z.-X.; *J. Am. Chem. Soc.* **2010**, *132*, 4506.

(6) Only two precedents for the direct alkenylation of pyrazole and imidazo[1,2-*a*]pyridine: (a) Itahara, T.; Kawasaki, K.; Ouseto, F. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3488. (b) Koubachi, J.; Raboin, S. B.; Mouaddib, A.; Guillaumet, G. *Synthesis* **2009**, 271.
(7) (a) Gottumukkala, A. L.; Derridj, F.; Djebbar, S.; Doucet, H. *Tetrahedron Lett.* **2008,** *49*, 2926. (b) Besselievre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008**, *10*, 4029.
(8) (a) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126,* 5074. (b) Liang, Z.; Zhao, J.; Zhang, Y. *J. Org. Chem.* **2010**, *75,* 170.
(9) Hiraki, K.; Fuchita, Y.; Takakura, S. *J. Organomet. Chem.* **1981**, *210,* 273.
(10) This is probably because the methyl group at 4-position in thiazole inhibited the unfavorable coordination of nitrogen to the palladium center necessary for the competitive cyclopalladation.
(11) Selected examples: (a) Shu, C.-F.; Wang, Y.-K. *J. Mater. Chem.* **1998**, *8,* 833. (b) Eckert, K.; Schröder, A.; Hartmann, H. *Eur. J. Org. Chem.* **2000**, 1327.
(12) The fact that the alkenylation of azoles **1** and **4a** occurs selectively at the relatively electrophile-susceptible 5-position rather than the 4-position is consistent with the relevant Pd-catalyzed direct arylation chemistry.
(13) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46,* 7996.
(14) Besselievre, F.; Piguel, S.; Lebrequier, S.; Mahuteau-Betzer, F. *Synthesis* **2009**, 3511.

Conclusion

Included in this thesis is the synthesis of multi-substituted heteroarenes via palladium-catalyzed C-H bond cleavage and decarboxylation. The contents of this thesis is summarized as follows.

Chapter 1 described that 2,3-diarylindoles can be readily prepared by the palladium-catalyzed direct and decarboxylative arylations of carboxyindoles. This approach led to the discovery of a highly luminescent solid blue emitter.

In chapter 2, the author had developed an effective method for the concise and convergent synthesis of 2,3-diarylbenzo[*b*]thiophenes from readily available 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene via nickel-catalyzed Suzuki–Miyaura cross-coupling and palladium-catalyzed decarboxylative arylation.

Chapter 3 addressed an effective palladium catalyst system for the direct alkenylation with thiazoles and oxazoles with alkenes. In addition, with the catalysis as the key transformation, the author succeeded in the efficient synthesis of π-conjugated 2,5-dialkenylated thiazoles of interesting optical properties.

This study showed that Pd-catalyzed C-H and C-C bond cleavages provided a new opportunity for C-C bond formation and contributed to the development of synthetic methods for multi-substituted heteroarenes. Moreover, the author revealed their applications to the efficient synthesis of organic fluorescent compounds.

List of Publications

The contents of this thesis are composed of the following papers:

(1) Fluorescent Diarylindoles by Palladium-Catalyzed Direct and Decarboxylative Arylations of Carboxyindoles

Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M.

Chem. Eur. J. **2009**, *15*, 3674-3677.

(2) Synthesis of 2,3-Diarylbenzo[*b*]thiophenes *via* Nickel-Catalyzed Suzuki-Miyaura Cross-Coupling and Palladium-Catalyzed Decarboxylative Arylation

Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M.

Adv. Synth. Catal. **2009**, *351*, 2683-2688.

(3) Palladium-Catalyzed Direct Oxidative Alkenylation of Azoles

Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M.

J. Org. Chem. **2010**, *75*, 5421-5424.

Supplementary List of Publications

(1) Preparation, Structures, and Thermal Reactivity of Alkoxycarbonyl(cyano)palladium(II) Complexes trans-Pd(COOR)(CN)(PPh_3)$_2$ (R = Me, Et, ^{n}Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, and Bn) as Intermediates of the Palladium-Catalyzed Cyanoesterification of Norbornene Derivatives

Nishihara, Y.; Miyasaka, M.; Inoue, Y.; Yamaguchi, T.; Kojima, M.; Takagi, K.

Organometallics **2007**, *26*, 4054-4060.

(2) Zirconocene-Mediated Highly Regio- and Stereoselective Synthesis of Multisubstituted Olefins Starting from 1-Alkynylboronates

Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K.

J. Am. Chem. Soc. **2007**, *129*, 12634-12635.

(3) Copper-Catalyzed Direct Sulfoxyimination of Azoles and Polyfluorobenzenes under Ambient Conditions

Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M.

Org. Lett. **2011**, *13*, 359-361.

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