Studies on Syntheses of Multi-Substituted Heteroarenes by Using Pd-Phenanthroline Complexes as Catalysts

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Abbreviation

Ar	aryl	*J*	coupling constant
Ac	acetyl	m	multiplet (spectra)
aq.	aqueous solution	M	mol per liter
BAr_F	Tetrakis[3,5-bis(trifluorome-thyl)phenylborate	Me	methyl
		min	minute(s)
Bu	butyl	mL	milliliter
calcd	calculated	μL	microliter
cat	catalyst	mp	melting point
Cy	cyclohexyl	ND	not detected
d	doublet (spectra)	NMR	nuclear magnetic resonance
DCE	1,2-dichloroethane	Ph	phenyl
dba	dibenzylideneacetone	Pr	propyl
DMA	*N,N*-dimethylacetoamide	phen	1,10-phenanthroline
DMF	*N,N*-dimethylformamide	Piv	pivaloyl
dppb	1,4-bis(diphenylphosphino) butane	PMP	4-methoxyphenyl
		q	quartet (spectra)
dppe	1,2-bis(diphenylphosphino) ethane	Rf	relative mobility
		rt	room temperature
δ	scale (NMR)	s	singlet (spectra)
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide	sat	saturated
		sept	septet (spectra)
EI	electron ionization	t	triplet (spectra)
ESI	electronspray ionization	temp	temperature
Et	ethyl	Tf	trifluoromethanesulfonyl
eq	equation	THF	tetrahydrofuran
FAB	fast atom bombardment	TIPS	tri(isopropylsilyl)
h	hour(s)	TLC	thin layer chromatography
HOBt	1-hydroxybenzotriazole	TMS	trimethylsilyl
HRMS	high-resolution mass spectra	TEMPO	2,2,6,6-tetramethylpiperidine-1-yl)oxyl
Hz	hertz		
IR	infrared spectroscopy	SEM	2-(trimethylsilyl)ethoxymethyl
HetAr	heteroaryl		

Chapter 1

General Introduction

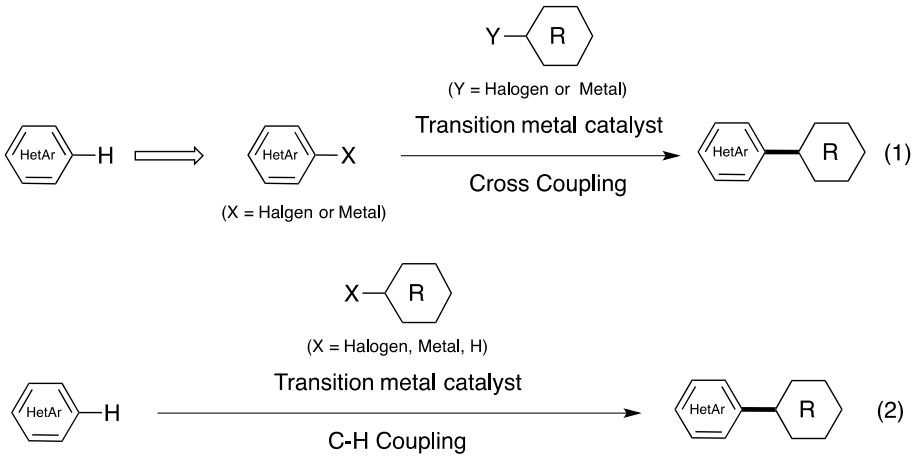
1. Synthesis of Multi-Substituted Heteroarenes

Multi-substituted heteroarenes represent a predominant structural motif in various pharmaceuticals[1] and functional materials.[2] Therefore, numerous synthetic methods to construct multi-substituted heteroarenes have been reported. Classically, multi-substituted heteroarenes have been obtained by the condensation-cyclization of functionalized substrates such as carbonyl and halogenated compounds.[3] In these cases, the desired substituent groups have to be introduced at early stage of synthesis. However, such early stage functionalization strategies have a disadvantage for synthesis of diverse derivatives, because:

(1) The introduced several functional groups often reduces the tolerance of substrates in subsequent transformations

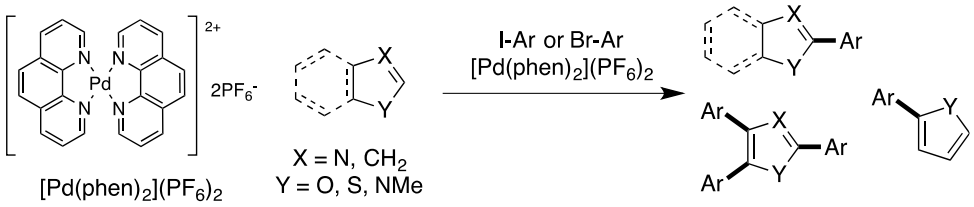
(2) Syntheses of the starting materials often require several steps from commercially available compounds.

Thus, late-stage functionalization methods are highly desired. As an alternative method, cross-coupling reaction allows late-stage functionalization of preformed heteroarenes and divergent synthesis of multi-substituted heteroarenes (eq 1).[4] However, parent heteroarenes must be pre-functionalized with a halogen or a metal group at the position where the desired functional groups are to be installed. The transition metal-catalyzed C-H coupling reaction has recently attracted much attention due to its operational simplicity avoiding the pre-functionalization of heteroarenes (eq 2). In particular, the direct arylation of azoles is a rapidly growing area of extensive research.[5]



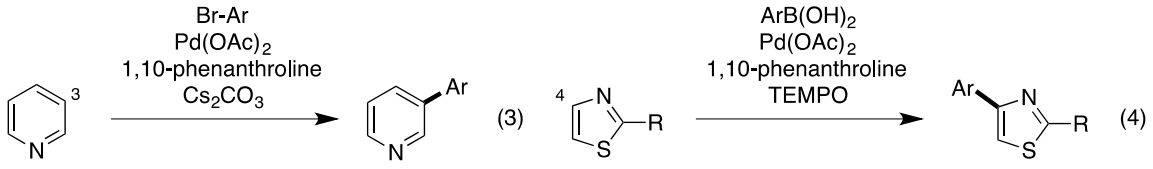
2. Direct Arylation of Heteroarenes by Using Pd-phenanthroline Complexes

Pd-phenanthroline complexes are used as a versatile catalyst for various transformations, for example polymerizations of olefins[6] and oxidations of alcohols.[7] However, only a few examples of C-C coupling reaction with the complexes have been reported, such as Negishi coupling by Iwai and co-workers,[8] and Suzuki coupling by Yang and co-workers.[9] Nevertheless, Pd-phenanthroline complexes have recently attracted attention as a catalyst for C-C coupling reaction since multiple direct arylation reactions of azoles with aryl halides catalyzed by Pd-phenanthroline complexes were reported (Scheme 1).[10] In this reaction, all of the C-H bonds, including less reactive C4 position[11] in the aromatic ring of azoles were cleaved, and aryl groups were introduced at those positions to give multi-arylated azoles.



Scheme 1. Multiple arylation reactions of azoles

Shortly after the report, Yu and co-workers developed direct arylation of six-membered electron-deficient *N*-heteroarenes such as pyridine with similar system (eq 3).[12] Itami and co-workers reported C4-selective direct oxidative coupling of C2-monosubstituted thiazoles and boronic acids with a $Pd(OAc)_2$/1,10-phenanthroline/TEMPO system (eq 4).[13] Since those reports, Pd-phenanthroline systems have been recognized as a representative catalytic system for direct C-H bond arylation reaction.

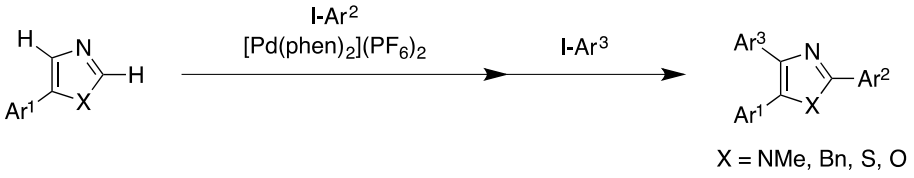


3. Outline of the Thesis

In the author's studies, he focused on the synthetic potential of Pd-phenanthroline complexes as catalysts for direct arylation reaction, and development of efficient synthetic methods for multi-substituted heteroarenes.

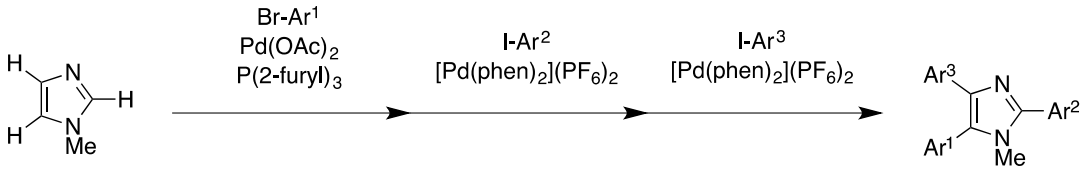
In chapter 2, the author initially describes one-pot sequential diarylation of 5-arylated

azoles by using Pd-phenanthroline complexes (Scheme 2). Recently, selective C-H bond direct arylation of simple azoles by using various catalytic systems has been reported.[14] Also, development of one-pot synthesis is an important topic in synthesis of complex molecule since it enables to eliminate several purifications, reduce chemical wastes and shorten time.[15] In 2011, sequential arylation of azoles by using Pd-phenanthroline complex as a catalyst was reported.[16a] In this case, azoles were coupled with aryl halides in the order of C5, C2 and C4 to afford triarylated azoles. In addition, one-pot sequential diarylation of imidazo[1,5-*a*]pyridine was also developed with an identical catalytic system.[16b] The author envisioned that this one-pot strategy could be applied to synthesis of triarylated azoles. Triarylated azoles were obtained by sequential addition of I-Ar^2 and I-Ar^3 to a solution of 5-arylated azoles in the presence of $[Pd(phen)_2](PF_6)_2$ as a catalyst.



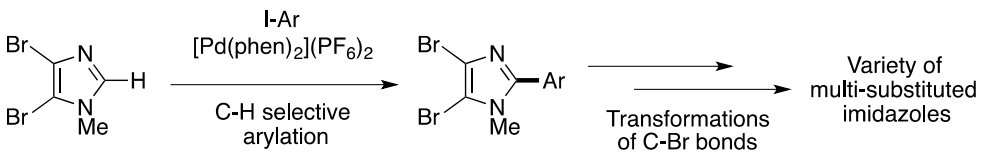
Scheme 2. One-pot sequential diarylation of 5-arylated azoles

The author also achieved one-pot sequential triarylation of simple imidazoles by using combination of $Pd(OAc)_2$-P(2-furyl)$_3$ and Pd-phenanthroline systems (Scheme 3).



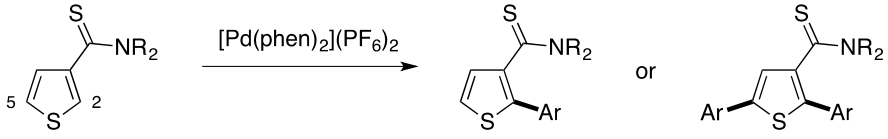
Scheme 3. One-pot sequential triarylation of imidazole

In chapter 3, the author describes synthesis of multi-functionalized imidazole by using C-H bond direct arylation of 4,5-dibromoimidazole followed by transformation of C-Br bonds (Scheme 4). During the studies on C-H bond direct arylation by using Pd-phenanthroline complex, the author realized that Pd-phenanthroline complexes were the less reactive toward oxidative addition than conventional Pd(0)-phosphine complexes. Then, the author speculated that the bromine atoms on substrates is intact under the Pd-phenanthroline-catalyzed conditions and can be used for further transformation. In fact, the reaction of commercially available 4,5-dibrominated imidazole and aryl iodides in the presence of the catalytic amount of $[Pd(phen)_2](PF_6)_2$ gave the C2-arylated imidazoles in good yield, while the carbon-bromine bonds were totally intact. Then, to demonstrate synthetic utility of this method, the author derived a variety of multi-substituted imidazoles by reactions at C-Br bonds with the obtained C2-arylated products.



Scheme 4. The synthetic strategy of multi-substituted imidazoles

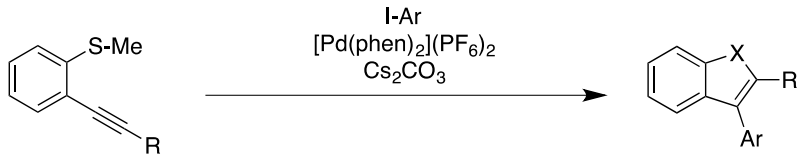
In chapter 4, the author describes direct arylation of thienyl thioamides by using $[Pd(phen)_2](PF_6)_2$ (Scheme 5). It is usually troublesome to apply conventional transition metal-catalyzed reaction to thiocarbonyl compounds. One of the reasons is that thiocarbonyl groups often deactivate catalyst. For example, those groups may directly react with transition metals and/or phosphine ligands. However, the reaction of 3-thienyl thioamides and aryl iodides when $[Pd(phen)_2](PF_6)_2$ was used as a catalyst afforded 2-monoarylated compounds in good yield. In addition, 2,5-diarylation products were obtained when the reaction was conducted with increasing amount of the catalyst. He also revealed that monoarylation and diarylation proceed through different catalytic cycles by the mechanistic studies.



Scheme 5. Direct arylation of thienyl thioamides

In chapter 5, the author describes arylative cyclization of 2-alkynylthioanisoles via S-C(sp^3) bond cleavage (Scheme 6). Unexpectedly, the author found that the reaction of 2-alkynylthioanisoles and aryl iodides under the conditions of Pd-phenanthroline-catalyzed direct C-H bond arylation afforded 3-arylbenzothiophenes. Further investigation revealed that the arylative cyclization was accelerated in the presence of inorganic base such as Cs_2CO_3

though those are not required from the viewpoint of stoichiometry of the reaction. The arylative cyclization of *N,N*-dimethyl-2-alkynylanilne also give the corresponding 3-arylated indole.



Scheme 6. Aryltive cyclization of 2-alkynylthioanisoles

As indicated above, the author has revealed high synthetic potentials of Pd-phen systems for constructing diverse poly-functionalized heteroarenes. The efforts should contribute to development of new organic functional materials, and high throughput screening of bioactive compounds.

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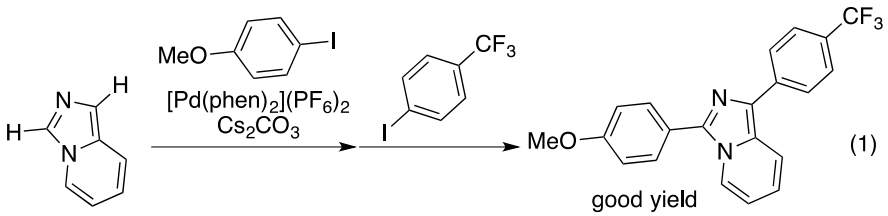
Chapter 2

One-Pot Synthesis of Triarylated Azoles via Sequential C-H Bond Arylation Strategies

Synthetic methods for triarylated azoles containing three different aryl groups via one-pot sequential multiple C−H bond arylations are described. The one-pot sequential diarylation of C5-monoarylated azoles was achieved by the simple sequential addition of two different aryl iodides with a $[Pd(phen)_2](PF_6)_2$ catalytic system. The one-pot triarylation of *N*-methylimidazole was achieved by the combination of a previously reported $Pd(OAc)_2$-P(2-furyl)$_3$ system and the present $[Pd(phen)_2](PF_6)_2$ system. In this case, portionwise addition of aryl halide, base and the catalyst in the final step significantly improved the overall yield of the desired triarylated product. These protocols led to triarylated azoles without a loss of efficiency compared to the corresponding previously reported stepwise syntheses via direct C−H bond arylation.

2.1. Introduction

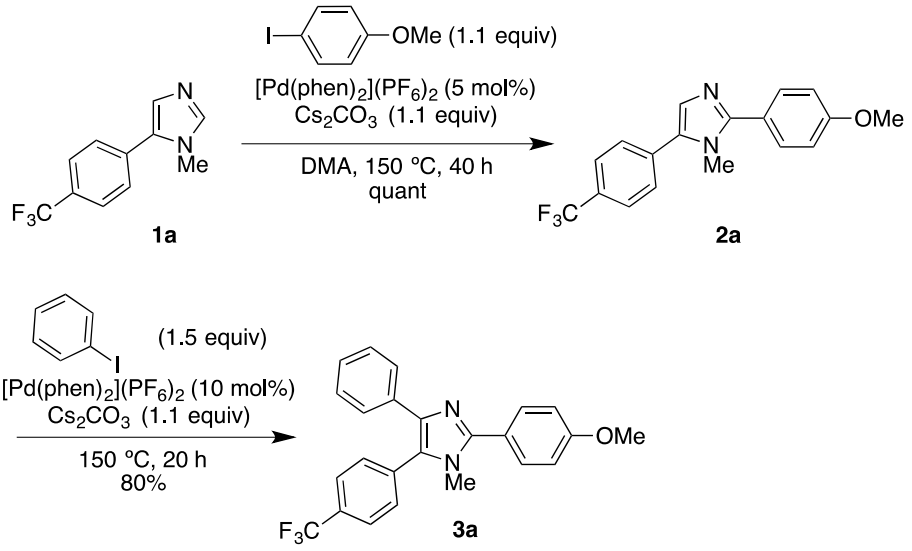
Multiple arylation reactions of azoles with aryl halides catalyzed by Pd-phenanthroline complexes such as $[Pd(phen)_2](PF_6)_2$ were reported.[1] Importantly, the stepwise operation of a similar catalytic reaction allows for the incorporation of three different aryl groups at all three C-H bonds in azoles. The author envisioned the use of above catalytic system for the multiple C-H bond arylation of azoles with different aryl iodides in one-pot as a time-integration approach,[2,3] which would make it possible to avoid chromatographic purification in each step. Recently, the diarylation of the azole derivative imidazo[1,5-*a*]pyridine with this one-pot multiple arylation strategy has been reported (eq 1).[4] As a result, diarylation proceeded without a significant loss of efficiency compared to a conventional stepwise method. The author describes here his efforts on the investigation of the one-pot sequential multiple arylation of imidazoles, oxazole and thiazole.



2.2. Results and Discussions

2.2.1. One-Pot Sequential Diarylation of 5-Arylated Azoles

Initially, the C2, C4-sequential one-pot diarylation of C5-arylated *N*-methylimidazoles was carried out. The combination that showed the best overall yield in stepwise synthesis of triarylated azoles (Scheme 1) was adopted for the one-pot sequential arylation of 5-(4-trifluoromethylphenyl)-*N*-methylimidazole with *p*-methoxyphenyl iodide and phenyl iodide (Table 1).[1b]

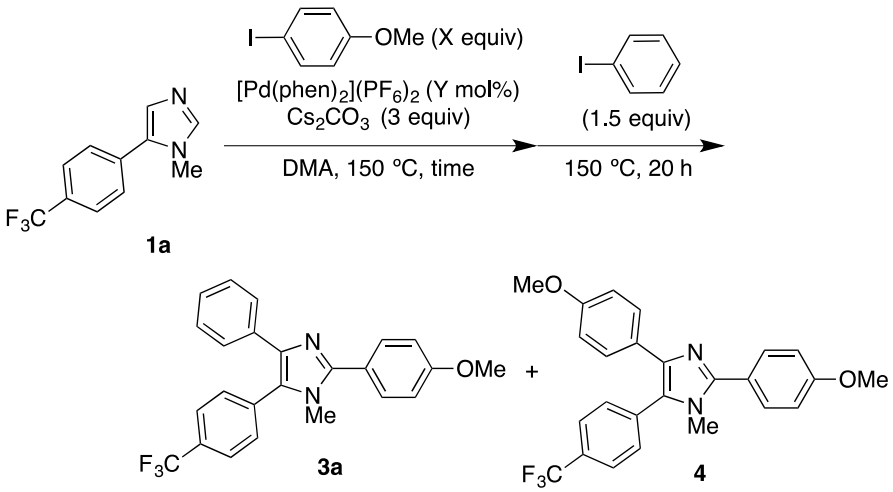


Scheme 1. Previous example of the stepwise sequential arylation of *N*-methylimidazole

Based on the previous stepwise conditions, 15 mol% (total amount of the two steps) of $[Pd(phen)_2](PF_6)_2$, and 3 equiv (excess amount for the two reactions) of Cs_2CO_3 were initially used, and *p*-methoxyphenyl iodide (1 equiv) and phenyl iodide (1.5 equiv) were added sequentially to the reaction solution in this order. In the first arylation, **1a** was consumed within 3.5 h confirmed by GC analysis. After the first arylation was

complete, phenyl iodide was added to the reaction solution, and the mixture was stirred for further 20 h at that temperature to give the desired imidazole **3a** containing three different aryl groups, along with bismethoxyphenylated imidazole **4**, in respective yields of 48% and 19% (entry 1). Notably, **3a** could be readily isolated by conventional flash column chromatography on silica gel. The yield of **3a** improved with a lower catalyst loading (5 mol%) probably due to suppression of a competitive over-reaction (C2 and C4 diarylation) in the first step (entry 2). Even in this case, the yield of **4** significantly increased with a higher amount of *p*-methoxyphenyl iodide (entries 3 and 4). The catalyst was likely deactivated after 48 h in the first step, and the subsequent second arylation scarcely proceeded (entry 5).

Table 1. Optimization of the one-pot sequential arylation of *N*-methylimidazole



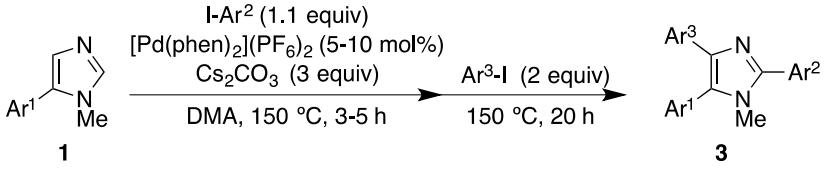
entry	X (equiv)	Y (mol%)	time (h)	yield (%)[a]	
				3a	**4**
1	1	15	3.5	48	19
2	1.1	5	3.5	56	14
3	1.3	5	4	47	30
4	1.5	5	4	38	53
5[b]	1.1	5	48	trace	13

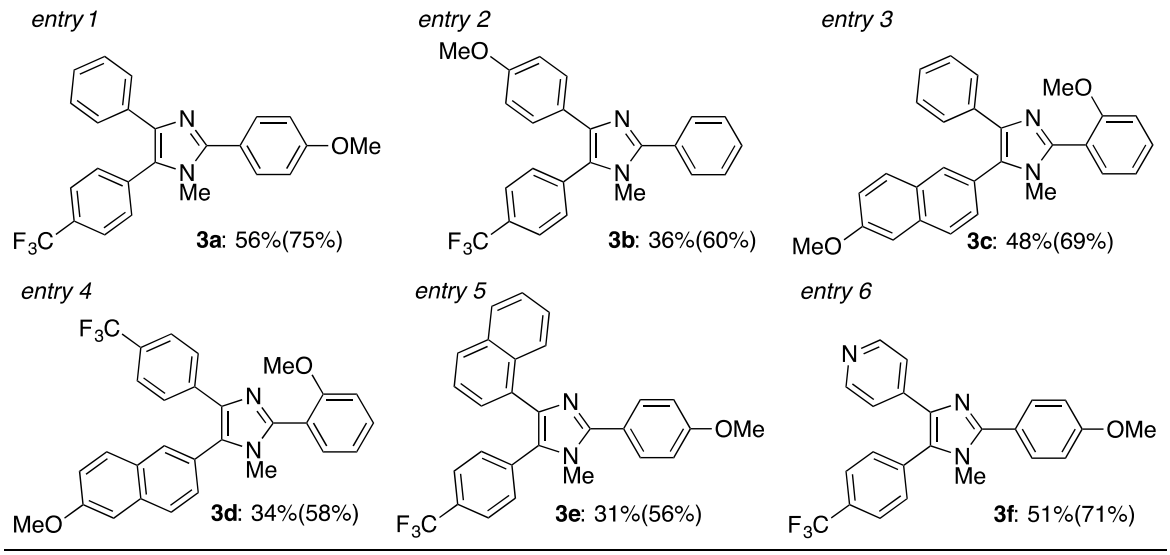
[a] Isolated yields. [b] Monoarylated products containing PMP or phenyl at the C2 position were obtained in respective yields of 54% and 19%.

With the results in hand, the scope of the one-pot diarylation was then investigated (Table 2). Regioisomers **3a** and **3b** were selectively obtained by simply changing the order of the addition of aryl iodides (entries 1 vs 2). Sterically hindered aryl groups such as 2-methoxyphenyl and 1-naphthyl groups were also allowed to couple at both the C2 and C4 positions under identical conditions in a selective manner (entries 3-5). In addition, a heteroaryl iodide, 4-pyridyl iodide, also coupled with the imidazole under the one-pot reaction conditions without a significant loss of efficiency (entry 6). It is

noteworthy that those products were easily isolated by flash column chromatography even if some byproducts formed.

Table 2. Examples of the one-pot sequential arylation of C5-arylated *N*-methylimidazoles[a]

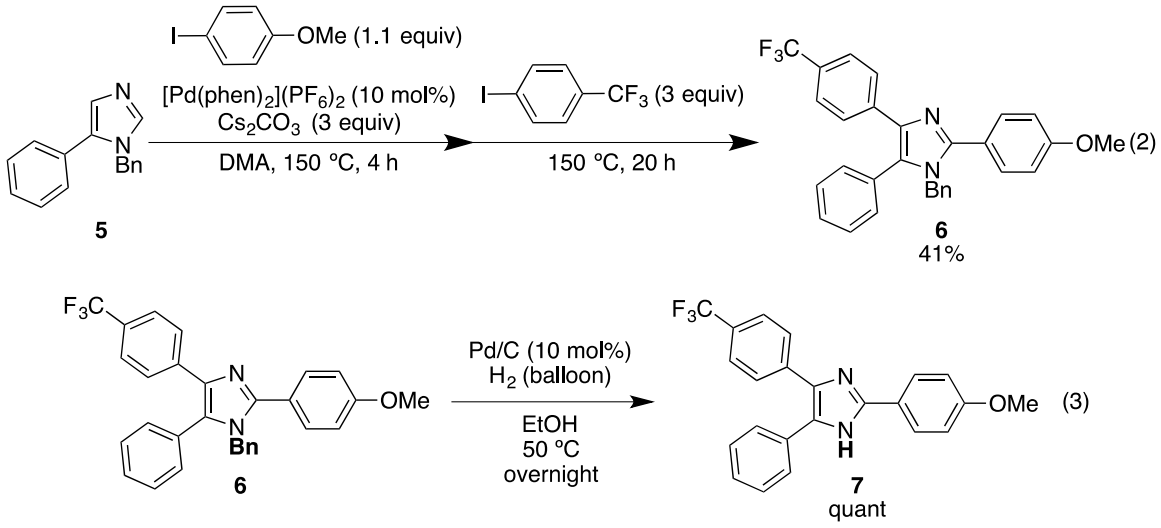




[a] Isolated yields are indicated and formal average yields of the two steps are shown in parentheses.

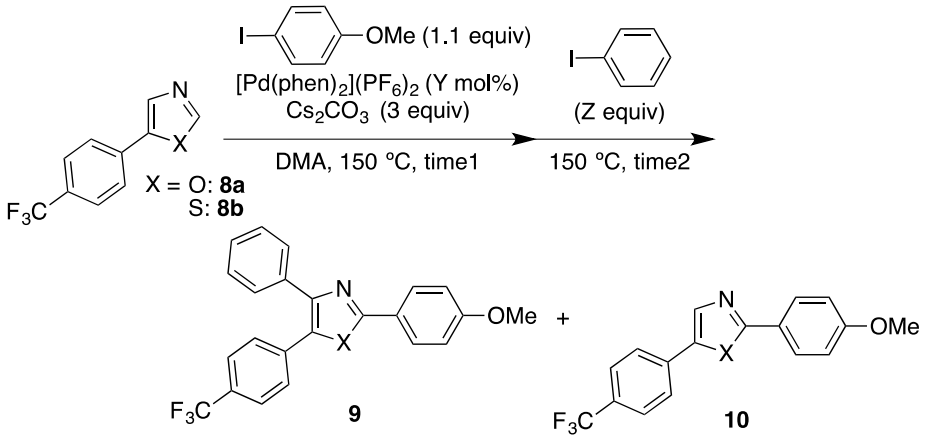
This strategy could be applied to a substrate bearing a different substituent on the amino nitrogen of imidazole. For example, the one-pot sequential arylation of 5-phenyl-*N*-benzylimidazole (**5**) with *p*-methoxyphenyl iodide and trifluoromethylphenyl iodide gave the corresponding triarylated imidazole **6** in 41% overall yield, although a slightly higher catalyst loading was required (eq 2). In

addition, the obtained **6** was readily debenzylated under conventional Pd/C-catalyzed hydrogenolysis conditions to give the imidazole **7** in quantitative yield (eq 3).



The one-pot sequential C2, C4-diarylation of oxazole and thiazole were then investigated (Table 3). The first C2-arylation of monoarylated azoles **8a** and **8b** with *p*-methoxyphenyl iodide was complete within 4 h regardless of the catalyst loading, as in the reaction of imidazoles. Meanwhile, longer reaction times were required for sufficient conversion in the second arylation in reactions of both substrates of azoles compared to that of *N*-methylimidazole. For example, the yield of triarylated **9a** improved to 52% when the reaction time of the second arylation was increased (entries 1-3). Similarly, the yield of **9b** reached 64% when the second reaction was carried out for 72 h (entry 5). Further prolongation of the reaction time did not affect the yield of the products **9**, perhaps due to deactivation of the catalyst.

Table 3. One-pot sequential arylation of oxazole and thiazole



entry	X	Y	Z	time1 (h)	time2 (h)	yield (%)[a]	
						9	**10**
1	O	5	2	3	20	26	41
2	O	10	2	4	48	36	26
3	O	5	3	4	72	52	15
4	S	10	2	4	20	21	51
5	S	10	3	4	72	64	32

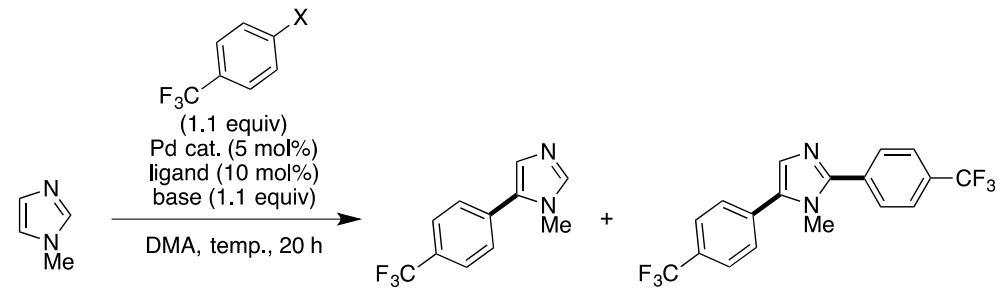
[a] Isolated yields.

2.2.2. One-Pot Sequential Triarylation of *N*-Methylimidazole

Finally, the one-pot triarylation of *N*-methylimidazole (**11**) was investigated. In the first arylation, the reaction of **11** and 4-trifluromethyl iodobenzene (1.1 equiv) in the presence of $[Pd(phen)_2](PF_6)_2$ (5 mol%) as a catalyst and Cs_2CO_3 (1 equiv) as a base was conducted at 150 ºC for 20 h to give a trace amount of monoarylated product **1a** and diarylated product **12** in 93% yield (Table 4, entry 1). By the lowering the reaction temperature to 140 ºC, desired product **1a** was obtained in 46%, but diarylated product

12 was still major product (entry 2), and the yield of **1a** was not improved when the reaction temperature was lowered to 130 ºC (entry 3). Due to the high catalytic activity of $[Pd(phen)_2](PF_6)_2$, the first arylation was performed under the Rossi's catalytic conditions to give **1a** and **12** in 67% and 11% yield respectively (Table 4, entry 4).[5] Therefore, Rossi's catalytic conditions were applied to the first arylation.

Table 4. C5-Arylation of *N*-methylimidazole



11 **1a** **12**

entry	X	Pd cat.	ligand	base	temp. (ºC)	**1a** (%)[a]	**12** (%)[a,b]
1	I	$[Pd(phen)_2](PF_6)_2$		Cs_2CO_3	150	trace	93
2	I	$[Pd(phen)_2](PF_6)_2$		Cs_2CO_3	140	46	54
3	I	$[Pd(phen)_2](PF_6)_2$		Cs_2CO_3	130	40	36
4[c]	Br	$Pd(OAc)_2$	P(2-furyl)$_3$	K_2CO_3	150	67	11

[a] Isolated yields [b] Based on the amount of I-Ar. [c] Br-Ar (1 equiv) and base (1 equiv) were used.

The reaction profile regarding the formation of monoarylated product **1a** was checked by GC analysis to determine the optimal reaction time for the first arylation (Figure 1). The results showed that the reaction for 4 h gave **1a** in the best yield. Further elongation of the reaction time decreased the yield of **1a** due to the formation of the

diarylated product **12**. On the basis of these observations, the reaction time was optimized to be 4 h for the first arylation.

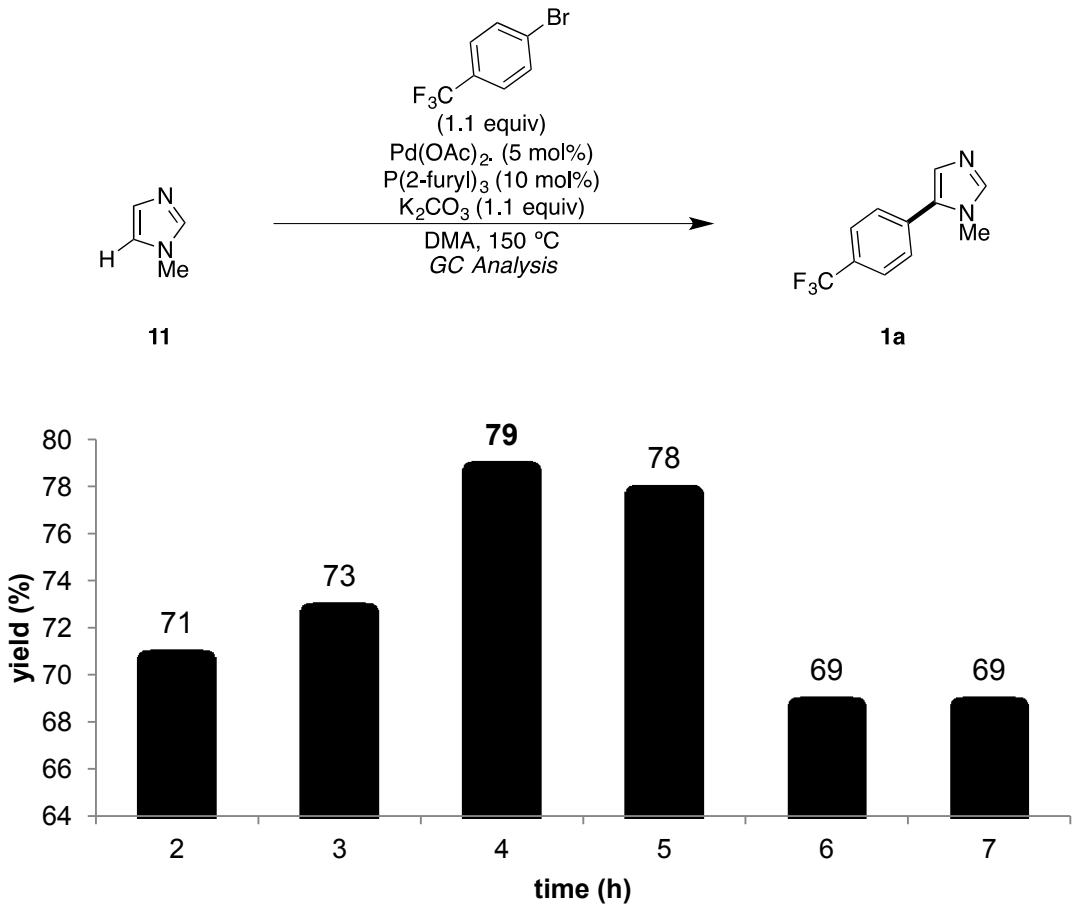
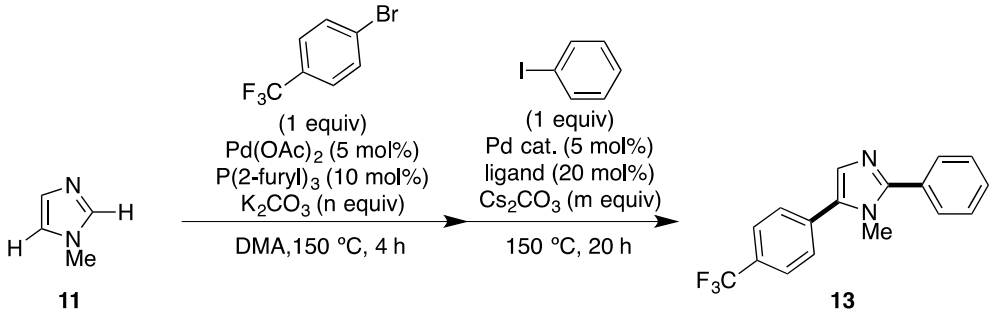


Figure 1. Reaction profile for the formation of **1a** under the conditions of (Table 4, entry 4). Yields for the respective time periods were determined by GC analysis using *n*-heptadecane as an internal standard.

In the second arylation, iodobenzene (1 equiv), $[Pd(phen)_2](PF_6)_2$ (5 mol%) and Cs_2CO_3 (1 equiv) were added to the reaction mixture after the first arylation completed. The resulting mixture was then stirred at 150 ºC for further 20 h to give the target diarylated product **13** in 43% yield (Table 5, entry 1). The additon of

1,10-phenanthroline (20 mol%) was not effective in the second arylation (entry 2). In the first arylation, K_2CO_3 (2 equiv) which was the total amounts of a base in the two reactions was added. In this case, the second arylation was performed by the addtion of iodobenzene (1 equiv) and $[Pd(phen)_2](PF_6)_2$ (5 mol%) to give **13** in 14% yield (entry 3).

Table 5. One-pot sequential diarylation of *N*-methylimidazole (**11**)



11 **13**

entry	n	m	Pd cat.	ligand	**13** (%)[a]
1	1	1	$[Pd(phen)_2](PF_6)_2$	-	43
2	1	1	$[Pd(phen)_2](PF_6)_2$	phen	2
3	2	0	$[Pd(phen)_2](PF_6)_2$	-	14

[a] Isolated yields.

The reaction profiles regarding the product formation and substrate comsumption were checked by GC analysis (Figure 2). The best yield of **13** was observed after 4 h, and iodobenzene was completely consumed after 6 h. The optimal reaction time for the second arylation was determined to be 4 h.

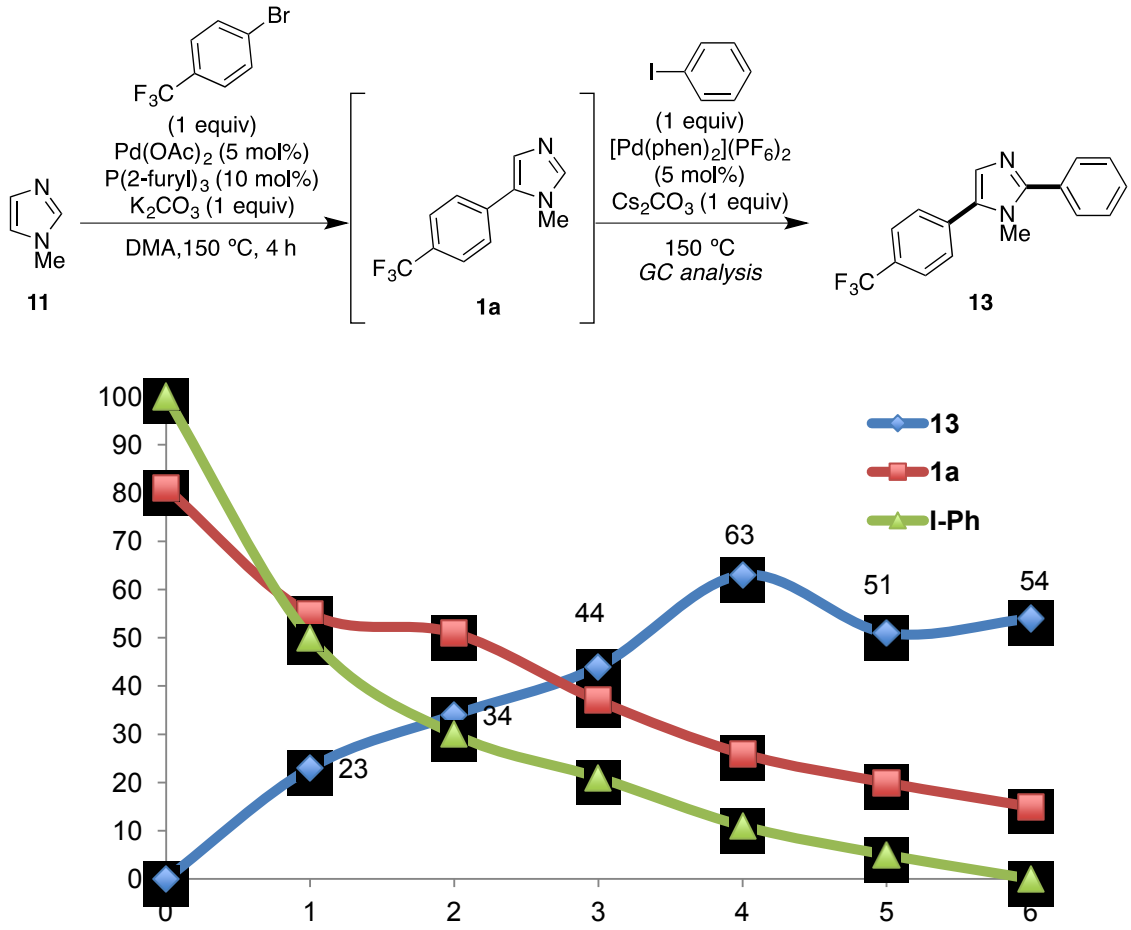
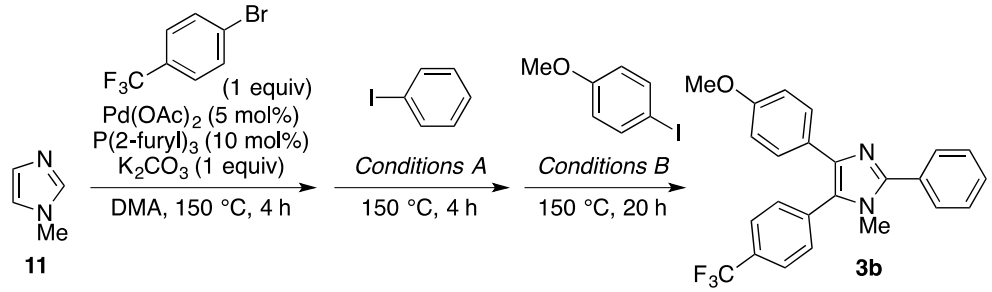


Figure 2. Reaction profile for **1a, 13** and I-Ph under the conditions of (Table 5, entry 1). Yields for the respective time periods were determined by GC analysis using *n*-heptadecane as an internal standard.

Finally in the third arylation was investigated. As a first attempt, $[Pd(phen)_2](PF_6)_2$ (5 mol%), Cs_2CO_3 (3 equiv), and iodobenzene (1.1 equiv) were added to the reaction mixture based on the conditions for the previous one-pot sequential diarylation (Table 2, entry 2). The resulting mixture was stirred for 4 h at 150 °C, and *p*-methoxy iodobenzene (2 equiv) was then added to the reaction mixture. The mixture was stirred for further 20 h, but this did not lead to the formation of the desired product **3b** (Table 4, entry 1). Meanwhile, a small amount of **3b** was obtained by split additions of

the base in each step (total 2.5 equiv) and further addition of the catalyst in the final step (entry 2). Finally, the further portionwise addition of the catalyst, halide, and base in the final step improved the yield of **3b** to 37% (average of each of the three steps: 72%) **(**entry 3**)**. This result was comparable to the overall yield of **3b** from *N*-methylimidazole with the stepwise method (23-40%).[1b]

Table 6. One-pot sequential triarylation of *N*-methylimidazole (**11**)



entry	Conditions A	Conditions B	yield (%)[a]
1	Ph-I (1 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol%) Cs_2CO_3 (3 equiv)	PMP-I (2 equiv)	ND
2	Ph-I (1 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol%) Cs_2CO_3 (1 equiv)	PMP-I (1.5 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol%) Cs_2CO_3 (1.5 equiv)	7
3[b]	Ph-I (1 equiv) $[Pd(phen)_2](PF_6)_2$ (5 mol%) Cs_2CO_3 (1 equiv)	PMP-I (3 equiv) $[Pd(phen)_2](PF_6)_2$ (15 mol%) Cs_2CO_3 (3 equiv)	37

[a] Isolated yields. [b] In the final step, the catalyst, PMP-I, and Cs_2CO_3 were split into 6 portions, and the portions were added every 0.5 h.

2.3. Conclusion

In conclusion, one-pot syntheses of triarylated azoles were developed based on $[Pd(phen)_2](PF_6)_2$-catalyzed sequential C-H bond arylation reactions. With these protocols, the resulting overall yields were comparable to those in the corresponding stepwise methods, and fewer chromatographic purification steps are necessary. Therefore, the one-pot protocols should be used as time- and cost-effective methods for the synthesis of triarylated azoles. Also, these protocols may be used as an attractive method for the high-throughput synthesis of triarylated azoles since the final product can be readily isolated by conventional chromatographic purification.

2.4. Experimental

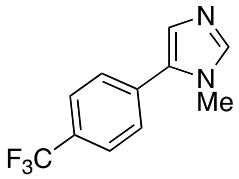
General remarks: ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were on a JEOL α-400 and ECS 400, 500 and 600. Chemical shifts of ^{1}H and ^{13}C are reported in δ□ □and are referenced to tetramethylsilane (δ□= 0) and $CDCl_3$ as internal standards, respectively. ^{19}F chemical shifts are expressed in δ□relative to the external standard CF_3COOH. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained by ionizing samples via electron ionization (EI) in positive mode using a magnetic sector analyzer, and were taken on a JEOL JNM 700 mass spectrometer and a SHIMADZU GC17A/GCMS-QP5050A gas chromatograph mass spectrometer. Preparative recycling gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-9201 and LC-908 recycling preparative HPLC equipped with JAIGEL-1H and -2H columns (chloroform as an eluent). Kugelrohr distillation was performed on SIBATA GLASS TUBE OVEN GTO-250RS. Melting points were determined using a Stanford Research Systems OptiMalt MPA100. IR spectra were obtained on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer. Gas chromatography (GC) was performed a SHIMADZU GC-14B equipped with SGE BP1 Capillary Column (30 m x 0.25 μm). All reactions were carried out under an argon atmosphere.

Material: Unless otherwise noted, reagents were obtained commercially and used without purification. DMA and DMF were distilled over calcium hydride under reduced pressure. Anhydrous Et_2O and THF were purchased from Kanto Chemical Co., Inc. $[Pd(phen)_2](PF_6)_2$ was prepared as described in the literature.[1a] Silica gel 60N (Spherical, Neutral, 40-50 mm) from Kanto Chemical CO., Inc. was used for flash column chromatography.

General Procedure for the C5 Arylation of Azoles

DMA (0.5 M) was added to a screw-capped test tube and degassed by a freeze−pump−thaw cycle (3 times). To this was added $Pd(OAc)_2$ (5 mol%), tri(2-furyl)phosphine (10 mol%), K_2CO_3 (1 equiv), azoles, and aryl bromides (1 equiv). The resulting mixture was stirred overnight at 150 °C under an argon atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel or by Kugelrohr distillation to give C5-arylated azoles **1a**, **5** and **8**.

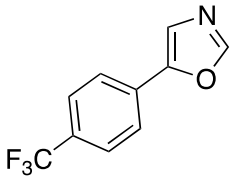
_N_-Methyl-5-(4-trifluoromethylphenyl)imidazole[1b] (1a)



Chemical Formula: $C_{11}H_9F_3N_2$
Exact Mass: 226.0718
Molecular Weight: 226.1978

68% yield, colorless oil, Rf = 0.10 (CH_2Cl_2 : MeOH = 100 : 1). ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 7.18 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.56 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H).

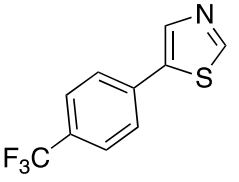
5-(4-Trifluoromethylphenyl)oxazole[11] (8a)



Chemical Formula: $C_{10}H_6F_3NO$
Exact Mass: 213.0401
Molecular Weight: 213.1559

29% yield, colorless solid, Rf = 0.45 (*n*-Hexane : EtOAc = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.98 (s, 1H).

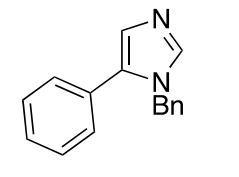
5-(4-Trifluoromethylphenyl)thiazole[12] (8b)



Chemical Formula: $C_{10}H_6F_3NS$
Exact Mass: 229.0173
Molecular Weight: 229.2215

47% yield, yellow solid, Rf = 0.60 (*n*-Hexane : EtOAc = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 8.15 (s, 1H), 8.83 (s, 1H).

_N_-Benzyl-5-(4-trifluoromethylphenyl)imidazole[13] (5)



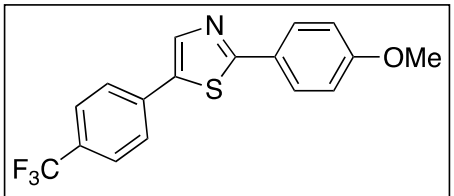
Chemical Formula: $C_{16}H_{14}N_2$
Exact Mass: 234.1157
Molecular Weight: 234.2958

48% yield, yellow solid, Rf = 0.25 (CH_2Cl_2 : MeOH = 100 : 3). ^{1}H NMR ($CDCl_3$) δ 5.16 (s, 2H), 7.00-7.02 (m, 2H), 7.16 (s, 1H), 7.26-7.33 (m, 5H), 7.35-7.39 (m, 3H), 7.73 (s, 1H).

General Procedure for the One-pot Sequential Direct Diarylation of C5-Arylated Azoles (Tables 2 and 3, eq 2)

DMA (0.5 M) was added to a screw-capped test tube and degassed by a freeze−pump−thaw cycle (3 times). To this was added $[Pd(phen)_2](PF_6)_2$ (5–10 mol%), Cs_2CO_3 (3 equiv), C5-arylated azoles (0.25 mmol), and aryl iodide (1.1 equiv). The reaction mixture was stirred for 3-5 h at 150 °C under an argon atmosphere and monitored by GC and TLC analysis. After the reaction was complete, the mixture was cooled to room temperature. To the resulting mixture was added another aryl iodide (2−3 equiv), and this was stirred for 20-72 h at 150 °C under an argon atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the 2,4-diarylated products **3**, **6** and **9** and 2-monoarylated products **10**.

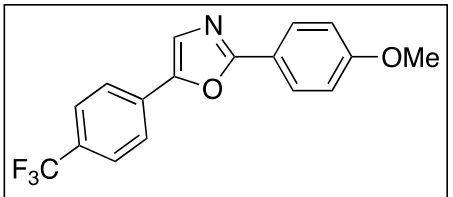
2-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)thiazole (10b)



Chemical Formula: $C_{17}H_{12}F_3NOS$
Exact Mass: 335.0592
Molecular Weight: 335.3435

32% yield, orange solid, mp 160-162 ºC, Rf = 0.63 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1603, 1438, 1330, 1262, 1173, 1123, 1071, 832 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 55.6 (OMe), 124.0 (q, *J* = 271.5 Hz), 125.8, 126.2 (q, *J* = 3.8 Hz), 126.7, 127.1, 128.3, 130.1 (q, *J* = 33.8 Hz), 134.9, 136.6, 139.5, 161.8, 168.6, ^{19}F NMR ($CDCl_3$) δ –50.4. MS (EI) *m/z* 335 (M^+). HRMS (EI); Calcd for $C_{17}H_{12}F_3NOS$ (M^+); 335.0592, Found; 335.0591.

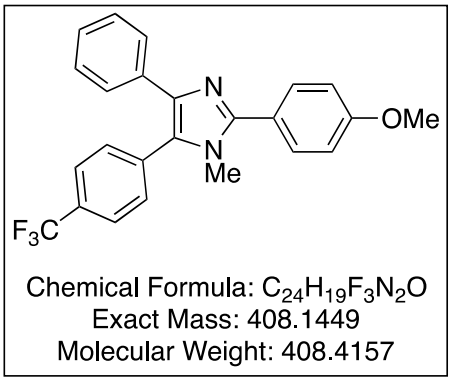
2-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)oxazole[14] (10a)



Chemical Formula: $C_{17}H_{12}F_3NO_2$
Exact Mass: 319.0820
Molecular Weight: 319.2779

15% yield, colorless solid, Rf = 0.11 (*n*-Hexane : EtOAc = 20 : 1). ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.00 (d, *J* = 9.0 Hz, 2H), 7.51 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 2H).

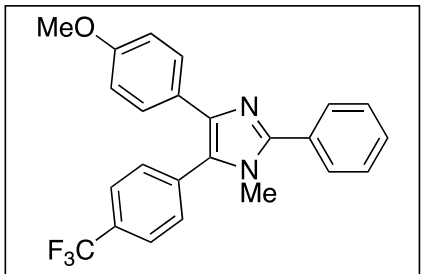
2-(4-Methoxyphenyl)-*N*-Methyl-4-phenyl-5-(4-trifluoromethylphenyl)imidazole[1b] (3a)



Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

56% yield, colorless solid, Rf = 0.45 (*n*-Hexane : EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 3.88 (s, 3H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.19-7.25 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H).

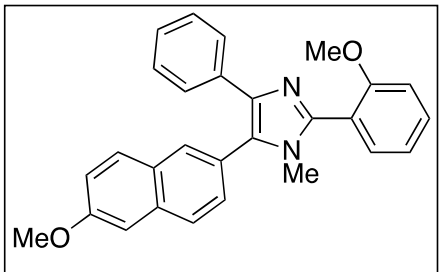
2-Phenyl-4-(4-methoxyphenyl)-*N*-methyl-5-(4-trifluoromethylphenyl)imidazole[1b] (3b)



Chemical Formula: $C_{24}H_{19}F_3N_2O$
Exact Mass: 408.1449
Molecular Weight: 408.4157

37% yield, yellow solid, Rf = 0.45 (*n*-Hexane : EtOAc = 1 : 1). ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H), 3.79 (s, 3H), 6.79 (d, *J* = 8.9 Hz, 2H), 7.45-7.48 (m, 5H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.83 (br, 2H).

2-(2-Methoxyphenyl)-*N*-methyl-4-phenyl-5-(6-methoxy-2-naphthyl)imidazole (3c)

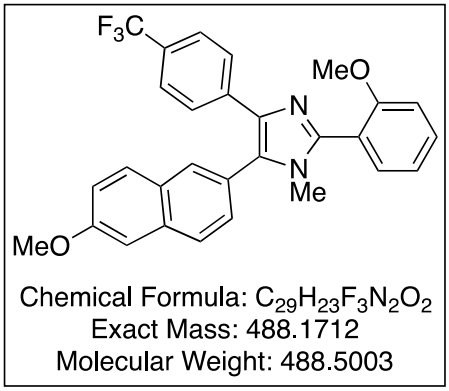


Chemical Formula: $C_{28}H_{24}N_2O_2$
Exact Mass: 420.1838
Molecular Weight: 420.5024

48% yield, yellow solid, mp 87-88 ºC, Rf = 0.15 (*n*-Hexane : EtOAc = 4 ; 1), IR (KBr) 2933, 1606, 1496, 1469, 1387, 1251, 1023, 909, 759, 726, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 7.02 (d, *J* = 8.5 Hz, 1H), 7.10-7.22 (m, 6H), 7.46-7.50 (m, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.77 (d, *J* = 9.4 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 32.4, 55.5, 55.7, 105.8, 111.0, 119.6, 121.2, 124.4 (q, *J* = 271.5 Hz), 125.1 (q, *J* = 3.8 Hz), 125.7, 126.8, 127.9, 127.9 (q, *J* = 32.0 Hz), 128.6, 129.1, 129.8, 130.0,

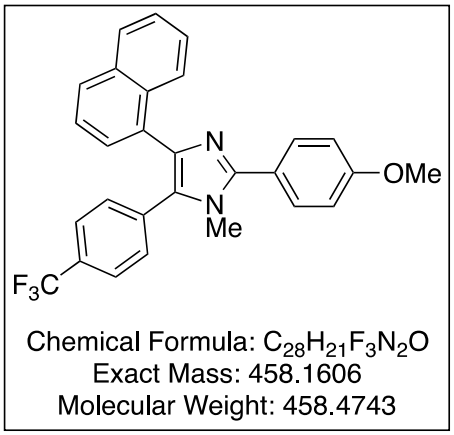
131.1, 131.4, 132.8, 134.6, 135.9, 138.0, 146.0, 157.6, 158.7. MS (EI) *m/z* 420 (M^+). HRMS (EI); Calcd for $C_{28}H_{24}N_2O_2$ (M^+); 420.1838, Found; 420.1841.

2-(2-Methoxyphenyl)-*N*-methyl-4-(4-trifluoromethylphenyl)-5-(6-methoxy-2-naphthyl)imidazole (3d)



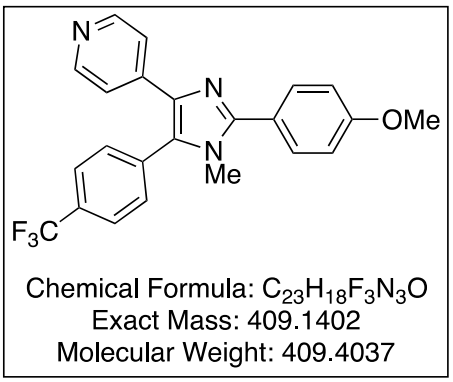
48% yield, yellow solid, mp 88-89 ºC, Rf = 0.68 (*n*-Hexane : EtOAc = 1 : 1). IR (KBr) 2924, 1617, 1493, 1325, 1251, 1165, 1122, 1064 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.34 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.11-7.15 (m, 1H), 7.21-7.23 (m, 3H), 7.38-7.44 (m, 3H), 7.66-7.71 (m, 2H), 7.76 (d, *J* = 9.4 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 32.4, 55.5, 55.7, 105.9, 111.1, 114.3, 119.7, 121.2, 124.1 (q, *J* = 271.5 Hz), 125.1 (q, *J* = 3.8 Hz), 125.7, 126.8, 127.9, 127.9 (q, *J* = 32.0 Hz), 128.6, 129.0, 129.8, 130.0, 131.1, 131.4, 132.8, 134.6, 135.9, 138.0, 146.0, 157.6, 158.7. ^{19}F NMR ($CDCl_3$) δ –58.7. MS (EI) *m/z* 488 (M^+). HRMS (EI); Calcd for $C_{29}H_{23}F_3N_2O_2$ (M^+); 488.1712, Found; 488.1707.

2-(4-Methoxyphenyl)-*N*-methyl-4-(1-naphthyl)-5-(4-trifluoromethylphenyl)imidazole (3e)



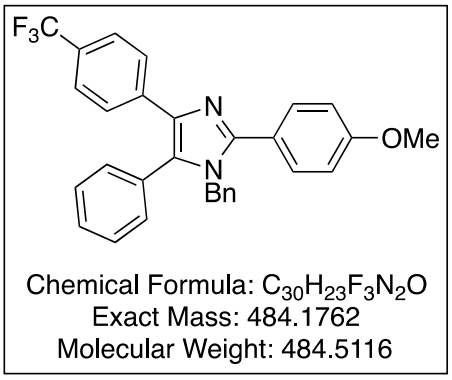
31% yield, white solid, mp 93-94 ºC, Rf = 0.18 (*n*-Hexane : EtOAc = 1 : 4). IR (KBr) 2936, 2360, 1613, 1455, 1323, 1252, 1168, 1122 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.87 (s, 3H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.30-7.33 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.41-7.45 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.81-7.84 (dd, *J* = 6.8 Hz, 1.8 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 34.2, 55.5, 114.1, 124.1 (q, *J* = 272.1 Hz), 123.0, 125.3, 125.6 (q, *J* = 3.8 Hz), 125.7, 126.0, 126.6, 128.1, 128.2, 128.6, 129.5 (q, *J* = 32.3 Hz), 130.2, 130.6, 130.9, 132.0, 132.6, 134.0, 134.3, 139.0, 149.0, 160.3. ^{19}F NMR ($CDCl_3$) δ –59.0. MS (EI) *m/z* 458 (M^+). HRMS (EI); Calcd for $C_{28}H_{21}F_3N_2O$ (M^+); 458.1606, Found; 458.1602.

2-(4-Methoxyphenyl)-*N*-methyl-4-pyridyl-5-(4-trifluoromethylphenyl)imidazole (3f)



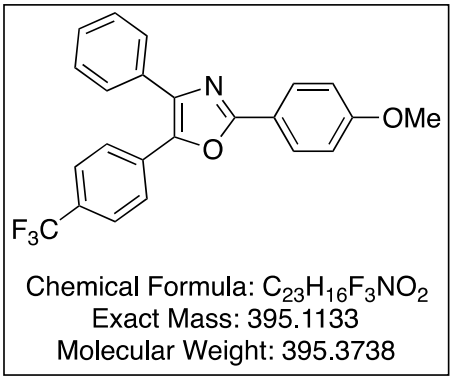
51% yield, yellow solid, mp 178-179 ºC, Rf = 0.10 (*n*-Hexane : EtOAc = 1 : 2), IR (KBr) 2923, 1600, 1332, 1255, 1121, 1072, 830 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 3.87 (s, 3H), 7.03 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 6.3 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 8.42 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.3, 55.4, 114.2, 121.1, 122.2, 123.8 (q, *J* = 271.8 Hz), 126.4 (q, *J* = 3.3 Hz), 130.4, 130.7, 131.4 (q, *J* = 33.0 Hz), 131.6, 134.0, 134.9, 143.3, 148.0, 149.4, 160.5. ^{19}F NMR ($CDCl_3$) δ –59.1. MS (EI) *m/z* 409 (M^+). HRMS(EI); Calcd for $C_{23}H_{18}F_3N_3O$ (M^+); 409.1402, Found; 409.1401.

***N*-Benzyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenylimidazole (6)**



56% yield, colorless solid, mp 134-136 ºC, Rf = 0.18 (*n*-Hexane : EtOAc = 4 : 1), IR (KBr) 2930, 1616, 1577, 12512, 1162, 1120, 1065 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.09 (s, 2H), 6.79-6.82 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H) 7.18-7.23 (m, 5H), 7.32-7.41 (m, 3H) 7. 44 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.66 (d *J* = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 48.2, 55.3, 114.1, 122.9, 124.4 (q, *J* = 271.8 Hz), 125.0 (q, *J* = 4.1 Hz), 125.9, 126.5, 127.4, 127.9 (q, *J* = 32.2 Hz), 128.6, 128.9, 129.0, 130.4, 130.6, 130.9, 131.0, 136.4, 137.3, 138.0, 148.3, 160.2. ^{19}F NMR ($CDCl_3$) δ –58.7. HRMS (EI); *m/z* 484 (M^+). Calcd for $C_{30}H_{23}F_3N_2O$ (M^+); 484.1762, Found; 484.1766.

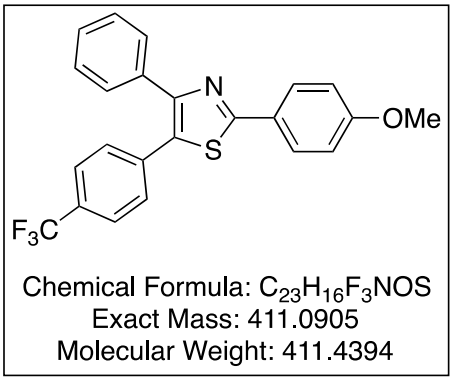
2-(4-Methoxyphenyl)-4-phenyl-5-(4-trifluoromethylphenyl)oxazole (8a)



Chemical Formula: $C_{23}H_{16}F_3NO_2$
Exact Mass: 395.1133
Molecular Weight: 395.3738

52% yield, colorless solid, mp 130-131 ºC, Rf = 0.18 (*n*-Hexane : EtOAc = 1 : 4). IR (KBr) 2360, 1615, 1500, 1326, 1257, 1169, 839 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.00 (d, *J* = 8.9 Hz, 2H), 7.39-7.45 (m, 3H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.67-7.69 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 8.10 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 114.2, 119.6 (Ar), 125.3 (q, *J* = 271.8 Hz), 125.6 (q, *J* = 4.1 Hz), 126.1, 128.3, 128.3, 128.7, 128.8, 129.8 (q, *J* = 32.3 Hz), 132.2, 132.4, 138.4, 143.4, 160.9, 161.6. ^{19}F NMR ($CDCl_3$) δ –63.1. MS (EI) *m/z* 395 (M^+). HRMS (EI); Calcd for $C_{23}H_{16}F_3NO_2$ (M^+); 395.1133, Found; 395.1123.

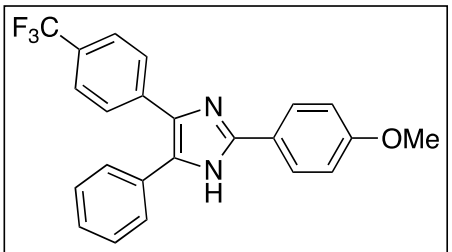
2-(4-methoxyphenyl)-4-phenyl-5-(4-trifluoromethylphenyl)thiazole (8b)



Chemical Formula: $C_{23}H_{16}F_3NOS$
Exact Mass: 411.0905
Molecular Weight: 411.4394

64% yield, yellow solid, mp 105-107 ºC, Rf = 0.63 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1605, 1326, 1257, 1169, 1119, 1070, 826, 699 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.33-7.35 (m, 3H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.55-7.57 (m, 4H), 7.96 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 114.3, 124.0 (q, *J* = 271.8 Hz), 125.7 (q, *J* = 4.1 Hz), 126.3, 128.0, 128.2, 128.5, 129.2, 129.7, 129.8 (q, *J* = 32.2 Hz), 130.1, 134.6, 136.0, 151.7, 161.4, 166.3. ^{19}F NMR ($CDCl_3$) δ –59.0. MS (EI) *m/z* 411 (M^+). HRMS (EI); Calcd for $C_{23}H_{16}F_3NOS$ (M^+); 411.0905, Found; 411.0890.

Debenzylation of *N*-Benzyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenyl-imidazole (6) Leading to 2-(4-Methoxyphenyl)-5-phenyl-4-(4-trifluoromethylphenyl)-1H-imidazole (7) (eq 3)



Chemical Formula: $C_{23}H_{17}F_3N_2O$
Exact Mass: 394.1293
Molecular Weight: 394.3891

To a solution of 1-benzyl-2-(4-methoxyphenyl)-4-(4-trifluoromethylphenyl)-5-phenylimidazole (**6**) (0.15 mmol) in EtOH (1 mL) was added Pd/C (10 mol%). The suspension was stirred overnight at 50 °C under a H_2 atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1) to give 2-(4-methoxyphenyl)-5-phenyl-4-(4-trifluoromethylphenyl)-1*H*-imidazole (**7**) in quantitative yield (59 mg) as yellow solid. mp 187-188 ºC, IR (KBr) 1614, 1469, 1410, 1250, 1163, 1118, 1065, 1021, 849 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.35-7.40 (m, 3H), 7.48 (d, *J* = 7.6 Hz), 7.54 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR δ 55.4, 114.4, 120.7, 124.2 (q, *J* = 271.5 Hz), 125.3 (q, *J* = 3.7 Hz), 127.8, 128.0, 128.3, 128.5, 128.9, 129.3 (q, *J* = 32.8 Hz), 129.8, 130.4, 132.4, 135.7, 146.3, 161.0. ^{19}F NMR ($CDCl_3$) δ –62.8. MS (EI) *m/z* 394 (M^+). HRMS (EI); Calcd for $C_{23}H_{17}F_3N_2O$ (M^+); 394.1293, Found; 394.1292.

The One-Pot Sequential Direct Triarylation of *N*-Methylimidazole (11) (Table 4, entry 3)

DMA (0.5 M) was added to a screw-capped test tube and degassed by freeze−pump−thaw cycle (3 times). To this was added $Pd(OAc)_2$ (5 mol%), tri(2-furyl)phosphine (10 mol%), K_2CO_3 (1 equiv), *N*-methylimidazole (**11**) (1 mmol), and 4-bromobenzotrifluoride (1 equiv). The mixture was stirred for 4 h at 150 °C under an argon atmosphere. The reaction mixture was then cooled to room temperature. To this was added iodobenzene (1 equiv), Cs_2CO_3 (1 equiv), and $[Pd(phen)_2](PF_6)_2$ (5 mol%), and the mixture was stirred for 4 h at 150 °C under an argon atmosphere. Subsequently, 4-iodoanisole (3 equiv), Cs_2CO_3 (3 equiv), and $[Pd(phen)_2](PF_6)_2$ (15 mol%) were split into 6 portions, respectively, and added portionwise to the reaction mixture every 0.5 h at 150 °C. The resulting mixture was stirred at that temperature for

20 h under an argon atmosphere. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 10 : 1) to give *N*-methyl-4-(4-methoxyphenyl)-2-phenyl-5-(4-trifluoromethylphenyl)-imidazole (**3b**) in 37% yield (151 mg).

References and notes

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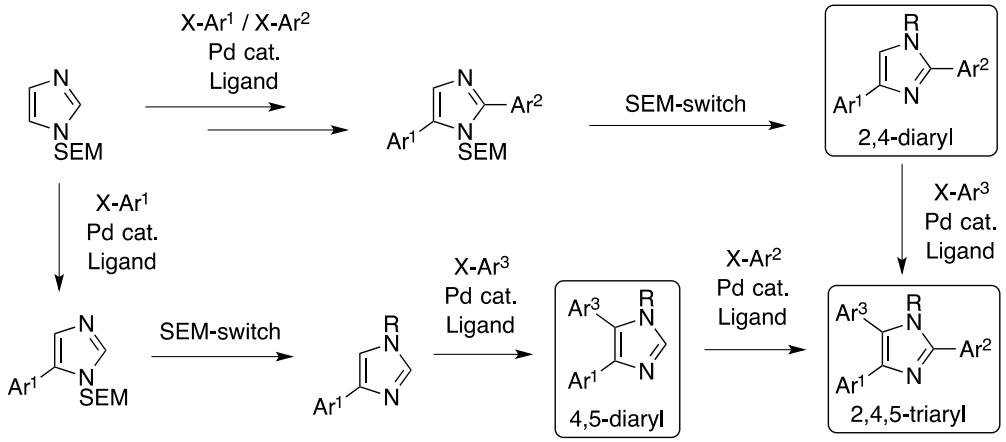
Chapter 3

Facile Synthetic Method for Diverse Polyfunctionalized Imidazoles by Means of Pd-Catalyzed C−H Bond Arylation of *N*- Methyl-4,5-dibromoimidazole

C−H bond-selective arylation reaction of 4,5-dibromoimidazole with aryl iodides catalyzed by the palladium-1,10-phenanthroline complex $[Pd(phen)_2](PF_6)_2$ has been developed. The process tolerates the presence of a variety of functional groups on the aryl halide substrates. The products formed in these reactions were transformed to a variety of polyfunctionalized imidazoles by taking advantage of selective reactions of remaining C−Br bonds.

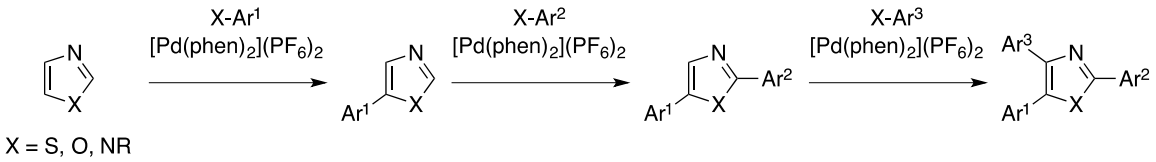
3.1. Introduction

Transition metal-catalyzed direct C–H functionalization reactions of imidazoles display a position dependent reactivity order of C2 ≈ C5 >> C4,[1g,3] and a C2 vs. C5 reactivity order that depends on the catalytic system used.[4] In addition, only few direct C4–H functionalization reactions of azoles, and in particular imidazoles, have been described owing to the low reactivity at this site.[1,2] Thus, 5-unsubstituted 2,4-substituted imidazoles and 2-unsubstituted 4,5-substituted imidazoles as well as 2,4,5-trisubstituted imidazoles are not readily prepared using direct C–H functionalization reactions of unsubstituted imidazoles. To circumvent the C4 reactivity issue, Sames and co-workers have devised a SEM-switch strategy that employ an indirect methods for introduction of a C4 aryl group in imidazole (Scheme 1).[3] This strategy allowed producing a variety of arylimidazoles such as 2,4-diaryl-, 4,5-diaryl- and 2,4,5-triarylimidazole. However, this protocol requires SEM protection and deprotection of nitrogen to achieve formal C4 arylation.



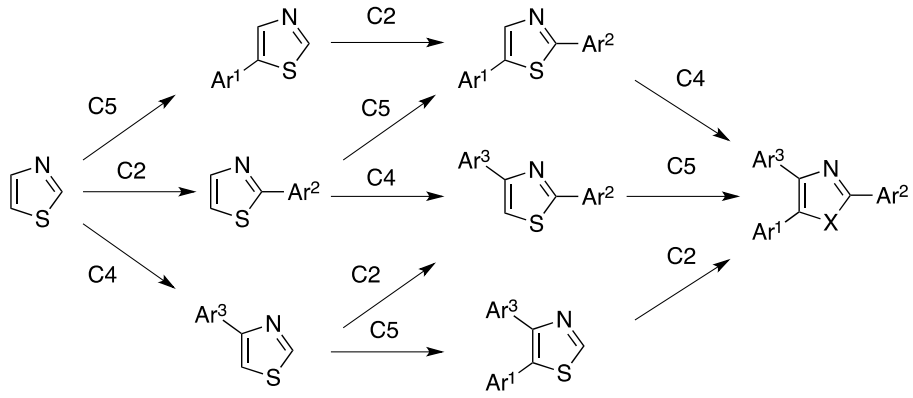
Scheme 1. SEM-switch strategy

In 2011, sequential tryarylation of simple azoles including imidazole by using $[Pd(phen)_2](PF_6)_2$ as a catalyst was reported (Scheme 2).[7b] Although, azoles were coupled with aryl halides in the order of C5, C2, then C4 to afford triarylazoles, this pathway could not lead to 2,4-diaryl- and 4,5-diaryl azoles.



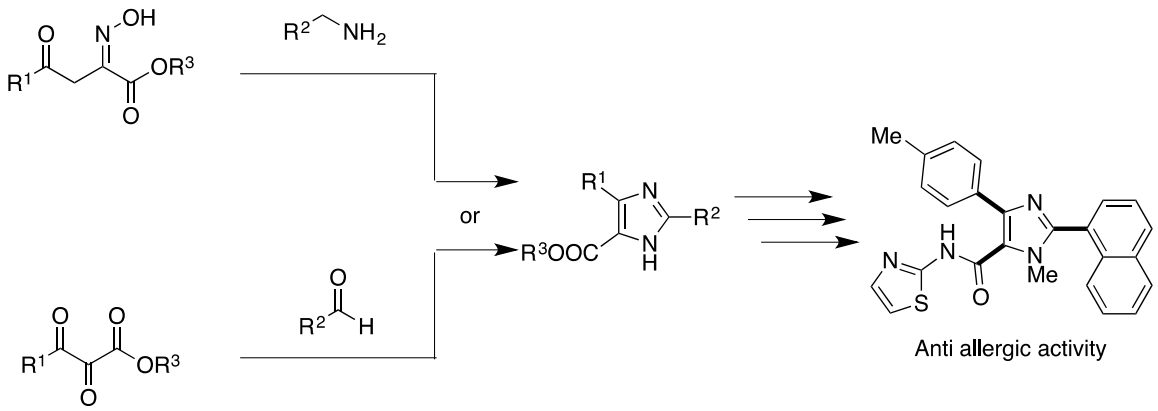
Scheme 2. Sequential arylation of simple azoles

In 2013, Itami and co-workers developed rare C4-selective oxidative direct arylation of thiazoles with boronic acids, and they have realized programmed synthesis of all patterns of mono-, di-, triarylated thiazoles by combination of their methods and previously reported direct C-H arylation reactions (Scheme 3).[8] However, the C4-selective arylation reaction did not take place with other azoles, in particular imidazole.



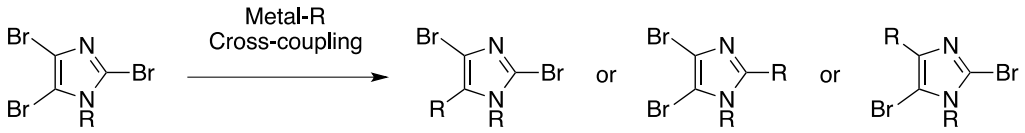
Scheme 3. Programmed synthesis of arylthiazoles

However, those strategies were limited to synthesis of arylazole, thus conventional condensation strategies are often still used for azoles bearing other substituents. For example, condensation reactions of imino esters and amines and carbonyl compounds and aldehydes are usually used for construction the imidazole which shows anti-allergic activity (Scheme 4). However, the synthesis of both imino esters and carbonyl compounds require long steps from commercially available compounds.



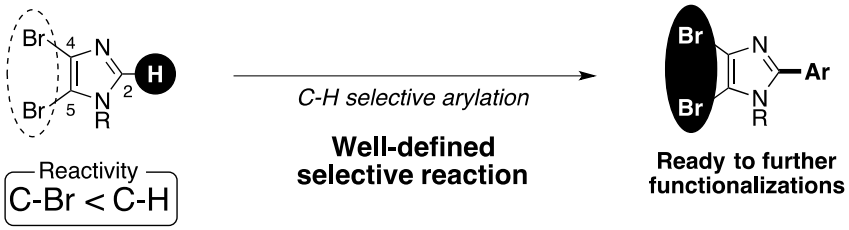
Scheme 4. Synthesis of highly substituted imidazoles

Some conventional cross-coupling reactions of multi-halogenated imidazoles have been employed to prepare polyfunctionalized derivatives, but site-selectivities associated with these processes are low (Scheme 5).[5] Thus, further investigation for developing methods to construct highly substituted imidazoles are still needed.



Scheme 5. Cross-coupling reaction of multi-halogenated imidazoles

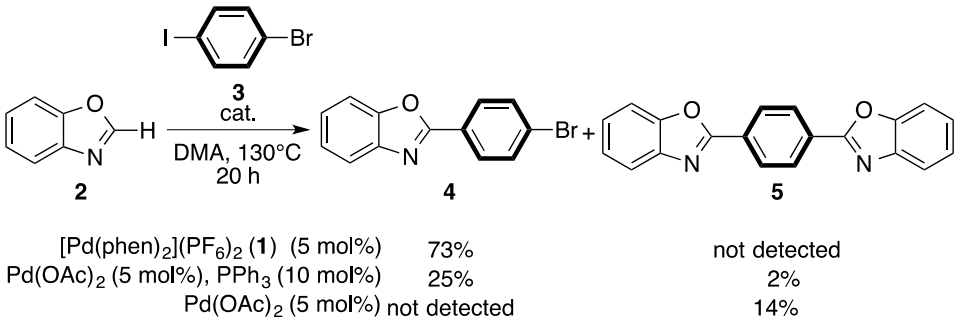
The author envisioned that if conditions could be devised to enable selective C–H bond arylation reactions of readily available azoles, which possess both C–H and C–Br bonds, a novel and concise method for preparation of polyfunctionalized imidazoles would become available (Scheme 6). Unfortunately, conventional catalytic systems used for direct C–H bond arylation reactions typically display low activities for C–H bond cleavage but high activities for oxidative addition of aryl halides,[6] and these catalysts therefore cannot promote the C–H selective reactions.



Scheme 6. New synthetic approach to polyfunctionalized imidazoles

On the other hand, an important characteristic of Pd–phenanthroline complexes are that they display relatively low activity in promoting reactions of aryl halides in contrast to C–H bond cleavage reactions. By considering this feature, the author envisaged that C–H bond selective arylation reactions of halogenated imidazoles might be possible if highly reactive aryl iodides are used as coupling partners. Importantly, in this case

halogen atoms in the azoles would serve as protecting groups for otherwise reactive C–H bonds as well. In fact, the results of a preliminary investigation showed that C–I bond selective reaction takes place between benzoxazole **2** and bromoiodobenzene **3** when **1** is utilized as the catalyst (Scheme 7). This result prompted a general investigation of C–H bond selective arylation reactions of brominated imidazoles. Below, the author describes the results of this study, which have led to the development of a novel and concise synthetic method for the preparation of polyfunctional imidazoles, which employs C–H bond selective arylation reactions of 1-methyl-4,5-dibromoimidazole promoted by Pd–1,10-phenathroline complexes as a key step.



Scheme 7. Preliminary result of C-I bond selective, direct C-H bond arylation reaction

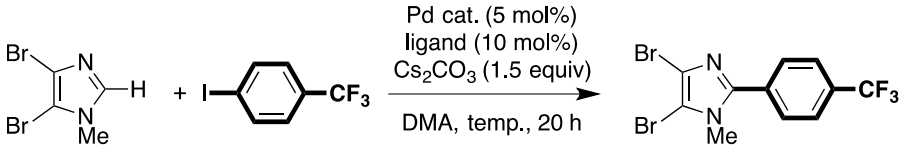
3.2. Results and Discussions

3.2.1. Investigations of Direct Arylation of a 4,5-Dibromoimidazole

In the initial phase of the studies, reaction of 1-methyl-4,5-dibromoimidazole (**6**) and 1-iodo-4-α,α,α-trifluoromethyltoluene (**7a**) was explored using several different

palladium complexes as catalysts (Table 1).[7,9] Reaction using $Pd(OAc)_2$ was found to give a complex product mixture from which the coupling product **8a** is isolated in only 37% yield (entry 1). The addition of PPh_3 or its analogues substituted electron-withdrawing and -donating groups to the $Pd(OAc)_2$ containing reaction mixture does not improve the yield of the process (entries 2-4). Moreover, **8a** was not generated when the bidentate phosphine ligand dppb was employed (entry 5), and the addition of *t*-Bu_3P does not cause an enhancement in the efficiency of the reaction (entry 6). An attempt to suppress side processes by carrying out reaction of **6** with **7a** in the presence of $Pd(OAc)_2$ and PPh_3 at lower temperature (130 °C) was not successful (entry 7). In contrast, addition of 2,2'-bipyridyl or 1,10-phenanthroline as a ligand dramatically suppressed the side processes, and only **8a** and substrates **6** and **7a** were recovered with high mass balance after the reaction, particularly with 1,10-phenanthroline as a ligand, though the product yield did not improve (entries 8 and 9). These results obviously indicated that the use of nitrogen-based ligands is critical for selective reaction with brominated substrates. Catalytic activity increased by adding $NaPF_6$ as an additive (entry 10). In addition, as anticipated, coupling reaction of **6** and **7a** takes place with high efficiency to form the C2-arylated product **8a** when preformed $[Pd(phen)_2](PF_6)_2$ (**1**) is utilized as the catalyst (entry 11). Studies on the effect of temperature (entries 11-14) showed that the reaction at 130 °C leads to an optimal yield of **8a** (85%, entry 12). Further lowering of the reaction temperature greatly affects the conversion of **6**, and the yields of **8a** drop at 110 and 90 °C (entries 13 and 14).

Table 1. Optimization of conditions for reaction of **6** with **7a**



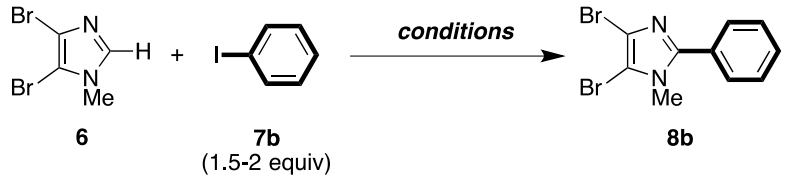
6 **7a** (1.5 equiv) **8a**

entry	Pd cat.	ligand	temp. (°C)	yield(%)[a]
1	$Pd(OAc)_2$	–	150	37
2	$Pd(OAc)_2$	PPh_3	150	38
3	$Pd(OAc)_2$	$P(4\text{-}CF_3C_6H_4)_3$	150	18
4	$Pd(OAc)_2$	$P(4\text{-}MeOC_6H_4)_3$	150	14
5	$Pd(OAc)_2$	dppb	150	ND
6	$Pd(OAc)_2$	tBu$_3$P·HBPh$_4$	150	36
7	$Pd(OAc)_2$	PPh_3	130	17
8	$Pd(OAc)_2$	2,2'-bipyridyl	150	36[c]
9	$Pd(OAc)_2$	phen	150	45[c]
10	$Pd(OAc)_2$	phen[b]	150	67[c]
11	**1**	–	150	73
12	**1**	–	130	85
13	**1**	–	110	37
14	**1**	–	90	20

[a] Isolated yields. [b] $NaPF_6$ (10 mol%) was added. [c] The yields were determined by using ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

In previous investigations, several C2-selective arylations of *N*-protected imidazoles were observed to occur when additives CuI,[3d] and $Ni(OAc)_2$,[3b] were employed. In a study exploring the potential utility of these catalysts, the author observed that C2-selective reaction of **6** with phenyl iodide (**7b**) to form **8b** does not take place, and in each case, a complex product mixture is produced (Scheme 8, conditions A-C). Also,

the yield of the desired product was low when the previously reported catalytic system for 1-methyl-4,5-dichloroimidazole is employed to promote C-H selective reaction (conditions D).[10] Again, the reaction proceeds smoothly with catalyst **1** to give **8b** in almost quantitative yield (conditions E).



6 **7b** (1.5-2 equiv) **8b**

conditions A	**conditions B**	**conditions C**
$Pd(OAc)_2$ (5 mol%)	**CuI** (10 mol%)	**$Ni(OAc)_2$** (10 mol%)
CuI (2 equiv)	**1,10-Phenathroline** (10 mol%)	**bpy** (10 mol%)
DMF	LiO*t*-Bu (1.5 equiv)	LiO*t*-Bu (1.5 equiv)
140 °C, 48 h	DMF, 85 °C, 18 h	1,4-dioxane
Not detected	**Not detected**	85 °C, 36 h
(Complex mixture)	**(49% Conversion)**	**No Reaction**

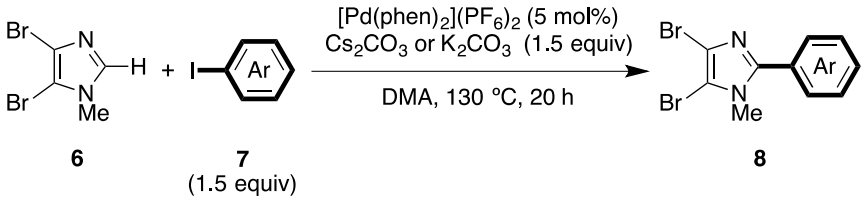
conditions D	**conditions E**
$Pd(OAc)_2$ (2 mol%), **PCy_3** (4 mol%)	**1** (5 mol%)
PivOH (30 mol%), K_2CO_3 (1.5 equiv)	Cs_2CO_3 (1.5 equiv)
DMA, 100 °C, 20 h	DMA
34%	150 °C, 20 h
(100% Conversion)	**99%**

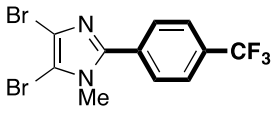
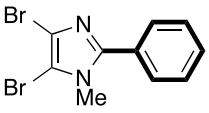
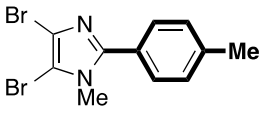
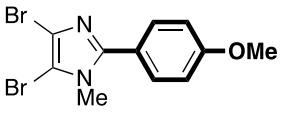
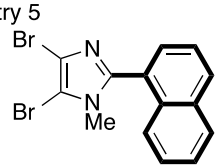
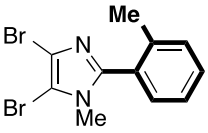
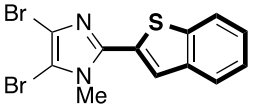
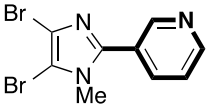
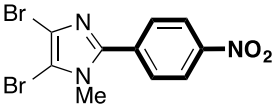
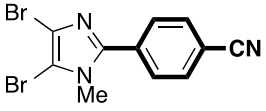
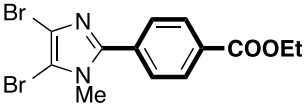
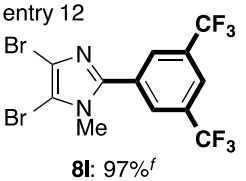
Scheme 8. Reactions under conventional C2-selective arylation conditions

3.2.2. Scope of Substrates

Based on the findings described above, the aryl iodide scope of the coupling reaction was investigated next. The results tabulated in Table 1 and represented in Scheme 7 show that the reaction of **6** with aryl iodides **7a** and **7b**, promoted by **1**, give the corresponding arylated imidazoles **8a** and **8b** in high yields (Table 2, entries 1 and 2). Relatively electron-rich aryl iodides, which are generally less reactive in oxidative addition processes, also react with **6** under these conditions to form the corresponding products **8c** and **8d** in high yields (entries 3 and 4). Steric hindrance in the aryl halides has little effect on the efficiencies of this process as exemplified by reactions with 1-naphthyl iodide **7e** and *o*-tolyl iodide **7f**, which generate the corresponding coupling products **8e** and **8f** in respective yields of 90% and 61%. It should be noted that the use of $Pd(phen)(OAc)_2$ instead of **1** as a catalyst gives higher yields for coupling reactions of these substrates. Reaction of imidazole **6** with 5-membered heteroaromatic iodide **7g** takes place to form arylation product **8g** in low yield (entry 7) but, in contrast, the 6-membered heteroaromatic iodide **7h** couples with **6** with high efficiency (entry 8). In addition, reactions of **6** with aryl iodides **7i-k**, containing strongly electron withdrawing groups such as nitro, cyano, and ethoxycarbonyl, form the corresponding adducts **8i-k** in moderate to good yields (entries 9-11). Notably, selective cleavage of the C–Br bond in the highly electron deficient 3,5-bis(trifluoromethylphenyl)bromide (**9l**) takes place in reaction with **6** while the C–Br bonds in the imidazole remain undisturbed (entry 12).

Table 2. Scope of reaction of **6** with aryl iodides **7**

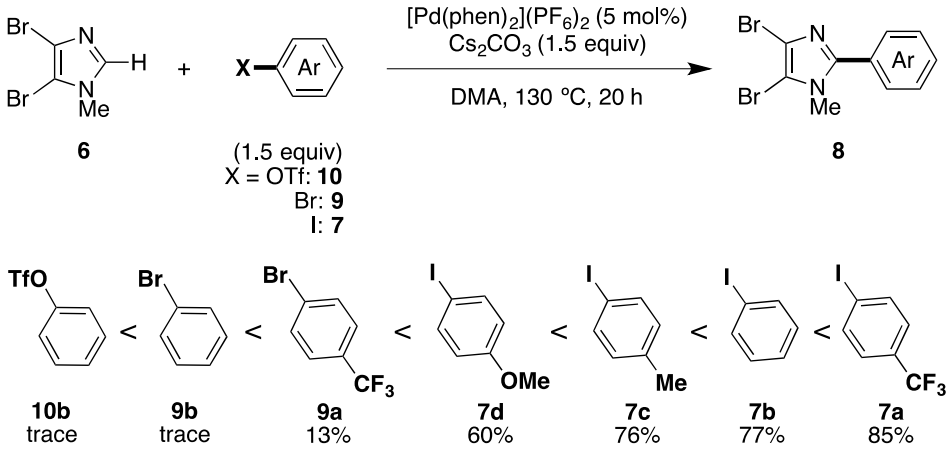


entry 1  **8a**: 85%[a]	entry 2  **8b**: 99%[a,c]	entry 3  **8c**: 76%[a]
entry 4  **8d**: 68%[a,c]	entry 5  **8e**: 90%[a,d]	entry 6  **8f**: 61%[a,d]
entry 7  **8g**: 36%[a,e]	entry 8  **8h**: 74%[b]	entry 9  **8i**: 45%[b]
entry 10  **8j**: 79%[b]	entry 11  **8k**: 70%[b]	entry 12  **8l**: 97%[f]

[a] Cs_2CO_3 was used. [b] K_2CO_3 was used. [c] Reaction was performed at 150 ºC. [d] $Pd(phen)(OAc)_2$ was used as a catalyst. [e] The yields were determined by ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [f] Aryl bromide was used instead of iodide.

The efficiencies and selectivities of the C–H arylation reactions of **6** are governed by the high reactivity of aryl halides in transition-metal catalyzed oxidative addition processes (Scheme 9).[11] In fact, reactions using less reactive aryl halides such as

phenyl triflate (**10b**) and phenyl bromide (**9b**) are observed to result in formation of complex mixtures that contain only trace amounts of coupling products **8**. In these cases, unidentified insoluble materials, which probably contain oligomerized imidazole, are formed in significant amounts. Although arylated imidazole products are generated in reactions using the more reactive aryl bromides such as bromo-*α,α,α*-trifluorotoluene (**9a**), the yields are low. In contrast, highly selective incorporation of aryl groups is achieved using aryl iodides as substrates.

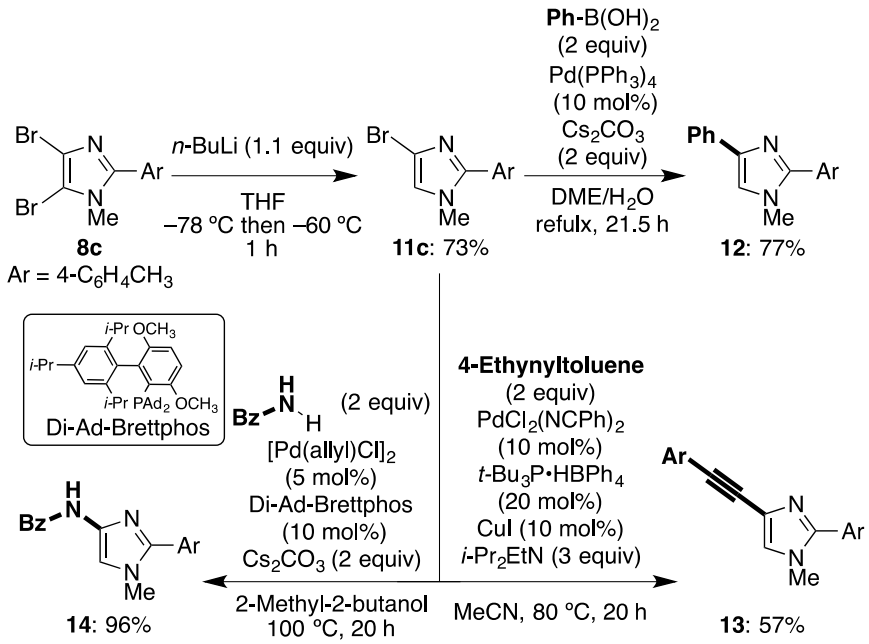


Scheme 9. Reactivity order of aryl halides and an aryl triflate

3.2.3. Synthetic Applications of the Selective Arylation Reaction

In this effort, the author also investigated synthetic applications of the C2-arylated imidazoles **8**. For example, 2,4-disubstituted imidazoles **12-14**, which are difficult to prepare from unsubstituted imidazoles by using conventional methods, are produced by utilizing straightforward pathways (Scheme 10). Treatment of dibromoimidazole **8c**

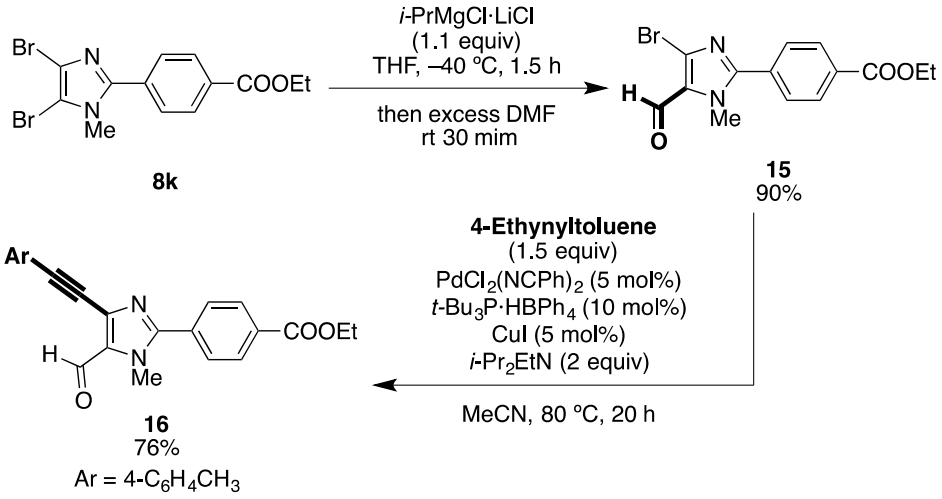
with an equivalent of *n*-butyllithium at –78 °C followed by aqueous quenching gave rise selectively to the debrominated imidazole **11c** in high yield.[12] The remaining C4-bromo group in **11c** can be used to introduce aryl or acetylenic groups by employing conventional cross-coupling reactions. For example, Suzuki-Miyaura coupling of **11c** with phenylboronic acid efficiently generates the 2,4-diarylated *N*-methylimidazole **12**.[13] Application of a Sonogashira coupling enabled generation of 4-alkynyl-2-arylimidazole **13** in high yield.[14] Furthermore, cross-coupling reaction of **11c** with benzamide under conditions described by Buchwald produces the C4-amidated imidazole **14** in 96% yield.[15]



Scheme 10. Synthesis of 2,4-substituted imidazoles

The C5-selective debromination protocol can be applied to other 2-aryl-3,4-dibromoimidazoles, as exemplified by the debromination of the

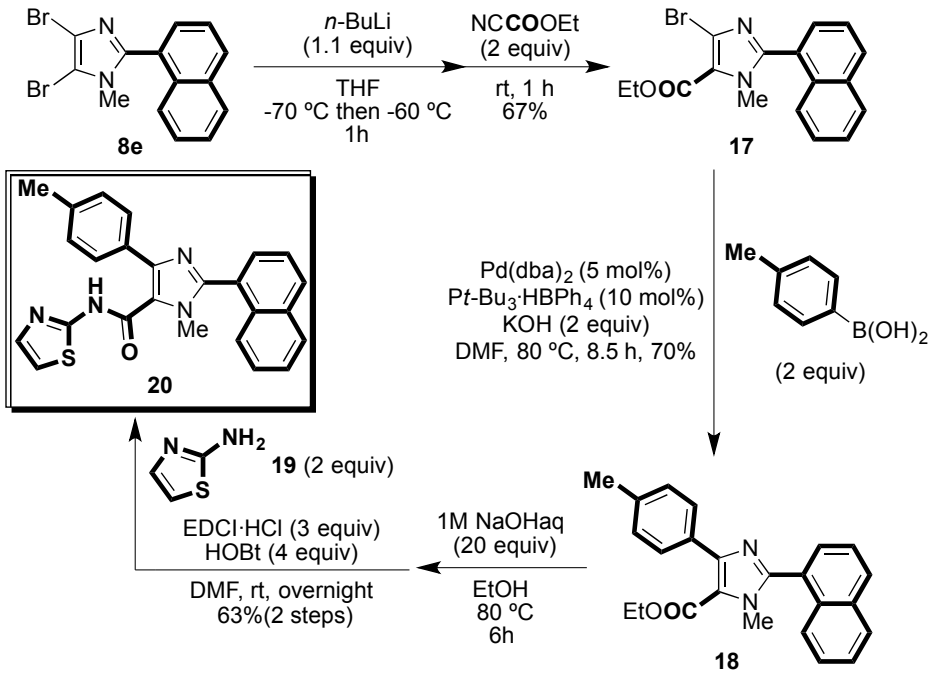
alkoxycarbonylated derivative **8k** under Knochel's conditions with *i*PrMgCl·LiCl,[16] which is more tolerant of ester moieties than is butyllithium. Addition of DMF to the crude reduction mixture formed in this manner gives rise to formyl-imidazole **15** in excellent yield (Scheme 10). These observations show that alkynyl and carbonyl groups, particularly a formyl group, which are typically sensitive to a variety of reagents, can be introduced at late stages of synthetic pathways using the new protocol. In fact, the formyl-imidazole derivative **15** can be coupled with a terminal alkyne by using Sonogashira conditions in last step to produce the highly substituted imidazole **16** (Scheme 6).



Scheme 11. Functionalization of dibromoimidazole bearing alkoxycarbonyl group

To demonstrate the power of the new method developed in the studies described above, the author employed it in the synthesis of the highly substituted imidazole **20**, which has been shown to possess antiallergic properties (Scheme 12).[22] In previous

efforts, **20** was synthesized by using conventional condensation strategies that are difficult to apply to the preparation of derivatives. In the strategy the author devised, the naphthyl group in the target is introduced in the first step through C–H arylation of 1-methyl-4,5-dibromoimidazole that provides **8e** (Table 2, entry 5). Selective C5 lithiation of **8e** followed by ethoxycarbonylation with ethyl cyanoformate efficiently generates ester **17**. The remaining bromo group in **17** is then used to direct Suzuki-Miyaura coupling with *p*-tolylboronic acid to give **18**, which is then transformed to **20** by hydrolysis followed by condensation with 2-aminothiazole (**19**).



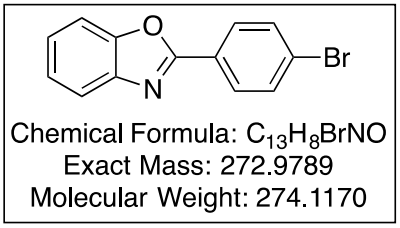
Scheme 12. Synthesis of **20**

3.3. Conclusion

In conclusion, a method for direct C-H selective arylation of a dibromoimidazole with aryl iodides, using Pd–1,10-phenathroline catalysts, was developed in the investigation described above. The catalyst used for this process finely discriminates C–Br bonds of the imidazole from bonds of the arylating agents and consequently promotes reactions that chemo- and regio-selectively form 2-aryl-4,5-dibromoimadazole products in high efficiencies. By employing this process, diversely functionalized azoles can be readily produced, making 4,5-dibromoimidazoles versatile precursors in the preparation of highly functionalized imidazoles.

3.4. Experimental

Reaction of benzoxazole (2) and 4-bromoiodobenzene[20] (3)



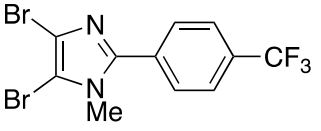
Chemical Formula: $C_{13}H_8BrNO$
Exact Mass: 272.9789
Molecular Weight: 274.1170

$[Pd(phen)_2](PF_6)_2$ (**1**) (5 mol%, 19 mg), Cs_2CO_3 (1.5 equiv, 245 mg), benzoxazole (**2**) (0.5 mmol, 60 mg), 4-bromoiodobenzene (**3**) (1.5 equiv, 212 mg), and DMA (1 mL) were added to a screw-capped test tube. The reaction mixture was stirred for 20 h at 130 °C under argon atmosphere. After the reaction completed, the mixture was cooled to room temperature. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (n-Hexane : EtOAc = 10 : 1, Rf = 0.63) to give 2-(4-bromophenyl)benzoxazole (**4**) in 56% yield (38 mg) as a colorless solid: 1H NMR ($CDCl_3$) δ 7.34-7.38 (m, 2H), 7.55-7.60 (m, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.74−7.79 (m, 1H), 8.12 (d, J = 8.8 Hz, 2H).

General Procedure for the C−H-Selective Arylation of 4,5-Dibromoimidazole

$[Pd(phen)_2](PF_6)_2$ (**1**) (5 mol%, 10 mg), Cs_2CO_3 (1.5 equiv, 122 mg) or K_2CO_3 (1.5 equiv, 52 mg), 4,5-dibromo-1-methylimdazole (**6**) (0.25 mmol, 60 mg), aryl iodides **7** (1.5 equiv), and DMA (0.5 mL) were added to a screw-capped test tube. The reaction mixture was stirred for 20 h at 130−150 °C under an argon atmosphere. After the reaction completed, the mixture was cooled to room temperature. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give 2-arylated 4,5-dibromoimidazole **8**.

4,5-Dibromo-1-methyl-2-(4-trifluoromethylphenyl)imidazole (8a)

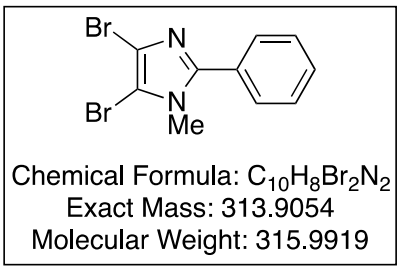


Chemical Formula: $C_{11}H_7Br_2F_3N_2$
Exact Mass: 381.8928
Molecular Weight: 383.9899

85% yield (82 mg), colorless solid, mp 97.0-97.6 ºC. Rf = 0.33 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1619, 1494, 1449, 1409, 1330, 1167, 1124, 1092, 1014, 971, 848 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.74 (s, 3H), 7.73 (br, 4H). ^{13}C NMR ($CDCl_3$) δ 34.8, 106.9, 117.4, 123.8 (q, J = 272.5 Hz), 125.8 (q, J = 3.8 Hz), 128.0, 131.5 (q, J = 32.9 Hz), 132.9, 147.0. ^{19}F NMR ($CDCl_3$) δ –50.5. MS (EI) *m/z*:

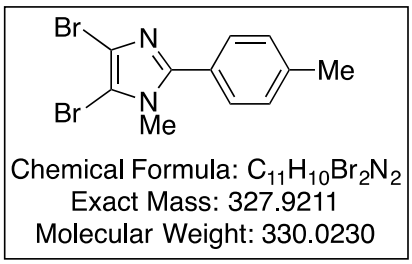
386 (45, M^++4), 384 (100, M^++2), 382 (49, M^+). HRMS (EI): Exact mass calcd for $C_{11}H_7{}^{79}Br_2F_3N_2$ (M^+); 381.8928, Found: 381.8932.

4,5-Dibromo-1-methyl-2-phenylimdazole[21] (**8b**)



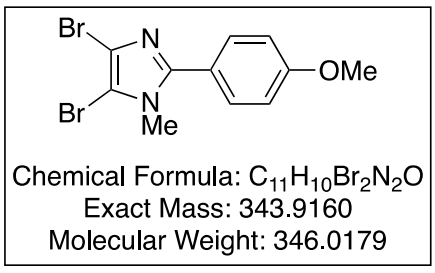
99% yield (78 mg), colorless solid. Rf = 0.29 (*n*-Hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 7.43-7.48 (m, 3H), 7.54-7.57 (m, 2H).

4,5-Dibromo-1-methyl-2-(4-methylphenyl)imidazole (**8c**)



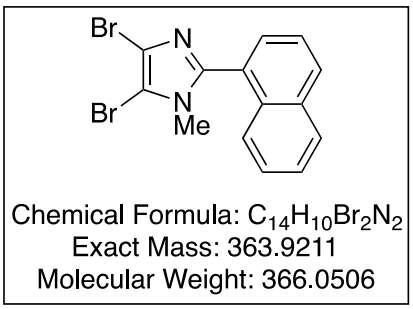
76% yield (63 mg), colorless solid, mp 99.5-100.0 ºC, Rf = 0.28 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1496, 1455, 1377, 1236, 1096, 968, 822, 721, 496 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.67 (s, 3H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.5, 34.7, 105.3, 116.7, 126.8, 128.7, 129.5, 139.8, 148.8. MS (EI) *m/z*: 332 (59, M^+ + 4), 330 (100, M^+ + 2), 328 (69, M^+). HRMS (EI): Exact mass calcd for $C_{11}H_{10}{}^{79}Br_2N_2$; 327.9211, Found: 327.9217.

4,5-Dibromo-1-methyl-2-(4-methoxyphenyl)imidazole (**8d**)



66% yield (57 mg), colorless solid, mp 126.4-129.6 ºC. Rf = 0.15 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1608, 1495, 1464, 1437, 1372, 1252, 1175, 1020, 968, 831 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 3.83 (s, 3H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 34.7, 55.5, 105.1, 114.2, 116.4, 122.0, 130.2, 148.6, 160.6. MS (EI) *m/z*: 348 (27, M^+ + 4), 346 (55, M^+ +2), 344 (27, M^+). HRMS (EI): Exact mass calcd for $C_{11}H_{10}{}^{79}Br_2N_2O$ (M^+); 343.9160, Found: 343.9161.

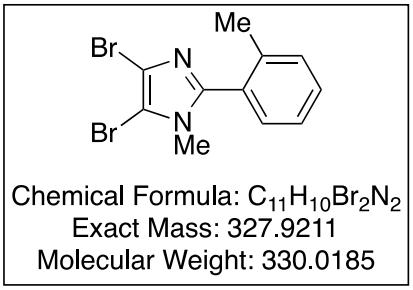
4,5-Dibromo-1-methyl-2-(1-naphtyl)imidazole (8e)



Chemical Formula: $C_{14}H_{10}Br_2N_2$
Exact Mass: 363.9211
Molecular Weight: 366.0506

90% yield (82 mg), colorless solid, mp 119.3-120.6 ºC, Rf = 0.25 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1502, 1453, 1369, 1235, 1095, 987, 956, 797, 775 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.43 (s, 3H), 7.50-7.55 (m, 4H, Ar), 7.64-7.67 (m, 1H), 7.89-7.93 (m, 1H), 7.95-7.99 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 34.2 (NMe), 105.0, 116.7, 125.1 (2C), 126.6, 127.1, 127.4, 128.6, 129.1, 130.6, 132.1, 133.6, 147.5 (Ar). MS (EI) *m/z*: 368 (54, $M^+ + 4$), 336 (100, $M^+ + 2$), 364 (49, M^+). HRMS (EI): Exact mass calcd for $C_{14}H_{10}{}^{79}Br_2N_2$ (M^+); 363.9211, Found: 363.9216.

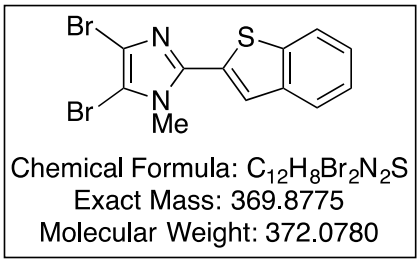
4,5-Dibromo-1-methyl-2-(2-methylphenyl)imidazole (8f)



Chemical Formula: $C_{11}H_{10}Br_2N_2$
Exact Mass: 327.9211
Molecular Weight: 330.0185

61% yield (50 mg), yellow solid, mp 82.9-86.2 ºC, Rf = 0.23 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 2923, 1493, 1442, 1378, 1221, 1086, 969, 775, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H), 3.43 (s, 3H), 7.25-7.30 (m, 3H), 7.34-7.38 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 19.8, 33.7, 104.3, 116.3, 125.9, 129.3, 130.1, 130.5, 130.6, 138.3, 148.2. MS (EI) *m/z*: 332 (36, $M^+ + 4$), 330 (72, $M^+ + 2$), 328 (40, M^+). HRMS (EI): Exact mass calcd for $C_{11}H_{10}{}^{79}Br_2N_2$ (M^+); 327.9211, Found: 327.9215.

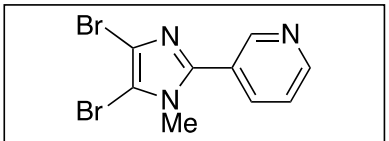
2-(2-Benzothienyl)-4,5-dibromo-2-methylimidazole (8g)



Chemical Formula: $C_{12}H_8Br_2N_2S$
Exact Mass: 369.8775
Molecular Weight: 372.0780

36% yield (33 mg), yellow solid, mp 158.7-163.5 ºC, Rf = 0.50 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1486, 1443, 938, 741, 723 cm^{-1}, ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.37-7.40 (m, 2H), 7.56 (s, 1H), 7.80-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 34.9, 106.9, 117.5, 122.3, 123.4, 124.3, 125.0, 125.6, 131.6, 139.5, 140.0, 142.8. MS (EI) *m/z*: 374 (42, $M^+ + 4$), 372 (88, $M^+ + 2$), 370 (42, M^+). HRMS (EI): Exact mass calcd for $C_{12}H_8{}^{79}Br_2N_2S$; 369.8775, Found: 369.8773.

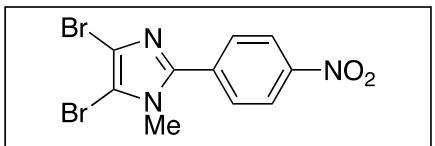
4,5-Dibromo-1-methyl-2-(3-pyridyl)imidazole (8h)



Chemical Formula: $C_9H_7Br_2N_3$
Exact Mass: 314.9007
Molecular Weight: 316.9840

74% yield (59 mg), brown oil, Rf = 0.04 (*n*-Hexane : EtOAc = 1 : 1). IR (KBr) 1570, 1487, 1413, 1374, 1228, 1092, 1020, 971, 813, 711 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 7.41-7.44 (m, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.68 (m, 1H), 8.83 (s, 1H). ^{13}C ($CDCl_3$) δ 34.8, 106.9, 117.6, 123.8, 126.1, 136.4, 145.5, 148.9, 150.3. MS (EI) *m/z*: 319 (57, $M^+ + 4$), 317 (100, $M^+ + 2$), 315 (50, M^+). HRMS (EI): Exact mass calcd for $C_9H_7{}^{79}Br_2N_3$; 314.9007, Found: 314.9005.

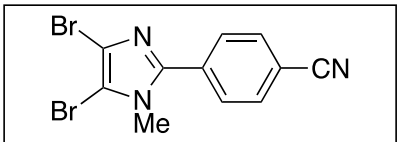
4,5-Dibromo-1-methyl-2-(4-nitrophenyl)imidazole (8i)



Chemical Formula: $C_{10}H_7Br_2N_3O_2$
Exact Mass: 358.8905
Molecular Weight: 360.9895

45% yield (41 mg), yellow solid, mp 177.2-178.4 ºC, Rf = 0.43 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1594, 1521, 1483, 1347, 970, 856, 708 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 7.81 (d, *J* = 8.8 Hz, 2H). 8.33 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 35.1, 107.9, 118.0, 124.1, 129.3, 135.4, 146.1, 148.1. MS (EI) *m/z*: 363 (53, $M^+ + 4$), 361 (100, $M^+ + 2$), 359 (46, M^+). HRMS (EI): Exact mass calcd for $C_{10}H_7{}^{79}Br_2N_3O_2$ (M^+); 358.8905, Found: 358.8900.

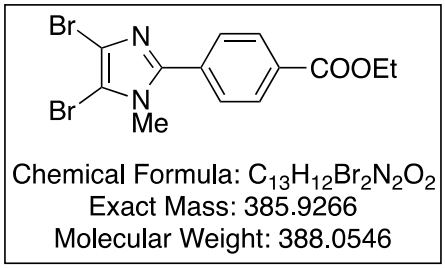
4,5-Dibromo-2-(4-cyanophenyl)-1-methylimidazole (8j)



Chemical Formula: $C_{11}H_7Br_2N_3$
Exact Mass: 338.9007
Molecular Weight: 341.0014

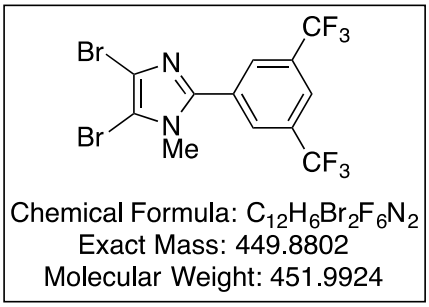
79% yield (67 mg), colorless solid, mp 190.3-192.6 ºC, Rf = 0.10 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 2224, 1604, 1487, 1448, 969, 843 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 35.0, 107.6, 113.2, 117.7, 118.3, 129.1, 132.6, 133.6, 146.4. MS (EI) *m/z*: 343 (44, $M^+ + 4$), 341 (86, $M^+ + 2$), 339 (50, M^+). HRMS (EI): Exact mass calcd for $C_{11}H_7{}^{79}Br_2N_3$ (M^+); 338.9007, Found: 338.9010.

4,5-Dibromo-2-(4-ethoxycarbonylphenyl)-1-methylimidazole (8k)



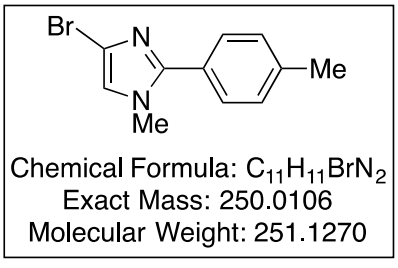
70% yield (68 mg), colorless solid, mp 128.2-129.6 ºC, Rf = 0.15 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 2923, 1713, 1281, 1110, 775, 714 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.73 (s, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 8.12 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.4 ($CH_2\underline{C}H_3$), 34.9, 61.4, 106.8, 117.4, 128.5, 130.0, 131.3, 133.5, 147.5, 166.0. MS (EI) *m/z*: 390 (57, $M^+ + 4$), 388 (100, $M^+ + 2$), 386 (47, M^+). HRMS (EI): Exact mass calcd for $C_{13}H_{12}{}^{79}Br_2N_2O_2$ (M^+); 385.9266, Found: 385.9268.

2-(3,5-Bistrifluoromethylphenyl)-4,5-dibromo-1-methylimidazole (8l)



97% yield (109 mg), colorless solid, mp 96.9-97.1 ºC, Rf = 0.25 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1482, 1354, 1277, 1183, 1134, 902 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 7.97 (s, 1H), 8.10 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 34.9, 107.8, 117.9, 123.0 (q, *J* = 273.4 Hz), 123.1 (q, *J* = 3.8 Hz), 128.6, 131.6, 132.5 (q, *J* = 33.8 Hz), 145.4. ^{19}F NMR ($CDCl_3$) δ –62.9. MS (EI) *m/z*: 454 (45, $M^+ + 4$), 452 (100, $M^+ + 2$), 450 (49, M^+). HRMS (EI): Exact mass calcd for $C_{12}H_6{}^{79}Br_2F_6N_2$; 449.8802, Found: 449.8801.

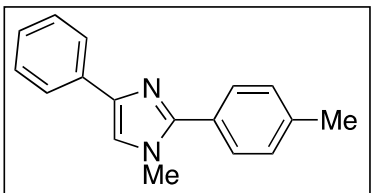
4-Bromoimidazole-1-methyl-2-(4-methylphenyl)imidazole (11c)



A solution of *n*-BuLi in *n*-hexane (1.5 M, 1.1 equiv) was added dropwise to a solution of 4,5-dibromo-1-methyl-2-(4-methylphenyl)imidazole (**8c**) (0.25 mmol, 83 mg) in anhydrous THF (1 mL) under an argon atmosphere at −78 °C. The mixture was stirred at −60 °C for 1 h. The reaction solution was quenched with cold H_2O then was warmed to room temperature and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.54) to give 4-bromo-1-methyl-2-(4-methyl-phenyl)imidazole

(**11c**) in 73% yield (46 mg) as a colorless solid. mp 96.3−98.0 °C. IR (KBr) 3110, 1505, 1461, 1447, 1390, 1250, 951, 770, 695 cm^{-1}. 1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.69 (s, 3H), 6.90 (s, 1H),7.24(d, *J* = 8.1Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.4, 34.7, 114.8, 121.0, 126.6, 128.7, 129.3, 139.3, 148.1. MS (EI) *m/z* 252 (95, M^++ 2), 250 (100, M^+). HRMS (EI) exact mass calcd for $C_{11}H_{11}{}^{79}BrN_2$; 250.0106, Found: 250.0103.

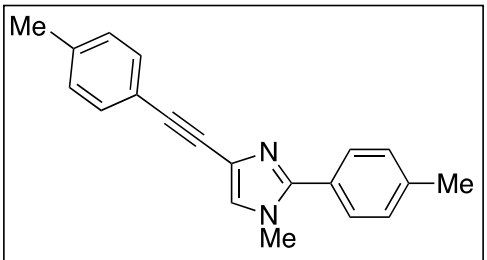
1-Methyl-2-(4-methylphenyl)-4-phenylimidazole (12)



Chemical Formula: $C_{17}H_{16}N_2$
Exact Mass: 248.1313
Molecular Weight: 248.3290

A solution of 4-bromo-1-methyl-2-(4-methylphenyl) imidazole (**11c**) (0.25 mmol, 63 mg), $PhB(OH)_2$ (2 equiv, 61 mg), Cs_2CO_3 (2 equiv, 163 mg), and $Pd(PPh_3)_4$ (10 mol %, 29 mg) in 1,2-dimethoxyethane (1 mL) and water (1 mL) was stirred at reflux under an argon atmosphere for 21.5 h. The mixture was diluted with citric acid (1 M) and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.59) to give 1-methyl-2-(4-methylphenyl)-4-phenylimidazole (**12**) in 77% yield (48 mg) as a brown solid. mp 99.3-101.4 ºC. IR (KBr) 1464, 1383, 827, 753, 729, 695 cm^{-1}. ^1H NMR (CD_3COCD_3) δ 2.37 (s, 3H), 3.81 (s, 3H), 7.14-7.18 (m, 1H), 7.28-7.33 (m, 4H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.5, 34.7, 117.9, 125.0, 126.9, 127.1, 128.6, 128.9, 129.4, 133.8, 139.0, 140.6, 148.3. MS (EI) *m/z*: 248 (M^+). HRMS (EI): Exact mass calcd for $C_{17}H_{16}N_2$; 248.1313, Found: 248.1313.

1-Methyl-2-(4-methylphenyl)-4-(4-tolylethynyl)imidazole (13)

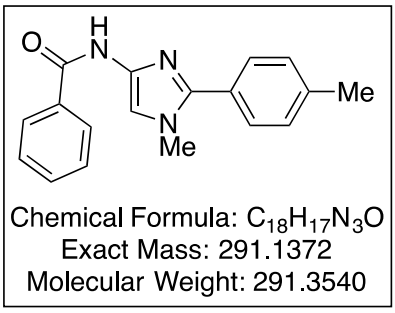


Chemical Formula: $C_{20}H_{18}N_2$
Exact Mass: 286.1470
Molecular Weight: 286.3780

To a solution of 4-bromo-1-methyl-2-(4-methylphenyl)imidazole (**11c**) (0.25 mmol, 63 mg) in MeCN (1.2 mL) were added $PdCl_2(NCPh)_2$ (10 mol%, 10 mg), $Pt\text{-}Bu_3{\cdot}HBPh_4$ (20 mol%, 26 mg), CuI (10 mol%, 5 mg), 4-ethynyltoluene (2 equiv, 70 μL), and *i*-Pr_2NEt (3 equiv, 130 μL) under an argon atmosphere. The resulting mixture was stirred at 80 °C for 20 h. The resulting mixture

was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 10 : 1, Rf = 0.09) to give 1-methyl-2-(4-methylphenyl)-4-(4-tolylethynyl)imidazole (**13**) in 57% yield (41 mg) as a brown solid. mp 142.6-144.3 ºC. IR (KBr) 2212, 1503, 1470, 1449, 1390, 822, 768, 732 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.39 (s, 3H,), 3.71 (s, 3H,), 7.11 (d, *J* = 7.6 Hz, 2H), 7.17 (s, 1H,), 7.25 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.5, 21.6, 34.9, 82.1, 89.9, 120.3, 123.4, 125.8, 126.6, 128.8, 129.1, 129.4, 131.5, 138.2, 139.4, 148.3. MS (EI) *m/z*: 286 (M^+). HRMS (EI): Exact mass calcd for $C_{20}H_{18}N_2$; 286.1470, Found: 286.1469.

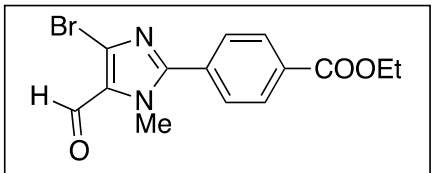
4-Benzamido-1-methyl-2-(4-methylphenyl)imidazole (14)



Chemical Formula: $C_{18}H_{17}N_3O$
Exact Mass: 291.1372
Molecular Weight: 291.3540

A solution of 4-bromo-1-methyl-2-(4-methylphenyl)imidazole (**11c**) (0.25 mmol, 63 mg), benzamide (2 equiv, 61 mg), Cs_2CO_3 (2 equiv, 163 mg), $[Pd(allyl)Cl]_2$ (2.5 mol%, 2 mg), and Di-Ad-BrettPhos (10 mol%, 16 mg) in 2-methyl-2-butanol (0.5 M, 0.5 mL) was stirred under an argon atmosphere for 20 h at 100 °C. The mixture was diluted with CH_2Cl_2, filtered through Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 1 : 1, Rf = 0.50) to give 4-benzamido-1-methyl-2-(4-methylphenyl)imidazole (**14**) in 96% yield (70 mg) as a brown solid. mp 85.4-93.1 ºC. IR (KBr) 1657, 1546, 1462, 826, 731, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.73 (s, 3H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.41-7.52 (m, 5H), 7.55 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 9.35 (br, 1H). ^{13}C NMR ($CDCl_3$) δ 21.4, 34.9, 110.3, 125.8, 127.3, 128.5, 128.8, 129.6, 131.9, 133.5, 136.2, 139.6, 143.1, 164.3. MS (EI) *m/z*: 291 (M^+). HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O$; 291.1372, Found: 291.1378.

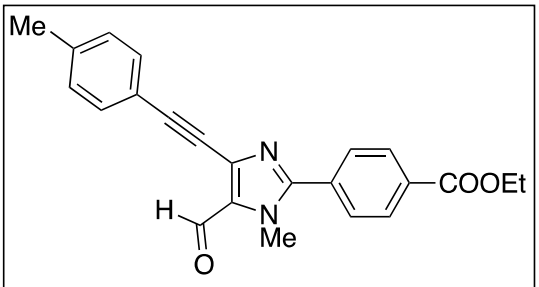
4-Bromo-2-(4-ethoxycarbonylphenyl)-5-formyl-1-methyl-imidazole (15)



Chemical Formula: $C_{14}H_{13}BrN_2O_3$
Exact Mass: 336.0110
Molecular Weight: 337.1730

A solution of *i*-PrMgCl·LiCl in THF (1.2 M, 1.1 equiv, 0.50 mL) was added dropwise to a solution of 4,5-dibromo-2-(4-ethoxycarbonylphenyl)-1-methyli midazole (**8k**) (0.55 mmol, 215 mg) in anhydrous THF (2.2 mL) under an argon atmosphere at −40 °C. The mixture was stirred for 1.5 h, and DMF (8 mL) was then added. The reaction mixture was stirred at room temperature for 30 min and quenched with H_2O. The crude mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.54) to give 4-bromo-2-(4-ethoxycarbonylphenyl)-5-formyl-1-methylimidazole (**15**) in 90% yield (167 mg) as a colorless solid. mp 95.6-98.2 ºC, IR (KBr) 1720, 1664, 1181, 1108, 720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.00 (s, 3H), 4.41 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 8.17 (d, *J* = 8.3 Hz, 2H), 9.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 34.8, 61.6, 128.1, 129.4, 130.0, 130.9, 131.7, 132.4, 152.2, 165.8, 179.8. MS (EI) *m/z*: 338 (91, $M^+ + 2$), 336 (100, M^+). Exact mass calcd for $C_{14}H_{13}{}^{79}BrN_2O_3$ (M^+); 336.0110, Found: 336.0109.

2-(4-Ethoxycarbonylphenyl)-5-formyl-4-(4-methylphenyl-ethynyl)-1-methylimidaz ole (16)

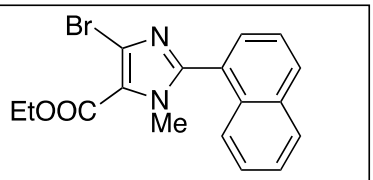


Chemical Formula: $C_{23}H_{20}N_2O_3$
Exact Mass: 372.1474
Molecular Weight: 372.4240

To a solution of 4-bromo-2-(4-ethoxycarbonylphenyl)-5-formyl-1-methyli midazole (**15**) (0.1 mmol, 34 mg) in MeCN (0.5 mL) were added $PdCl_2(NCPh)_2$ (5 mol%, 2 mg), *t*-Bu_3P·$HBPh_4$ (10 mol%, 5 mg), CuI (5 mol%, 1 mg), 4-ethynyltoluene (1.5 equiv, 24 μL), and *i*-Pr_2NEt (2 equiv, 33 μL) under an argon atmosphere. The resulting mixture was stirred at 80 °C for 9.5 h. The resulting mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.38) to give 2-(4-ethoxycarbonylphenyl)-5-formyl-4-(4-methylphenylethynyl)-1-methylimidazole

(**16**) in 76% yield (28 mg) as a brown solid. mp 165.1-168.5 ºC, IR (KBr) 1718, 1660, 1279, 1108, 722 cm^{-1}. ^1H NMR (CDCl) δ 1.47 (t, *J* = 7.2 Hz, 3H), 4.02 (s, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 8.18 (d, *J* = 8.5 Hz, 2H), 10.07 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 21.7, 34.7, 61.5, 79.6, 95.4, 118.8, 129.3, 129.4, 130.0, 131.9, 132.2, 132.3, 133.2, 137.7, 139.7, 152.5, 165.8, 179.8. MS (EI) *m/z*: 372 (M^+). HRMS (EI): Exact mass calcd for $C_{23}H_{20}N_2O_3$; 372.1474, Found: 372.1475.

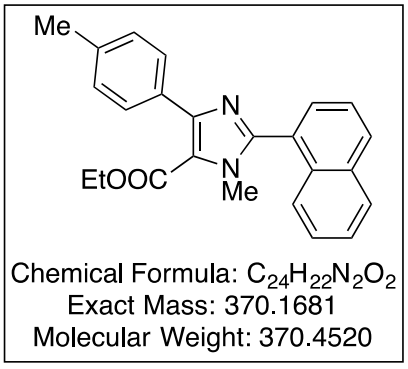
4-Bromo-5-ethoxycarbonyl-1-methyl-2-(1-naphthyl)imidazole (17).



Chemical Formula: $C_{17}H_{15}BrN_2O_2$
Exact Mass: 358.0317
Molecular Weight: 359.2230

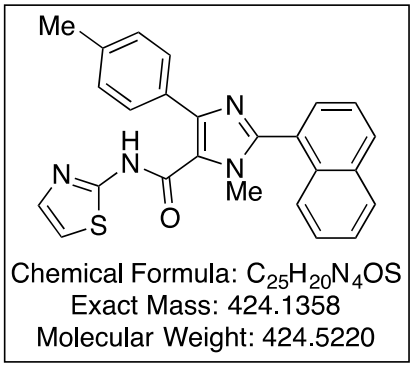
A solution of *n*-BuLi in *n*-hexane (1.5 M, 1.1 equiv, 0.18 mL) was added dropwise to a solution of 4,5-dibromo-1-methyl-2-(1-naphthyl)imidazole (**8e**) (0.25 mmol, 92 mg) in anhydrous THF (0.5 M, 0.50 mL) under an argon atmosphere at −78 °C. The mixture was stirred at −60 °C for 1 h, and ethyl cyanoformate (2 equiv, 49 μL) was then added. The reaction mixture was warmed to room temperature. After 2 h, the reaction was quenched with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 1 : 4, Rf = 0.43) to give 4-bromo-5-ethoxycarbonyl-1-methyl-2-(1-naphthyl)-imidazole (**17**) in 76% yield (68 mg) as a colorless oil. IR (KBr) 1707, 1244, 1125, 1108, 781 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 3.67 (s, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 7.51-7.57 (m, 5H), 7.91-7.93 (m, 1H), 7.99-8.01 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 35.2, 61.1, 121.5, 124.0, 125.0, 125.1, 126.3, 126.6, 127.5, 128.6, 129.2, 130.8, 132.0, 133.6, 150.7, 160.1. MS (EI) *m/z*: 360 (100, $M^+ + 2$), 358 (91, M^+). HRMS (EI): Exact mass calcd for $C_{17}H_{15}{}^{79}BrN_2O_2$ (M^+); 358.0317, Found: 358.318.

5-Ethoxycarbonyl-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)imidazole[22] (**18**)



To a solution of 4-bromo-5-ethoxy-carbonyl-1-methyl-2-(1-naphthyl)imidazole (**17**) (1.1 mmol, 382 mg) in DMF were added 4-methylphenylboronic acid (1.5 equiv, 216 mg), KOH (2 equiv, 118 mg), Pd(dba)2 (10 mol%, 61 mg), and P*t*-Bu_3·$HBPh_4$ (20 mol%, 111 mg) under an argon atmosphere, and the mixture was stirred at 80 °C for 8.5 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by GPC to give 5-ethoxycarbonyl-1-methyl-4-(4-methyl-phenyl)-2-(1-naphthyl)imidazole (**18**) in 70% yield (285 mg) as a colorless oil (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.44). 1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.38 (s, 3H), 3.69 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.49−7.66 (m, 5H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.91−7.93 (m, 1H), 8.00 (d, *J* = 8.1 Hz, 1H)

5-Carboxamide-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)-*N*-(2-thiazolyl)imidaz ole[22] (**20**)



To a solution of 5-ethoxycarbonyl-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)imidazole (**18**) (0.17 mmol, 63 mg) in EtOH (10 ml) was added 1M NaOHaq (20 equiv, 3.4 ml), and the mixture was stirred at 80 ºC for 4 h. The reaction mixture was neutralized by addition of 5% HClaq and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo.* To a solution of the crude product in DMF (3.4 ml) was added 2-aminothiazole (**19**) (2 equiv, 34 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiinide hydrochloride (3 equiv, 98 mg) and 1-hydroxy-benzotriazole (4 equiv, 92 mg) and stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with H_2O twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.33) to give 5-carboxamide-1-methyl-4-(4-methylphenyl)-2-(1-naphthyl)-*N*-(2-thiazolyl)imidazole (**20**) in 63% yield (45 mg) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.77 (s,

3H), 7.26 (d, J = 8.1 Hz, 2H), 7.40-7.45 (m, 2H), 7.52-7.64 (m, 3H), 7.69-7.74 (m, 2H), 7.87 (d, J = 8.1 Hz, 2H), 7.94-7.97 (m, 1H), 8.03-8.08 (m, 2H).

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Chapter 4

Direct C-H Bond Arylation of Thienyl Thioamides Catalyzed by Pd-phenanthroline Complexes

A direct C-H bond arylation method for thienyl thioamides catalyzed by $[Pd(phen)_2](PF_6)_2$ was developed. This reaction selectively afforded 2-monoarylated products, while the corresponding amide thiophene derivatives furnished 2,5-diarylated products. Mechanistic studies revealed that a Pd(II)-bisthioamide complex should be the active species for the reaction of thienyl thioamides in the presence of catalytic amounts of $[Pd(phen)_2](PF_6)_2$. Similar to the reaction with amides, the reaction with thioamides selectively generated the 2,5-diarylated products when a preformed Pd(phen)PhI complex was used.

4.1. Introduction

Carbonyl-containing π-conjugated moieties are a frequently encountered structural motif in modern organic functional materials. This is mostly due to the energy levels of their lowest unoccupied molecular orbitals (LUMOs), which usually render these compounds good accepting materials.[1] Thiocarbonyl-containing π-conjugated systems are also attracting significant attention, especially as semiconducting materials.[2] Generally, thiocarbonyl containing compounds are obtained from the treatment of the corresponding carbonyls with phosphorus sulfides such as Lawesson's reagent.[3] However, this method can be problematic for the preparation of functional materials, as the thus obtained products remain frequently contaminated with inseparable organophosphorous-based byproducts. Transition metal-catalyzed C-C bond formations between preformed thiocarbonyl-containing compounds and/or other building blocks represent attractive alternatives for the construction of thiocarbonyl-containing π-conjugated systems,[4] even though transition metal catalysts usually loose their catalytic activity after reacting with thiocarbonyl-containing substrates.[5] Due to this shortcomings, only few examples for transition metal catalyzed reactions of thiocarbonyl-containing compounds, such as the asymmetric aldol-type reaction of thioamides by Kumagai and Shibasaki,[6] and the thiocarbonyl-directed ortho-selective alkenylation of aryl thioamides with alkynes by Satoh[7] have been reported. However, these reactions do not include redox processes of the catalyst metal, which are usually involved in cross-coupling reactions.

Accordingly, the development of transition metal-catalyzed reactions including such processes still remains an important research target.

The author described direct arylation of C-H bond arylation of heteroarenes by using Pd-phenathroline systems. The author envisioned that these catalytic systems should also be applicable to thiocarbonyl-containing compounds, since nitrogen-based bidentate ligands are inert to thiocarbonyl groups, and usually strongly coordinate to the catalyst metal and are thus inert to ligand replacement reactions induced by thiocarbonyl groups. Below, the author describes his efforts on the direct C-H bond arylation of aryl thioamides catalyzed by Pd-phenanthroline complexes.

4.2. Results and Discussions

4.2.1. Direct C-H Bond Arylation of Thienyl Thioamides

Initially, the author evaluated several catalytic systems for the reaction between *N,N*-di-iso-propyl-3-thiophenecarbothioamide (**1a**) and phenyl iodide (**2a**) (Table 1). When using $[Pd(phen)_2](PF_6)_2$ (10 mol%) and Cs_2CO_3 (3 equiv), 2-monoarylated **3aa** was obtained in high yield (82%), and the corresponding desulfurized compounds were not observed in significant quantities (entry 1). Notably, this result is in stark contrast to the reactions of amide **1a'** and other thiophene derivatives under identical conditions; there, the corresponding 2,5-diarylated products were obtained exclusively, even when an equimolar amount of aryl halide was used (eq 1).[8a,b] Although the addition of pivalic acid often accelerates Pd-catalyzed direct C-H bond arylations, it inhibited this reaction and **1a** was recovered almost quantitatively (entry 2). Moreover, the reaction

using $Pd(OAc)_2$ (10 mol%) and Cs_2CO_3 (3 equiv) in the absence of ligand did not proceed readily (entry 3). Conversely, in the presence of various phosphine ligands such as PPh_3, PCy_3 or dppe, **1a** was consumed completely, but yielded complex product mixtures that did not contain **3aa** (entries 4-6). In these cases, substantial amounts of the corresponding desulfurized mono- and diarylated amides (**4a,b**) and the desulfurized starting material **1a'** were observed by GC-MS. Finally, the author tested $Pd(dba)_2$ with 1,10-phenanthroline as a ligand, and observed similar results as for the $Pd(OAc)_2$/phosphine systems (entry 7).

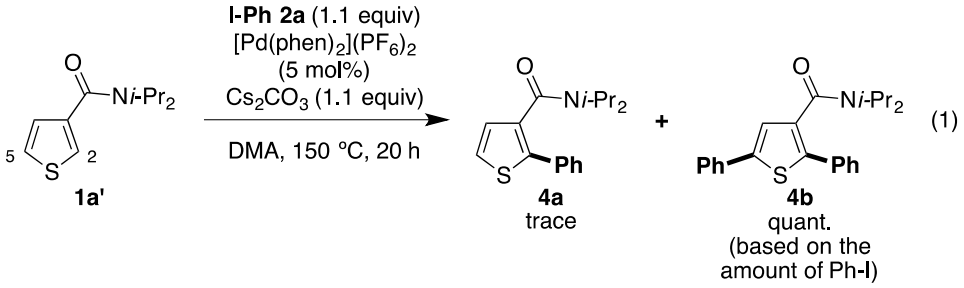
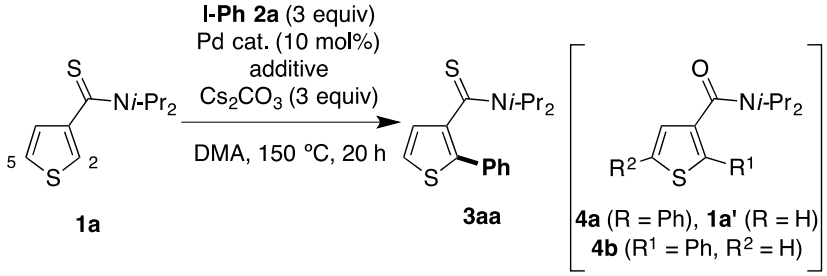


Table 1. Optimization of the conditions for the reaction between **1a** and **2a**



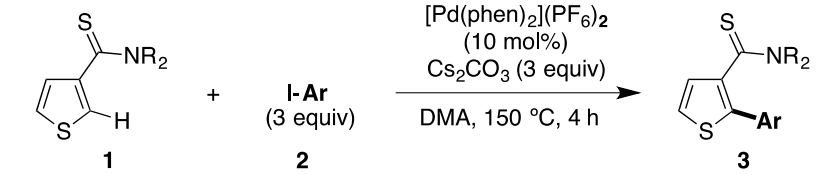
entry	Pd cat.	additive (mol%)	yield (%)[a]	conv. (%)
1	$[Pd(phen)_2](PF_6)_2$	-	82 (7)[b]	93 (39)[b]
2	$[Pd(phen)_2](PF_6)_2$	PivOH (40 mol%)	12	31
3	$Pd(OAc)_2$	–	trace	36
4	$Pd(OAc)_2$	dppe (20 mol%)	ND	100
5	$Pd(OAc)_2$	PCy_3 (20 mol%)	ND	100
6	$Pd(OAc)_2$	PPh_3 (20 mol%)	ND	100
7	$Pd(dba)_2$	phen (20 mol%)	ND	100

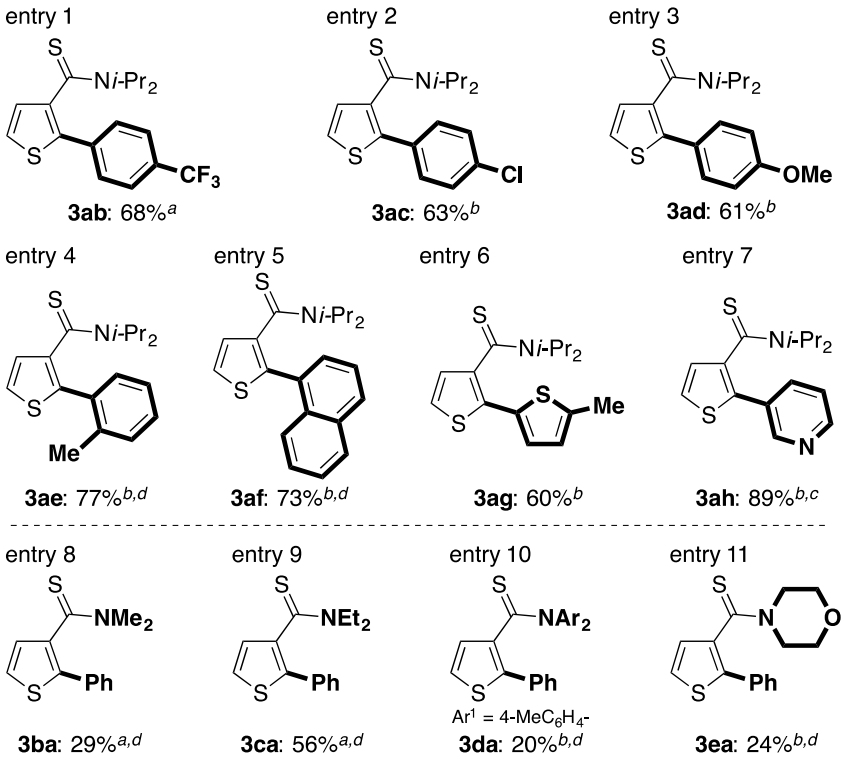
[a] Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] Phenyl bromide was used instead of phenyl iodide.

Encouraged by these results, the author examined the substrate scope using $[Pd(phen)_2](PF_6)_2$ (Table 2). The electronic character and steric hindrance of the aryl iodides (**2**) did not affect the reaction efficiency, and the reaction of aryl iodides **2b-f**

furnished the monoarylated products **3ab-3af** in good yield (entries 1-5). Heteroaryl iodides such as thienyl iodide **2g** and pyridyl iodide **2h** were also converted efficiently to afford **3ag** (60%) and **3ah** (89%). *N,N*-di-iso-propyl group should prevent a decomposition of the thiocarbonyl group into S^{2-} species, which could poison the catalyst. The reaction of thioamides with diarylamino and morpholino groups (**1d** and **1e**) also afforded the corresponding products **3db** and **3eb**, albeit in low yields (entries 10-11).

Table 2. Substrate scope of thienyl thioamides **1** and aryl iodides **2**





[a] The yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

[b] Isolated yields. [c] K_2CO_3 was used instead of Cs_2CO_3. [d] Reaction was performed for 20 h.

4.2.2. Mechanistic Studies

The selective formation of monoarylated compounds made him curious about the origin of the selectivity. Consequently, the author investigated the Pd species present during the induction period of the catalysis in detail. Initially, stoichiometric reactions between $[Pd(phen)_2](PF_6)_2$ and phenyl iodide (**2a**) or thienyl thioamide **1a**, respectively, were conducted. While the reaction with thioamide **1a** furnished palladacycle **5** in almost quantitative yield even at room temperature (eq 2),[9] the reaction did not proceed with **2a**, even at 150 °C. However, **5** is most likely not the catalytically active species for this reaction, because the stoichiometric reaction of **5** and **2a** did not furnish any products (eq 3). Nevertheless, at 150 °C, **5** catalyzed the reaction with further thioamide **1a** and **2a** to give monoarylated **3aa** in good yield (eq 4). This result clearly indicated that **5** works as a catalyst in the presence of further thioamide **1a**. Based on this result, the author speculated that excess **1a** might also participate in the reaction as a supporting ligand for the catalyst. Even though the major species detected by ESI-MS in the stoichiometric reaction mixture between **5** and **1a** at 150 °C was Pd(II)-bisthioamide **7** (eq 5, Figure 1), it could not yet be isolated. In contrast, formation of a similar palladacycle with amide **1a'** did not occur under identical conditions. In addition, the homocoupling product **6** was not detected in the reaction mixture of eq 4. This result suggested that the reduction of palladium via the reductive elimination of two thiophene moieties from **7** is implausible under these conditions, at least in the initial stage of the reaction, which also renders the possibility of a conventional Pd(0)/Pd(II) cycle (e.g. cycle II in Scheme 1) for the first arylation

unlikely.

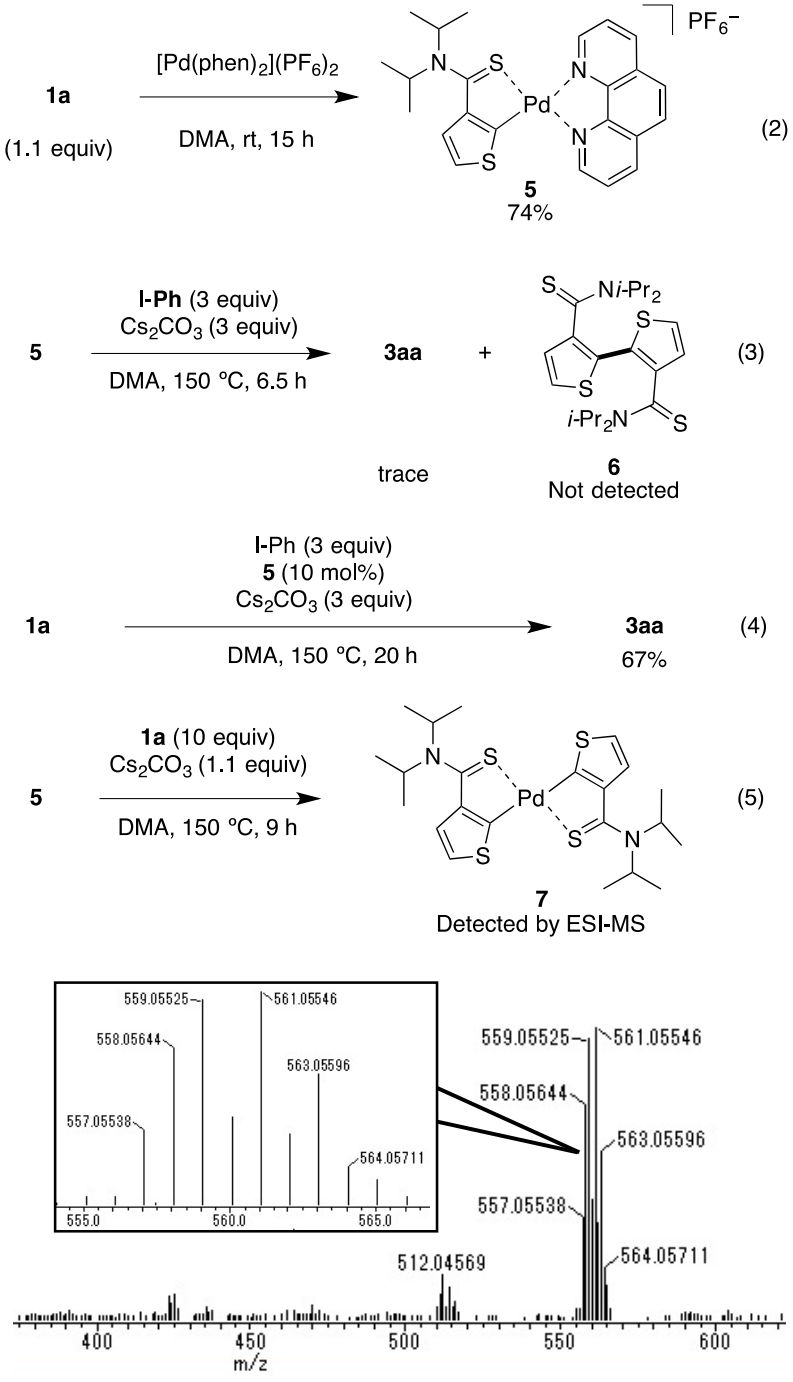
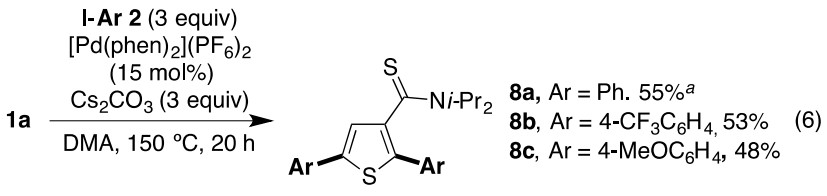


Figure 1. ESI-MS spectrum of the reaction mixture from eq 5. The observed isotope pattern around m/z = 560 is consistent with the simulated isotope pattern for **7**.

A slightly higher catalyst loading (15 mol%) generated 2,5-diarylated **8** (eq 6), and the solid-state structure of **8a** was determined by single-crystal X-ray diffraction (Figure 2). This result demonstrated that the second arylation is not controlled by the thiocarbonyl group. The author checked the reaction profile regarding product formation and substrate consumption by GC analysis (Figure 3A), and found that the second arylation took place after the complete consumption of **1a**. The author speculated that regeneration of **7** at the ultimate stage of the first arylation should not proceed efficiently, due to the limited amount of **1a** available in the reaction mixture. It seems plausible that conventional catalytically active species, e.g. Pd(phen)ArX, are generated from unpoisoned Pd species and catalyze the second arylation, even though the details of the reduction of these Pd species still remains unclear. When pre-formed Pd(phen)PhI[10] was used instead of $[Pd(phen)_2](PF_6)_2$, **8** was obtained as the major product (eq 6). This result is consistent with previously obtained results using thiophene derivatives.[8a-b] In addition, **8** was generated in the initial stages of the reaction (Figure 3B), which is in stark contrast to the results of the reaction using $[Pd(phen)_2](PF_6)_2$.



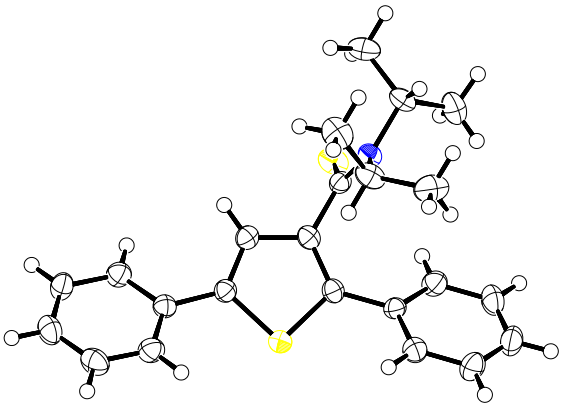


Figure 2. Molecular structure of **8a**; atomic displacement parameters set at 50% probability (yellow = S, blue = N).

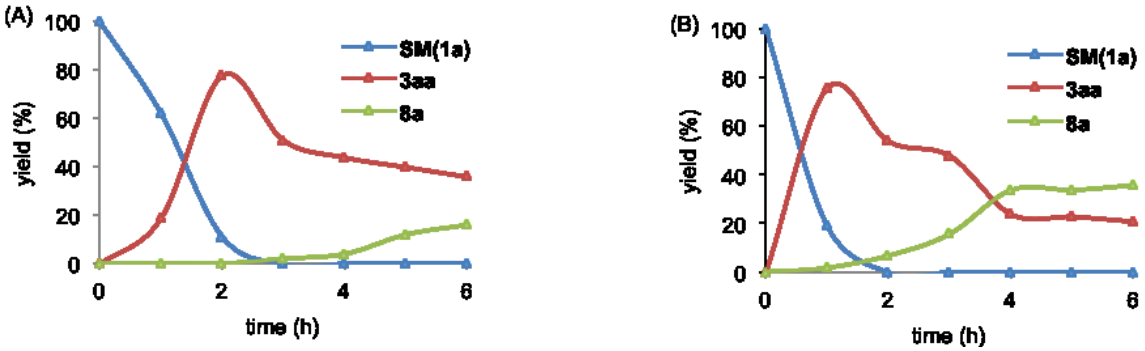
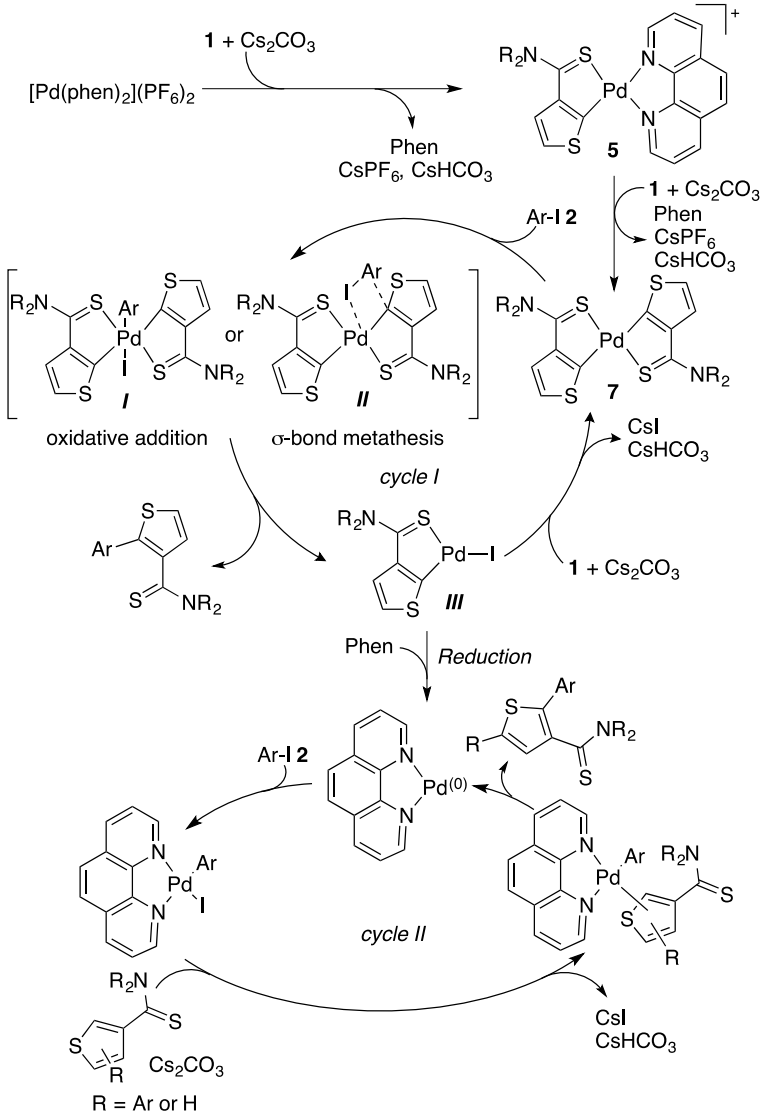


Figure 3. Reaction profiles for product formation and substrate consumption with $[Pd(phen)_2](PF_6)_2$ (15 mol%) (A), or Pd(phen)PhI (10 mol%) (B) in DMA (1 M) at 150 °C. Yields for the respective time periods were determined by GC analysis using icosane as an internal standard.

On the basis of these observations, the author would like to propose plausible catalytic cycles (Scheme 1). When using $[Pd(phen)_2](PF_6)_2$, a twofold C-H palladation of **1** should generate Pd(II)-bisthioamide **7** (induction period for *cycle I*), which should be electron-rich, due to the presence of two carbanions and two electron-donating sulfur

ligands. This might facilitate the generation of bisthioamide-Pd(IV)ArI (*I*) via oxidative addition of the aryl iodide.[11,12] Reductive elimination of the product to give Pd(II)-monothioamido complex *II* should then occur immediately. A σ-bond metathesis of **2** and **7** to directly afford **3** and *III* may also be possible.[13] During the last stage of the first arylation, regeneration of **7** may be hampered by low concentrations of **1**. This could lead to reductions of the palladium species, e.g. C-H palladation at C5 of the thienyl group in **3aa** prior to reductive elimination. Subsequently, the thus generated Pd(0) species could catalyze the arylation via the conventional reaction pathway to furnish the corresponding diarylated products (*cycle II*).



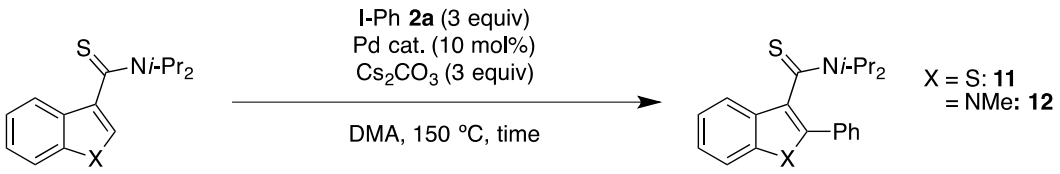
Scheme 1. Proposed catalytic cycles for the direct arylation of C-H bonds in thienyl thioamides using Pd-phenanthroline complexes

4.3. Direct Arylation of Heteroaryl Thioamides Catalyzed by Pd(phen)PhI

Mechanistic studies showed that Pd(phen)PhI was also used as a catalyst for direct arylation of thienyl thioamides. Therefore, Pd(phen)PhI catalyzed direct arylation reaction of other heteroaryl thioamides was investigated (Table 3). In the presence of catalytic amount of Pd(phen)PhI, the reaction of 3-benzothienyl thioamide **9** or 3-indolyl thioamide **10** with iodobenzne (**2a**) furnished the corresponding arylated

products **11** and **12** in 51% and 62% yield, respectavely (entries 1-2). Although, $[Pd(phen)_2](PF_6)_2$ was also be used as a catalyst, the yields were decreased (entries 3-4).

Table 3. Direct arylation of other heteroaryl thioamides



entry	X	Pd cat.	time (h)	yield (%)[a]
1	S (**9**)	Pd(phen)PhI	3	51
2	NMe (**10**)	Pd(phen)PhI	3	62
3	S (**9**)	$[Pd(phen)_2](PF_6)_2$	20	27
4	NMe (**10**)	$[Pd(phen)_2](PF_6)_2$	20	35

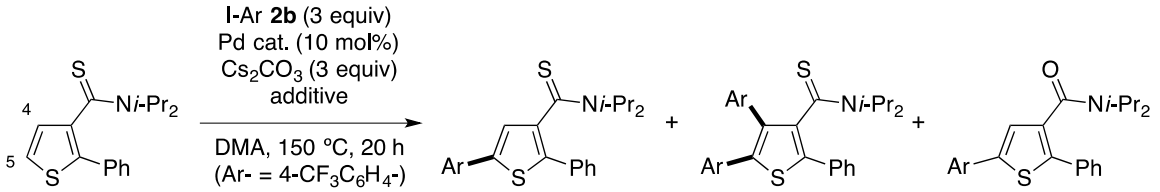
[a] Isolate yields.

4.4. Further Arylation of Monoarylated Thienyl Thioamides

Further arylation took place when 2-arylated thienyl thiamides **3aa** was used as a substrate (Table 4). The reaction of **3aa** and aryl iodide **2a** in the presence of $[Pd(phen)_2](PF_6)_2$ as a catalyst gave 2,5-diarylthiophene **8d** in 62% yield (entry 1). On the other hand, 2,4,5-triarylthiophene **13** was obtained as a major product when $Pd(phen)X_2$ (X = OAc, I) was used as a catalyst (entries 2-3). Interestingly, selective formation of **8d** was observed when further 1,10-phenanthroline (20 mol%) was added to the reaction mixture of the conditions in the presence of $Pd(phen)(OAc)_2$ as a catalyst, and the result was similar to the reaction by using $[Pd(phen)_2](PF_6)_2$ (entry 4). The addition of $NaPF_6$ (40 mol%) did not affect the selectivity, and **8d** was obtained as a major product (entry 5). The ratio of 1,10-phenanthroline ligand to Pd likely

consistent with the selectivity of formation of **8d** and **13**. Although detail of the mechanism is unclear at this stage, the author assumes that other active species was generated from $Pd(phen)X_2$ which is not be sufficiently stabilized by phenanthroline ligand.

Table 4. Direct arylation of 2-monoarylated thienyl thioamide



entry	Pd cat.	additive	**8d** (%)	**13** (%)[b]	**14** (%)[b]	conv. (%)
1	$[Pd(phen)_2](PF_6)_2$	-	62[a](41[b])	-		79
2	$Pd(phen)(OAc)_2$	-	-	44	40	90
3	$Pd(phen)I_2$	-	-	35	25	100
4	$Pd(phen)(OAc)_2$	phen (20 mol%)	60[a](41[b])		26	90
5	$Pd(phen)(OAc)_2$	phen (20 mol%) $NaPF_6$ (40 mol%)	45[a](39[b])		14	92

[a] The yields were determined by ^1H NMR using 1,1,2,2,-tetrachloroethane as an internal standard.

[b] Isolated yields.

4.5. Conclusion

In conclusion, the author developed a catalytic C-C cross-coupling method to afford aryl thioamides, mediated by Pd-phenanthroline complexes. Depending on the concentration of thienyl thioamides, these complexes most likely catalyze different reaction pathways. The author's observations imply that due to the highly

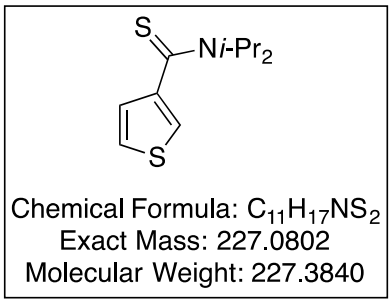
electron-rich C,S-ligands, one of the pathways proceeds via an unusual Pd(II)/Pd(IV) cycle.

4.6. Experimental

General procedure for the synthesis of 1a-1e

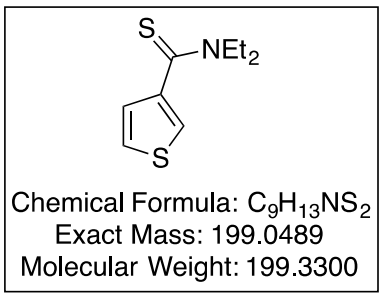
A solution of the amide (5.0 mmol) was treated with sulfur (1.1 equiv, 180 mg), 1,4-diazabicyclo[2.2.2]octane (1.1 equiv, 620 mg) in toluene (10 mL), and trichlorosilane (1.1 equiv, 0.56 mL). The mixture was stirred overnight at 115 ºC, before being quenched by addition of saturated aqueous $NaHCO_3$. Subsequently, the reaction mixture was diluted with Et_2O, filtered, and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The obtained residue was purified by flash column chromatography on silica gel to give analytically pure **1**. However, the thus obtained product contained undetectable amounts of sulfur derivatives, which lead to problems with the reproducibility in the ensuing reaction steps. Accordingly, further purification of **1** by flash column chromatography on silica gel was needed in order to ensure good reproducibility; the product yield was not affected by this additional purification step.

N,N-Diisopropylthiophene-3-carbothioamide (1a)



97% yield (1.1 g), yellow solid, Rf = 0.25 (*n*-Hexane : EtOAc = 10 : 1). mp 82.6-83.4 ºC. IR (KBr) 3107, 2968, 1486, 1334, 1238, 785 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.19 (br, 6H), 1.71 (br, 6H), 3.51 (br, 1H), 4.20 (br, 2H), 7.00 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.11 (dd, *J* = 3.1, 1.4 Hz, 1H), 7.24 (dd, *J* = 4.9, 3.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.5, 20.9, 51.7, 57.1, 120.4, 125.6, 126.3, 145.7, 194.9. MS (EI) *m/z*: 227 (16, M^+), 184 (19, M^+ – *i*-Pr), 127 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{11}H_{17}NS_2$ (M^+); 227.0802, Found: 277.0809.

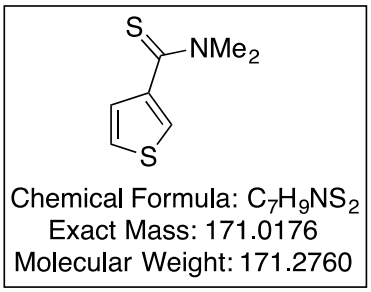
N,N-Diethylthiophene-3-carbothioamide (1b)



99% yield (990 mg), yellow oil, Rf = 0.50 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1491, 1278, 1245, 1136, 784 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 3.52 (q, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 7.07 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.24-7.28 (m,

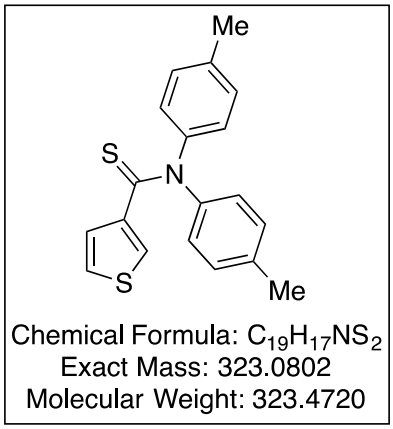
2H). ^{13}C NMR ($CDCl_3$) δ 11.3, 14.2, 46.5, 47.9, 121.8, 125.7, 126.7, 143.6, 194.9. MS (EI) *m/z*: 199 (33, M^+), 166 (62, $M^+ - NEt_2$). HRMS (EI): Exact mass calcd for $C_9H_{13}NS_2$ (M^+); 199.0489, Found: 199.0481.

_N,N_-Dimethylthiophene-3-carbothioamide (1c)[15]



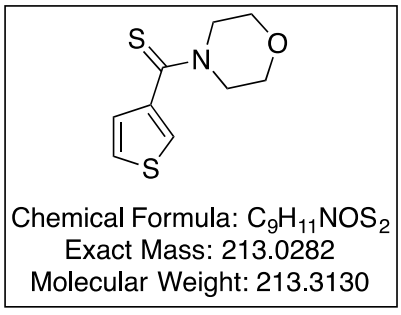
73% yield (620 mg), brown oil, Rf = 0.23 (*n*-hexane : EtOAc = 4 : 1). ^{1}H NMR ($CDCl_3$) δ 3.27 (s, 3H), 3.57 (s, 3H), 7.14 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.26 (dd, *J* = 5.0, 3.2 Hz, 1H), 7.35 (dd, *J* = 3.2, 1.3 Hz, 1H).

_N,N_-Bis(4-methylphenyl)thiophene-3-thiocarbothioamide (1d)



88% yield (1.4 g), yellow solid, mp 143.4-143.6 ºC. Rf = 0.53 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 1505, 1347, 1303, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 6H), 6.98-7.00 (m, 1H), 7.03-7.04 (m, 1H), 7.10 (br, 8H), 7.44-7.45 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.2, 124.3, 126.9, 128.6, 128.9, 130.1 (2C), 137.2, 144.7, 197.3. MS (EI) *m/z*: 323 (7, M^+), 200 (100, M^+ – S – 4-MeC_6H_4). HRMS (EI): Exact mass calcd for $C_{19}H_{17}NS_2$ (M^+); 323.0802, Found: 323.0808.

Morpholino(thiophen-3-yl)methanethione (1e)

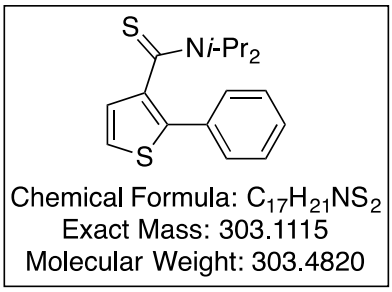


89% yield (950 mg), yellow solid, mp 90.4-91.1 ºC. Rf = 0.05 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 1471, 1278, 1109, 1028, 809 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.67 (br, 2H), 3.73 (br, 2H), 3.86 (br, 2H), 4.41 (br, 2H), 7.09 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.29 (dd, *J* = 5.0, 3.2 Hz, 1H), 7.35 (dd, *J* = 3.2, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 49.9, 52.7, 66.6, 66.8, 124.3, 126.1, 127.0, 142.5, 195.0. MS (EI) *m/z*: 213 (98, M^+), 127 (100, $M^+ - C_4H_8NO$). HRMS (EI): Exact mass calcd for $C_9H_{11}NOS_2$ (M^+); 213.0282, Found: 213.0287.

General procedure for direct mono arylation of 1a

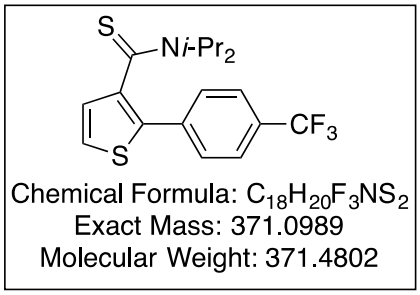
A screw-capped test tube was charged with Cs_2CO_3 (3 equiv, 250 mg), which was subsequently dried *in vacuo* using a heatgun. $[Pd(phen)_2](PF_6)_2$ (10 mol%, 19 mg), **1a** (0.25 mmol, 57 mg), aryl iodide **2** (3 equiv), and DMA (0.5 M, 0.5 ml) were added to this vessel, before the reaction mixture was stirred at 150 °C. After completion of the reaction, the mixture was cooled to room temperature, and filtered through a pad of celite, before being concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel and GPC to give **3**.

***N,N*-Diisopropyl-2-phenylthiophene-3-carbothioamide (3aa)**



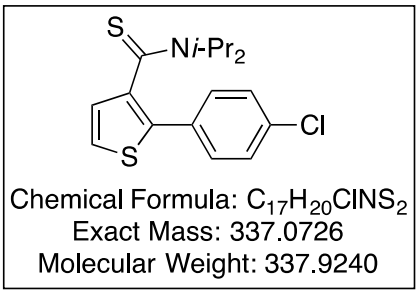
75% yield (57 mg), yellow solid, mp 139.0-141.0 ºC. Rf = 0.45 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 3112, 2968, 2928, 1329, 1147, 767 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.50 (br, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 1.68 (br, 3H), 1.79 (br, 3H), 4.00 (br, 1H), 4.11 (sept, *J* = 6.7 Hz, 1H), 6.96 (d, *J* = 5.4 Hz, 1H), 7.20-7.29 (m, 3H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 17.9, 19.0, 20.0, 20.8, 51.1, 57.5, 124.9, 125.7, 127.9, 128.7, 129.0, 133.7, 134.0, 140.8, 194.6. MS (EI) *m/z*: 303 (18, M^+), 203 (56, M^+ – N*i*-Pr$_2$). HRMS (EI): Exact mass calcd for $C_{17}H_{21}NS_2$ (M^+); 303.1115, Found: 303.1118.

***N,N*-Diisopropyl-2-(4-trifluoromethylphenyl)thiophene-3-carbothioamide (3ab)**



51% yield (52 mg), yellow solid, mp 142.1-143.1 ºC. Rf = 0.35 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1486, 1322, 1203, 1144, 757, 687 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.58 (br, 3H), 0.61 (br, 3H), 1.69 (br, 3H), 1.80 (br, 3H), 3.86 (br, 1H), 4.07 (sept, *J* = 6.7 Hz, 1H), 6.98 (d, *J* = 5.4 Hz, 1H), 7.31 (d, *J* = 5.4 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.1, 19.3, 19.9, 20.8, 51.1, 57.3, 124.1 (q, *J* = 272.5 Hz), 125.7 (q, *J* = 3.7 Hz), 126.2, 128.3, 128.9, 129.7 (q, *J* = 32.9 Hz), 132.1, 137.2, 141.8 (Ar), 194.1. ^{19}F NMR ($CDCl_3$) δ –62.9. MS (EI) *m/z*: 371 (21, M^+), 328 (25, M^+ – *i*-Pr), 271 (93, M^+ – N*i*-Pr$_2$). HRMS (EI): Exact mass calcd for $C_{18}H_{20}F_3NS_2$; 371.0989, Found: 317.0991.

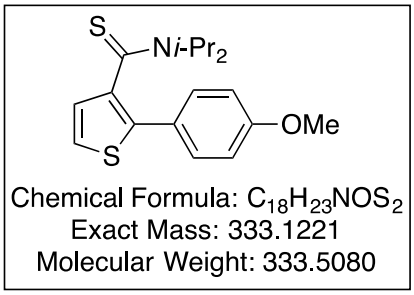
***N,N*-Diisopropyl-2-(4-chlorophenyl)thiophene-3-carbothioamide (3ac)**



Chemical Formula: $C_{17}H_{20}ClNS_2$
Exact Mass: 337.0726
Molecular Weight: 337.9240

73% yield (62 mg), yellow solid, mp 152.3-153.5 ºC. Rf = 0.37 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1485, 1378, 1329, 1257, 1146 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.59 (br, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.70 (br, 3H), 1.81 (br, 3H), 3.79 (br, 1H), 4.07 (sept, *J* = 6.7 Hz, 1H), 6.95 (d, *J* = 5.3 Hz, 1H), 7.24 (d, *J* = 5.3 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.0, 19.4, 19.9, 20.8, 51.0, 57.2, 125.3, 128.9 (2C), 129.4, 132.2, 132.5, 133.8, 141.1, 194.3. MS (EI) *m/z*: 337 (21, M^+), 294 (22, M^+ – *i*-Pr), 237 (65, M^+ – N*i*-Pr$_2$). HRMS (EI): Exact mass calcd for $C_{17}H_{20}ClNS_2$ (M^+); 337.0726, Found: 337.0730.

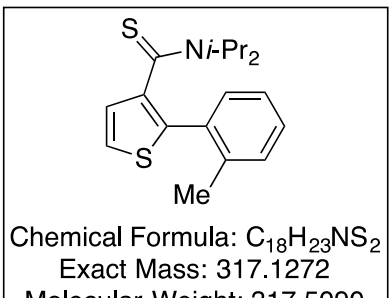
***N,N*-Diisopropyl-2-(4-methoxyphenyl)thiophene-3-carbothioamide (3ad)**



Chemical Formula: $C_{18}H_{23}NOS_2$
Exact Mass: 333.1221
Molecular Weight: 333.5080

61% yield (51 mg), yellow solid, mp 147.1-148.0 ºC. Rf = 0.33 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 2965, 1486, 1327, 1248, 1146 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.54 (br, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 1.67 (br, 3H), 1.79 (br, 3H), 3.62 (br, 1H), 3.83 (s, 3H), 4,13 (sept, *J* = 6.7 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 5.4 Hz, 1H), 7.17 (d, *J* = 5.4 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.0, 20.0, 20.8, 20.9, 51.0, 55.2, 57.1, 114.1, 124.1, 126.3, 128.8, 129.6, 133.9, 140.1, 159.4, 194.9. MS (EI) *m/z*: 333 (35, M^+), 290 (34, M^+ – *i*-Pr), 233 (100, M^+ – N*i*-Pr$_2$). HRMS (EI): Exact mass calcd for $C_{18}H_{23}NOS_2$; 333.1221, Found: 333.1221.

***N,N*-Diisopropyl-2-(2-methylphenyl)thiophene-3-carbothioamide (3ae)**

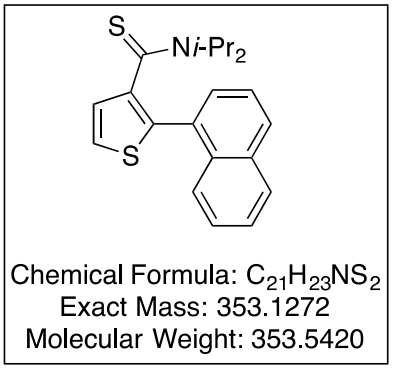


Chemical Formula: $C_{18}H_{23}NS_2$
Exact Mass: 317.1272
Molecular Weight: 317.5090

77% yield (61 mg), yellow solid, mp 133.8-134.7 ºC. Rf = 0.34 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1490, 1380, 1328, 1254, 1149, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.56 (br, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.76 (br, 3H), 2.40 (s, 3H), 3.70 (br, 1H), 4.29 (br, 1H), 7.03 (d, *J* = 5.4 Hz, 1H), 7.14-7.22 (m, 3H), 7.28 (d, *J* = 5.4 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.1, 19.3, 20.1, 20.9, 21.4, 50.7, 56.9, 125.3, 125.8, 128.2, 128.6,

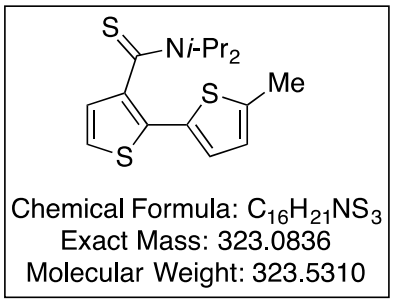
130.5, 131.5, 132.4, 132.8, 137.1, 142.4, 194.1. MS (EI) *m/z*: 317 (11, M^+), 274 (8, M^+ – *i*-Pr), 217 (40, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{18}H_{23}NS_2$ (M^+); 317.1272, Found: 317.1273.

_N,N_-Diisopropyl-2-(1-napthyl)thiophene-3-carbothioamide (3af)



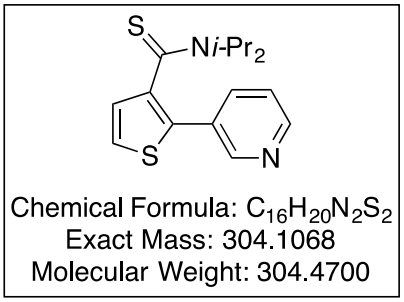
73% yield (65 mg), yellow solid, mp 186.8-188.5 ºC. Rf = 0.41 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1493, 1323, 1225, 775, 753 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.02 (br, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.75 (br, 3H), 3.57 (br, 1H), 4.33 (br, 1H), 7.18 (d, *J* = 5.4 Hz, 1H), 7.43 (d, *J* = 5.4 Hz, 1H), 7.47-7.51 (m, 3H), 7.85-7.90 (m, 3H), 8.27-8.29 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 17.9, 19.1, 20.2, 20.6, 50.6, 56.9, 125.3, 125.9, 126.0, 126.1, 126.5, 128.4, 128.8, 129.1, 129.5, 130.3, 131.5, 132.4, 133.7, 143.1, 193.9. MS (EI) *m/z*: 353 (18, M^+), 310 (4, M^+–*i*-Pr), 253 (10, M^+ – N*i*-Pr_2), 221 (23, M^+ – S – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{21}H_{23}NS_2$; 353.1272, Found: 353.1265.

_N,N_-Diisopropyl-2-(5-methylthienyl)thiophene-3-carbothioamide (3ag)



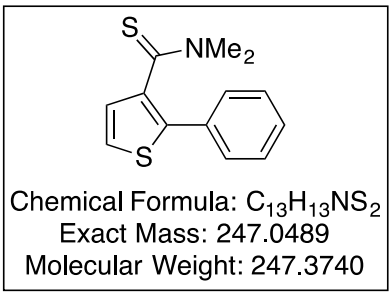
57% yield (46 mg), yellow solid, mp 148.6-149.3 ºC. Rf = 0.38 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1491, 1380, 1252, 1144, 798, 723 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.85 (br, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.75 (br, 6H), 3.51 (br, 1H), 4.11 (sept, *J* = 6.7 Hz, 1H), 6.63 (dd, *J* = 3.6, 0.9 Hz, 1H), 6.83 (d, *J* = 4.7 Hz, 1H), 7.10-7.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 15.4, 18.4, 19.7 (2C), 20.7, 51.0, 57.2, 124.2, 125.8, 126.1, 127.8, 128.5, 132.6, 139.9, 140.6, 194.3. MS (EI) *m/z*: 323 (29, M^+), 280 (11, M^+ – *i*-Pr), 223 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{16}H_{21}NS_3$ (M^+); 323.0836, Found: 323.0835.

***N,N*-Diisopropyl-2-(3-pyridyl)thiophene-3-carbothioamide (3ah)**



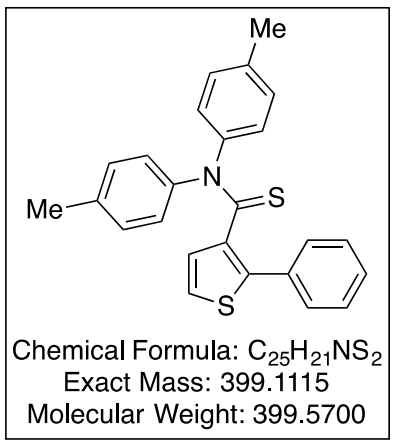
89% yield (68 mg), yellow solid, mp 96.3-97.0 ºC. Rf = 0.08 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1492, 1330, 1147, 723, 707 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.62 (br, 3H), 1.04 (d, *J* = 6.7 Hz. 3H), 1.68 (br, 3H), 1.77 (br, 3H), 3.82 (br, 1H), 4.07 (sept, *J* = 6.7 Hz, 1H), 6.98 (d, *J* = 5.2 Hz, 1H), 7.26-7.29 (m, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 8.12 (m, 1H), 8.51 (dd, *J* = 3.0, 1.8 Hz, 1H), 8.84 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.2, 19.5, 19.8, 20.9, 51.2, 57.2, 123.5, 126.2, 128.7, 129.8, 130.1, 135.4, 142.2, 148.5, 148.5, 193.9. MS (EI) *m/z*: 304 (29, M^+), 261 (46, M^+ – *i*-Pr), 204 (100, M^+ – N*i*-Pr$_2$). HRMS (EI): Exact mass calcd for $C_{16}H_{20}N_2S_2$ (M^+); 304.1068, Found: 304.1068.

***N,N*-Dimethyl-2-phenylthiophene-3-carbothioamide (3ba)**



25% yield (16 mg), yellow oil, Rf = 0.24 (*n*-Hexane : EtOAc = 4 : 1). IR (KBr) 1506, 1283, 1132, 769, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 3.43 (s, 3H), 7.13 (d, *J* = 5.2 Hz, 1H), 7.24 (d, *J* = 5.2 Hz, 1H), 7.30-7.38 (m, 3H), 7.49-7.51 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 42.9, 43.1, 124.9, 127.7, 128.1, 129.1, 129.9, 133.7, 136.9, 138.8, 195.7. MS (EI) *m/z*: 247 (100, M^+), 203 (49, M^+ – NMe_2). HRMS (EI): Exact mass calcd for $C_{13}H_{13}NS_2$ (M^+); 247.0489, Found: 247.0495.

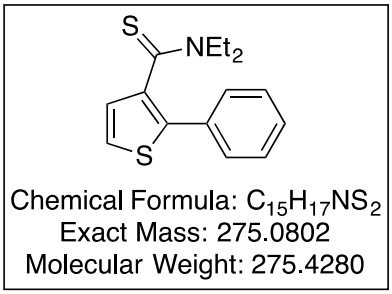
***N,N*-Di-p-tolyl-2-phenylthiophene-3-carbothioamide (3da)**



13% yield (13 mg), sticky yellow oil, Rf = 0.53 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1505, 1347, 1303, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.31 (s, 3H), 6.16 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 7.12-7.19 (m, 5H), 7.25-7.26 (m, 2H), 7.31-7.35 (m, 3H), 7.40 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 21.3, 124.5, 125.9, 126.8, 128.1, 128.5, 128.7, 128.8, 130.2, 131.9, 133.7, 136.0, 137.5, 137.8, 140.1,

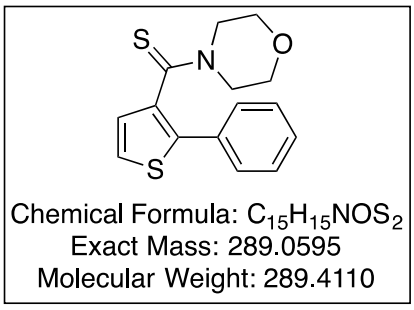
142.9, 144.2, 198.9. MS (EI) *m/z*: 399 (8, M^+), 276 (100, $M^+ - CH_3C_6H_4 - S$), 203 (22, $M^+ - N(CH_3C_6H_4)_2$). HRMS (EI): Exact mass calcd for $C_{25}H_{21}NS_2$ (M^+); 399.1115, Found: 399.1117.

_N,N_-Diethyl-2-phenylthiophene-3-carbothioamide (3ca)



48% yield (33 mg), yellow oil, Rf = 0.25 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1490, 1442, 1259, 1140, 765, 694 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 3.38 (q, *J* = 7.2 Hz, 1H), 3.05 (q, *J* = 7.2 Hz, 1H), 3.60 (q, *J* = 7.2 Hz, 1H), 4.53 (q, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 5.4 Hz, 1H), 7.24 (d, *J* = 5.4 Hz, 1H), 7.28-7.36 (m, 3H), 7.58-7.60 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 10.5, 13.2, 46.0, 47.6, 124.9, 128.0, 128.0, 128.9, 129.4, 133.4, 135.5, 138.9, 195.0. MS (EI) *m/z*: 275 (50, M^+), 242 (76, $M^+ - i$-Pr), 203 (100, $M^+ - N i$-Pr_2). HRMS (EI): Exact mass calcd for $C_{15}H_{17}NS_2$ (M^+); 275.0802, Found: 275.0798.

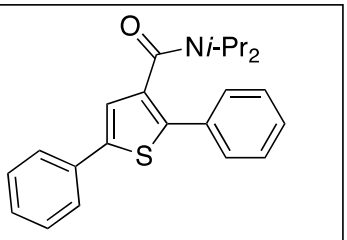
Morpholino(2-phenylthiophen-3-yl)methanethione (3ea)



28% yield (20 mg), yellow solid, mp 117.2-118.3 ºC. Rf = 0.12 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1475, 1285, 1110, 901, 770 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.50-2.57 (m, 1H), 3.24-3.33 (m, 3H), 3.45-3.50 (m, 1H), 3.72-3.77 (m, 1H), 4.07-4.13 (m, 1H), 4.42-4.47 (m, 1H), 7.14 (d, *J* = 5.4 Hz, 1H), 7.26 (d, *J* = 5.4 Hz, 1H), 7.32-7.41 (m, 3H), 7.51-7.54 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 49.2, 51.7, 65.7, 65.8, 125.2, 128.2, 128.6, 129.2, 130.3, 133.3, 136.6, 137.9, 195.1. MS (EI) *m/z*: 289 (100, M^+), 187 (83, $M^+ - C_4H_8NO$). HRMS (EI): Exact mass calcd for $C_{15}H_{15}NOS_2$ (M^+); 289.0595, Found: 289.0596.

_N,N_-Diisopropyl-2,5-diphenylthiophene-3-carboxamide (4b)

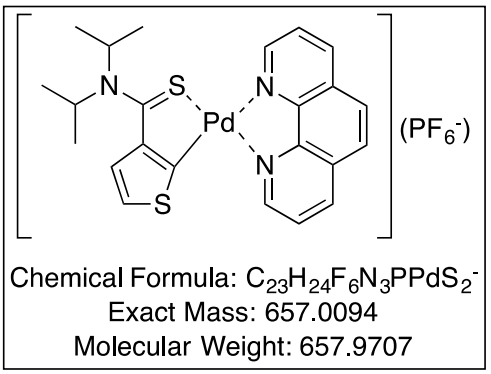
A screw-capped test tube containing was placed Cs_2CO_3 (1.1 equiv, 90 mg), which was then dried by a heatgun *in vacuo*. To this vessel were added $[Pd(phen)_2](PF_6)_2$ (5 mol%, 10 mg), *N,N*-diisopropylthiophene-3-carboxamide (0.25 mmol, 53 mg), iodobenzene (1.1 equiv, 31 μl) and DMA (0.5 M, 0.5 ml). The reaction mixture was



Chemical Formula: $C_{23}H_{25}NOS$
Exact Mass: 363.1657
Molecular Weight: 363.5190

stirred for 20 h at 150 °C. After completion of the reaction, the mixture was cooled to room temperature. The reaction mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 4 : 1, Rf = 0.52) to give **4a** in 100% yield (50 mg) based on amount of iodobenzene as a colorless solid. mp 177.2-179.3 ºC. IR (KBr) 1621, 752, 689 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.51 (br, 3H), 0.97 (br, 3H), 1.51 (br, 6H), 3.35 (sept, J = 6.9 Hz, 1H), 3.79 (sept, J = 6.9 Hz, 1H), 7.25 (s, 1H), 7.28-7.31 (m, 2H), 7.35-7.40 (m, 4H), 7.60 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 20.3, 21.1, 46.0, 51.0, 123.3, 125.8, 128.0, 128.2, 128.2, 128.8, 129.1, 133.5, 133.8, 136.1, 138.2, 144.0, 167.1. MS (EI) *m/z*: 363 (24, M^+), 320 (10, M^+ – *i*-Pr), 263, (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{23}H_{25}NOS$ (M^+); 363.1657, Found: 363.1660.

Pd(phen)[3-(diisopropylamino)thioxomethyl]-2-thienyl-C^2,S^3](PF_6) (5)



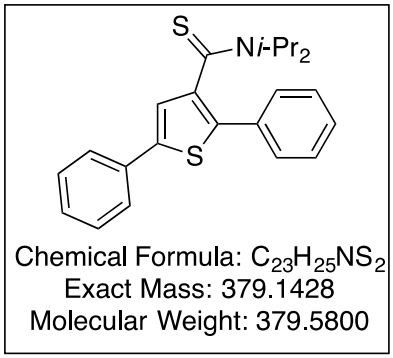
Chemical Formula: $C_{23}H_{24}F_6N_3PPdS_2^-$
Exact Mass: 657.0094
Molecular Weight: 657.9707

To a solution of $[Pd(phen)_2](PF_6)_2$ (0.5 mmol, 380 mg) in DMA (5 ml) was *N,N*-diisopropylthiophen-3-carbothioamide (**1a)** (1.1 equiv, 130 mg) under an argon atmosphere. The reaction mixture was stirred for 16 h at room temperature. The mixture was diluted with MeOH and the precipitate was filtered. The solid was washed with CH_2Cl_2 to give **5** as yellow solid in 84% yield (280 mg). IR (KBr) 1508, 842, 714, 557 cm^{-1}. ^1H NMR (DMF-d_7) δ 1.58 (d, J = 6.3 Hz, 6H), 1.84 (d, J = 6.3 Hz, 6H), 4.63 (br, 1H), 5.20 (sept, J = 6.3 Hz, 1H), 7.40 (d, J = 5.3 Hz, 1H), 7.66 (d, J = 5.3 Hz, 1H), 8.21 (br, 2H), 8.30 (s, 2H), 8.92 (br, 1H), 9.01 (d, J = 7.6 Hz, 2H), 9.63 (br, 1H). ^{13}C NMR (DMSO-d_6) δ 19.9, 20.2, 52.5, 59.5, 124.2, 125.9, 126.1, 127.6, 130.2, 140.1, 145.2, 150.3, 151.3, 163.8, 186.6. ^{19}F NMR (DMSO-d_6) δ –71.7 (d, J = 287.9 Hz). ^{31}P NMR (DMSO-d_6) δ –143.5 (sept, J = 287.9 Hz). MS (FAB) *m/z*: 512 (46, M^+ – PF_6), 514 (40, M^+ + 2 – PF_6), 516 (19, M^+ + 4 – PF_6), 510, (16, M^+ – 2 – PF_6), 513 (16, M^+ + 1 – PF_6). HRMS (FAB): Exact mass calcd for $C_{23}H_{24}N_3PdS_2$ (M^+ – PF_6); 512.0446, Found: 512.0444.

General procedure for direct diarylation of 3-thiophenecarbothioamide 8a-8c

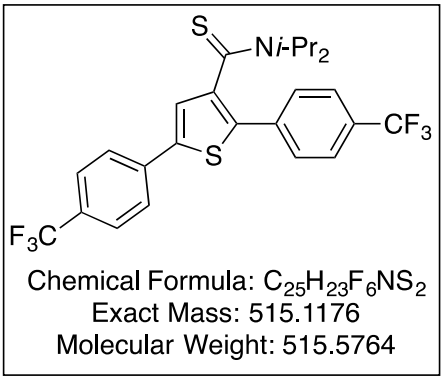
A screw-capped test tube was charged with Cs_2CO_3 (3 equiv, 250 mg), which was subsequently dried *in vacuo* using a heatgun. $[Pd(phen)_2](PF_6)_2$ (15 mol%, 29 mg), **1a** (0.25 mmol, 57 mg), aryl iodides **2** (3 equiv) and DMA (0.5 M, 0.5 mL) were added to this vessel, before the reaction mixture was stirred for 20 h at 150 °C. After completion of the reaction, the mixture was cooled to room temperature, and filtered through a pad of celite, before being concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel and GPC ($CHCl_3$) to give **8**.

***N,N*-Diisopropyl-2,5-diphenylthiophene-3-thiocarboamide (8a)**



36% yield (34 mg), yellow solid. mp 186.4-190.0 ºC. Rf = 0.32 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1610, 1323, 1209, 1169, 825 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.04 (br, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.70 (br, 3H), 1.81 (br, 3H), 3.82 (br, 1H), 4.23 (sept, *J* = 6.7 Hz, 1H), 7.25 (s, 1H), 7.25-7.31 (m, 2H), 7.34-7.39 (m, 4H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 17.9, 19.0, 20.0, 20.9, 51.0, 57.3, 124.7, 125.7, 128.0, 128.0, 128.1, 128.8, 129.0, 133.0, 133.6, 133.7, 141.5, 143.5, 194.2. MS (EI) *m/z*: 379 (33, M^+), 279 (100, M^+ – N*i*-Pr2). HRMS (EI): Exact mass calcd for $C_{23}H_{25}NS_2$ (M^+); 379.1428, Found: 379.1433.

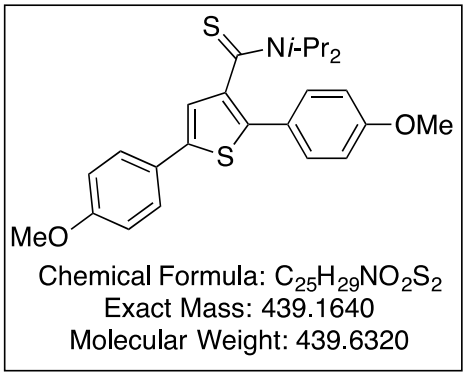
***N,N*-Diisopropyl-2,5-bis(4-trifluoromethylphenyl)thiophene-3-thiocarboamide (8b)**



42% yield (54 mg), yellow solid, mp 174.4-176.1 ºC. Rf = 0.37 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1613, 1490, 1323, 1112, 1068, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.61 (br, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.70 (br, 3H), 1.81 (br, 3H), 3.51 (br, 1H), 4.17 (sept, *J* = 6.3 Hz, 1H), 7.28 (s, 1H), 7.62-7.64 (m, 4H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.0, 19.9, 20.9, 29.8, 51.2, 57.5, 124.0 (q, *J* = 272.5 Hz), 124.1 (q, *J* = 272.5 Hz), 125.8 (q, *J* = 3.8 Hz), 125.9, 126.1 (q, *J* = 3.8 Hz), 126.0, 128.2, 130.0 (q, *J* = 32.9 Hz), 132.2, 136.6, 142.7, 142.8,

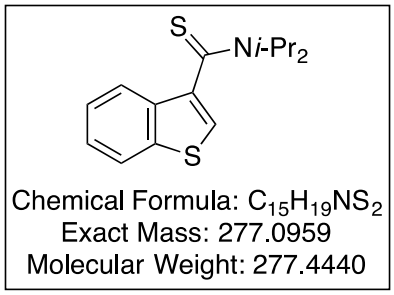
193.5. Some of peaks of carbon atoms in aromatic field were overlapped. MS (EI) *m/z*: 515 (15, M^+), 472 (29, M^+ – *i*-Pr), 415 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{25}H_{23}F_6NS_2$ (M^+); 515.1176, Found 515.1164.

_N,N_-Diisopropyl-2,5-bis(4-methoxyphenyl)thiophene-3-thiocarboamide (8c)



32% yield (35 mg), yellow solid, mp 168.2-169.0 ºC. Rf = 0.22 (*n*-Hexane : EtOAc = 10 : 1). IR (KBr) 1608, 1504, 1261, 1035, 1879 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.57 (br, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.69 (br, 3H), 1.81 (br, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 4.25 (sept, *J* = 6.7 Hz, 1H), 6.88 (d, *J* = 6.1 Hz, 2H), 6.90 (d, *J* = 6.1 Hz, 2H), 7.05 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.0, 19.2, 20.0, 20.9, 51.0, 55.4, 55.5, 57.2, 114.1, 114.4, 123.5, 126.4, 126.7, 127.0, 129.4, 132.0, 140.7, 142.6, 159.4, 159.4, 194.7. MS (EI) *m/z*: 439 (46, M^+), 396 (39, M^+ – *i*-Pr), 339 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{25}H_{29}NO_2S_2$ (M^+); 439.1640, Found: 439.1641.

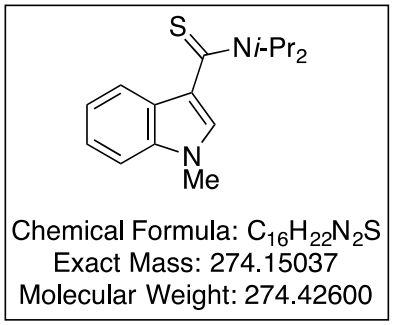
_N,N_-Diisopropylbenzothiophen-3-carboxthioamide (9)



A solution of *N,N*-diisopropylbenzo-3-thiophenecarboxamide (1.0 mmol, 260 mg) was treated with sulfur (1.1 equiv, 35 mg), 1,4-diazabicyclo[2.2.2]octane (1.1 equiv, 120 mg) in toluene (2 mL), and trichlorosilane (1.1 equiv, 0.11 ml). The mixture was stirred at 115 ºC for 5 h, before being quenched by addition of saturated aqueous $NaHCO_3$. Subsequently, the reaction mixture was diluted with Et_2O, filtered, and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 10 : 1, Rf = 0.55) to give analytically pure **11** in 66% yield (180 mg) as a pale yellow solid. mp 191.1-192.0 ºC. IR (KBr) 1482, 1322, 1216, 1146, 734 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (br, 12H), 3.74 (br, 2H), 7.16 (s, 1H), 7.35-7.41 (m, 2H), 7.75-7.77 (m, 1H), 7.84-7.87 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 21.0, 51.3, 57.4, 119.8, 122.6, 124.7, 124.8, 125.0,

136.7, 139.6, 140.3, 193.5. MS (EI) *m/z*: 277 (23, M^+), 234 (18, M^+ – *i*-Pr), 177 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{15}H_{19}NS_2$ (M^+); 277.0959, Found: 277.0954.

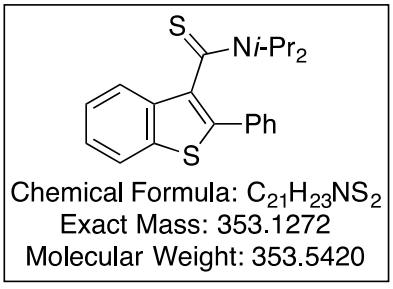
_N,N_-Diisopropyl-1-methyl-1H-indole-3-carbothioamide (10)



Chemical Formula: $C_{16}H_{22}N_2S$
Exact Mass: 274.15037
Molecular Weight: 274.42600

A solution of *N,N*-diisopropyl-1-methyl-1H-indole-3-carboxamide (5.0 mmol, 1.3 g) was treated with sulfur (1.1 equiv, 180 mg), dibenzylamine (1.1 equiv, 1.1 ml) in toluene (10 mL), and trichlorosilane (1.1 equiv, 0.55 mL). The mixture was stirred at 115 ºC for 16.5 h, before being quenched by addition of saturated aqueous $NaHCO_3$. Subsequently, the reaction mixture was diluted with Et_2O, filtered, and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 1 : 4, Rf = 0.41) to give analytically pure **9** in 23% yield (320 mg) as pale yellow. mp 86.6-147.5 ºC (decomposed). IR (KBr) 2965, 1485, 1317, 1224, 745 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.47 (br, 12H), 3.76 (s, 3H), 4.51 (br, 2H), 7.07 (s, 1H), 7.13 (dt, *J* = 6.7, 1.3 Hz, 1H), 7.22 (dt, *J* = 6.7, 1.3 Hz, 1H), 7.25-7.28 (m, 1H), 7.56-7.58 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.6 (2C), 21.5, 109.5, 120.0, 120.3, 121.6, 122.4, 125.4, 126.1, 136.3, 194.4. MS (EI) *m/z*: 274 (10, M^+), 231 (10, M^+ – *i*-Pr), 174 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{16}H_{22}N_2S$ (M^+); 274.1504, Found: 274.1499.

_N,N_-Diisopropyl-2-phenylbenzothiophen-3-carbothioamide (11)

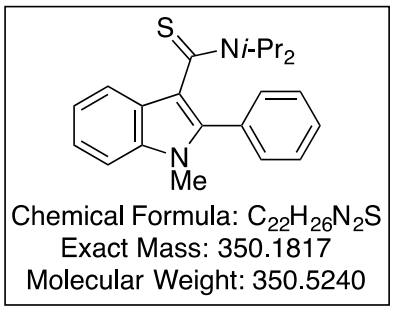


Chemical Formula: $C_{21}H_{23}NS_2$
Exact Mass: 353.1272
Molecular Weight: 353.5420

A screw-capped test tube was charged with Cs_2CO_3 (3 equiv, 250 mg), which was subsequently dried *in vacuo* using a heatgun. Pd(phen)IPh (10 mol%, 12 mg), **11** (0.25 mmol, 69 mg), iodobenzene (3 equiv, 84 μl) and DMA (0.5 M, 0.5 ml) were added to this vessel, before the reaction mixture was stirred for 3 h at 150 °C. After completion of the reaction, the mixture was cooled to room temperature, and filtered through a pad of celite, before being concentrated *in vacuo*. The residue was purified by

flash column chromatography on silica gel (*n*-Hexane : EtOAc = 20 : 1, Rf = 0.47) to give **12** in 51% yield (45 mg) as a yellow solid. mp 195.9-197.6 ºC. IR (KBr) 1492, 1199, 1148, 756, 730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.54 (br, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.76 (br, 3H), 1.92 (br, 3H), 3.89 (br, 1H), 4.05 (sept, *J* = 6.7 Hz, 1H), 7.29-7.41 (m, 5H), 7.75 (dd, *J* = 7.9, 7.2 Hz, 2H), 7.90 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.3, 19.4, 20.0, 21.2, 51.1, 57.4, 122.1, 123.1, 125.0, 125.0, 128.5, 128.8, 128.8, 129.2, 133.5, 138.9, 193.5. MS (EI) *m/z*: 353 (42, M^+), 340 (25, M^+ – *i*-Pr), 253 (100, M^+ – N*i*-Pr_2). HRMS (EI): Exact mass calcd for $C_{21}H_{23}NS_2$ (M^+); 353.1272, Found: 353.1283.

***N,N*-Diisopropyl-1-methyl-2-phenyl-1H-indole-3-carbothioamide (12)**



Chemical Formula: $C_{22}H_{26}N_2S$
Exact Mass: 350.1817
Molecular Weight: 350.5240

A screw-capped test tube was charged with Cs_2CO_3 (3 equiv, 120 mg), which was subsequently dried *in vacuo* using a heatgun. Pd(phen)PhI (10 mol%, 6.1 mg), **9** (0.125 mmol, 35 mg), **2a** (3 equiv, 42 μl) and DMA (0.5 M, 0.25 ml) were added to this vessel, before the reaction mixture was stirred for 3 h at 150 °C. After completion of the reaction, the mixture was cooled to room temperature, and filtered through a pad of celite, before being concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-Hexane : EtOAc = 1 : 4, Rf = 0.53) to give **10** in 62% yield (27 mg) as a yellow solid. mp 218.6-219.1 ºC. IR (KBr) 2965, 1492, 1314, 1200, 746 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.38 (br, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 1.63 (brd, *J* = 6.3 Hz, 3H), 1.88 (br, 3H), 3.69 (s, 3H), 3.75 (br, 1H), 4.24 (sept, *J* = 6.7 Hz, 1H), 7.17 (m, 1H), 7.22-7.26 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.34-7.38 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.65-7.68 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 18.3, 19.3, 20.4, 21.3, 31.4, 50.6, 56.9, 109.7, 119.9, 119.9, 120.7, 122.7, 126.5, 128.3, 128.6, 130.2, 131.2, 131.7, 137.9, 196.3. MS (EI) *m/z*: 350 (12, M^+), 250 (100, M^+ – N*i*-Pr_2), 235 (14, M^+ – N*i*-Pr_2 – Me). HRMS (EI): Exact mass calcd for $C_{22}H_{26}N_2S$ (M^+); 350.1817, Found: 350.1807

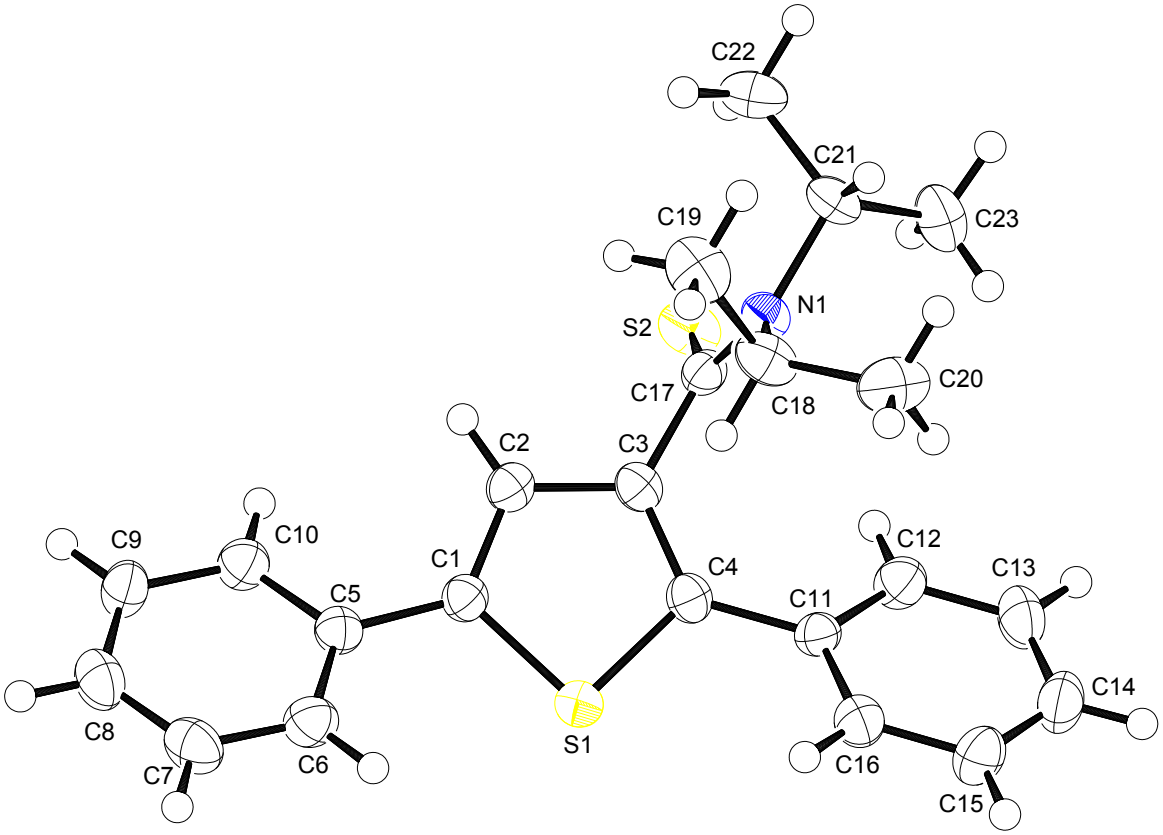


Figure 3. ORTEP drawing of **8a**

Table 5. Crystal data and structure refinement for **8a**

Empirical formula	$C_{23}H_{25}NS_2$	
Formula weight	379.56	
Temperature	293(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 7.4977(14) Å	α= 90°
	b = 11.606(2) Å	β= 91.639(3)°
	c = 23.037(5) Å	γ= 90°
Volume	2003.7(7) $Å^3$	
Z	4	
Density (calculated)	1.258 Mg/m^3	
Absorption coefficient	0.272 mm^{-1}	
F(000)	808	
Crystal size	0.31 x 0.09 x 0.03 mm^3	
Theta range for data collection	1.97 to 27.49°	
Index ranges	-7<=h<=9, -15<=k<=10, -29<=l<=28	
Reflections collected	16661	
Independent reflections	4587 [R(int) = 0.0702]	
Completeness to theta = 27.49°	99.9 %	
Max. and min. transmission	0.9919 and 0.9204	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4587 / 0 / 239	
Goodness-of-fit on F^2	1.088	
Final R indices [I>2sigma(I)]	R_1 = 0.0648, wR_2 = 0.1384	
R indices (all data)	R_1 = 0.1112, wR_2 = 0.1616	
Largest diff. peak and hole	0.295 and -0.339 e.$Å^{-3}$	

Table 6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **8a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3461(1)	4127(1)	2131(1)	33(1)
S(2)	3445(1)	7297(1)	651(1)	39(1)
N(1)	114(3)	6738(2)	935(1)	30(1)
C(1)	3620(4)	3657(2)	1425(1)	29(1)
C(2)	3104(4)	4507(2)	1044(1)	29(1)
C(3)	2505(4)	5524(2)	1324(1)	28(1)
C(4)	2617(4)	5453(2)	1916(1)	29(1)
C(5)	4191(4)	2470(2)	1294(1)	29(1)
C(6)	3893(4)	1563(2)	1672(1)	37(1)
C(7)	4326(5)	455(2)	1528(2)	42(1)
C(8)	5094(5)	214(2)	1005(2)	41(1)
C(9)	5423(4)	1101(2)	625(2)	38(1)
C(10)	4984(4)	2224(2)	768(1)	35(1)
C(11)	2073(4)	6292(2)	2357(1)	29(1)
C(12)	2271(4)	7471(2)	2273(1)	36(1)
C(13)	1706(5)	8239(3)	2693(2)	42(1)
C(14)	970(5)	7851(3)	3195(2)	44(1)
C(15)	800(5)	6681(3)	3289(2)	43(1)
C(16)	1345(4)	5916(2)	2871(1)	37(1)
C(17)	1859(4)	6538(2)	971(1)	28(1)
C(18)	-1202(4)	5958(3)	1208(2)	39(1)
C(19)	-2299(5)	5320(3)	742(2)	49(1)
C(20)	-2355(5)	6584(3)	1639(2)	52(1)
C(21)	-693(4)	7717(2)	592(1)	35(1)
C(22)	-378(5)	7642(3)	-56(2)	45(1)
C(23)	-175(5)	8885(2)	849(2)	54(1)

Table 7. Bond lengths [Å] for **8a**.

S(1)-C(1)	1.722(3)	C(12)-H(12)	0.9300
S(1)-C(4)	1.732(3)	C(13)-C(14)	1.371(5)
S(2)-C(17)	1.669(3)	C(13)-H(13)	0.9300
N(1)-C(17)	1.329(4)	C(14)-C(15)	1.382(4)
N(1)-C(18)	1.491(4)	C(14)-H(14)	0.9300
N(1)-C(21)	1.500(3)	C(15)-C(16)	1.380(4)
C(1)-C(2)	1.370(4)	C(15)-H(15)	0.9300
C(1)-C(5)	1.476(4)	C(16)-H(16)	0.9300
C(2)-C(3)	1.423(4)	C(18)-C(20)	1.521(5)
C(2)-H(2)	0.9300	C(18)-C(19)	1.525(5)
C(3)-C(4)	1.367(4)	C(18)-H(18)	0.9800
C(3)-C(17)	1.502(4)	C(19)-H(19)	0.9600
C(4)-C(11)	1.474(4)	C(19)-H(19A)	0.9600
C(5)-C(6)	1.387(4)	C(19)-H(19B)	0.9600
C(5)-C(10)	1.395(4)	C(20)-H(20)	0.9600
C(6)-C(7)	1.369(4)	C(20)-H(20A)	0.9600
C(6)-H(6)	0.9300	C(20)-H(20B)	0.9600
C(7)-C(8)	1.379(5)	C(21)-C(22)	1.521(5)
C(7)-H(7)	0.9300	C(21)-C(23)	1.525(4)
C(8)-C(9)	1.378(4)	C(21)-H(21)	0.9800
C(8)-H(8)	0.9300	C(22)-H(22)	0.9600
C(9)-C(10)	1.387(4)	C(22)-H(22A)	0.9600
C(9)-H(9)	0.9300	C(22)-H(22B)	0.9600
C(10)-H(10)	0.9300	C(23)-H(23)	0.9600
C(11)-C(16)	1.388(4)	C(23)-H(23A)	0.9600
C(11)-C(12)	1.390(4)	C(23)-H(23B)	0.9600
C(12)-C(13)	1.391(4)		

Symmetry transformations used to generate equivalent atoms.

Table 8. Bond angles [º] for **8a**.

C(1)-S(1)-C(4)	92.62(14)	N(1)-C(17)-S(2)	126.4(2)
C(17)-N(1)-C(18)	122.0(2)	C(3)-C(17)-S(2)	115.4(2)
C(17)-N(1)-C(21)	123.1(2)	N(1)-C(18)-C(20)	112.4(3)
C(18)-N(1)-C(21)	114.8(2)	N(1)-C(18)-C(19)	110.4(3)
C(2)-C(1)-C(5)	128.3(3)	C(20)-C(18)-C(19)	112.7(3)
C(2)-C(1)-S(1)	110.6(2)	N(1)-C(21)-C(22)	113.7(2)
C(5)-C(1)-S(1)	121.1(2)	N(1)-C(21)-C(23)	112.0(3)
C(1)-C(2)-C(3)	113.2(3)	C(22)-C(21)-C(23)	112.7(3)
C(4)-C(3)-C(2)	113.0(2)		
C(4)-C(3)-C(17)	126.6(3)		
C(2)-C(3)-C(17)	120.4(3)		
C(3)-C(4)-C(11)	129.7(3)		
C(3)-C(4)-S(1)	110.5(2)		
C(11)-C(4)-S(1)	119.7(2)		
C(6)-C(5)-C(10)	118.0(3)		
C(6)-C(5)-C(1)	121.8(3)		
C(10)-C(5)-C(1)	120.1(3)		
C(7)-C(6)-C(5)	121.2(3)		
C(6)-C(7)-C(8)	120.6(3)		
C(9)-C(8)-C(7)	119.4(3)		
C(8)-C(9)-C(10)	120.2(3)		
C(9)-C(10)-C(5)	120.6(3)		
C(16)-C(11)-C(12)	118.4(3)		
C(16)-C(11)-C(4)	120.2(3)		
C(12)-C(11)-C(4)	121.4(3)		
C(11)-C(12)-C(13)	119.8(3)		
C(14)-C(13)-C(12)	121.0(3)		
C(13)-C(14)-C(15)	119.7(3)		
C(16)-C(15)-C(14)	119.5(3)		
C(15)-C(16)-C(11)	121.6(3)		
N(1)-C(17)-C(3)	118.2(3)		

Table 9. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **8a**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	37(1)	32(1)	29(1)	2(1)	0(1)	5(1)
S(2)	30(1)	42(1)	45(1)	12(1)	5(1)	-2(1)
N(1)	28(2)	30(1)	32(2)	3(1)	1(1)	3(1)
C(1)	26(2)	31(1)	28(2)	-2(1)	1(1)	1(1)
C(2)	25(2)	35(2)	29(2)	-1(1)	3(1)	-1(1)
C(3)	22(2)	29(1)	33(2)	2(1)	3(1)	0(1)
C(4)	25(2)	29(1)	32(2)	0(1)	3(1)	1(1)
C(5)	27(2)	31(1)	31(2)	0(1)	0(1)	0(1)
C(6)	39(2)	41(2)	32(2)	3(1)	4(2)	1(1)
C(7)	47(2)	28(2)	50(2)	6(1)	-4(2)	-3(1)
C(8)	41(2)	29(2)	52(2)	-5(1)	-2(2)	2(1)
C(9)	43(2)	34(2)	36(2)	-7(1)	4(2)	1(1)
C(10)	38(2)	33(2)	33(2)	1(1)	2(2)	-2(1)
C(11)	27(2)	34(1)	24(2)	-1(1)	-1(1)	4(1)
C(12)	41(2)	35(2)	33(2)	-1(1)	1(2)	-3(1)
C(13)	44(2)	29(2)	52(2)	-8(1)	0(2)	3(1)
C(14)	44(2)	46(2)	42(2)	-14(2)	3(2)	9(2)
C(15)	45(2)	51(2)	34(2)	-4(2)	11(2)	5(2)
C(16)	42(2)	34(2)	35(2)	1(1)	3(2)	4(1)
C(17)	28(2)	31(1)	24(2)	-2(1)	2(1)	1(1)
C(18)	23(2)	44(2)	48(2)	12(1)	2(2)	1(1)
C(19)	33(2)	46(2)	68(3)	-1(2)	-5(2)	-6(2)
C(20)	30(2)	85(3)	41(2)	9(2)	6(2)	2(2)
C(21)	30(2)	36(2)	41(2)	8(1)	-4(2)	7(1)
C(22)	42(2)	51(2)	42(2)	10(2)	-12(2)	1(2)
C(23)	65(3)	35(2)	63(3)	-4(2)	0(2)	14(2)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **8a**.

	x	y	z	U(eq)
H(2)	3142	4428	643	35
H(6)	3390	1711	2028	45
H(7)	4100	-140	1786	50
H(8)	5386	-540	910	49
H(9)	5942	945	272	45
H(10)	5219	2819	511	42
H(12)	2781	7745	1936	43
H(13)	1830	9027	2633	50
H(14)	586	8374	3471	53
H(15)	322	6410	3631	52
H(16)	1221	5129	2935	44
H(18)	-516	5375	1427	46
H(19)	-3047	5859	533	74
H(19A)	-3028	4750	921	74
H(19B)	-1512	4951	478	74
H(20)	-1604	6991	1914	78
H(20A)	-3069	6035	1840	78
H(20B)	-3119	7121	1436	78
H(21)	-1986	7650	634	43
H(22)	836	7845	-129	68
H(22A)	-1167	8164	-260	68
H(22B)	-604	6870	-188	68
H(23)	-386	8884	1258	81
H(23A)	-879	9477	664	81
H(23B)	1067	9027	788	81

References and notes

(1) For recent examples, see: (a) Kan, B.; Zhang, Q.; Liu, F.; Wan, X.; Wang, Y.; Ni, W.; Long, G.; Yang, X.; Feng, H.; Zuo, Y.; Zhang, M.; Huang, F.; Cao, Y.; Russell, T. P.; Chen, Y. *J.* Am. *Chem. Soc.* **2015**, *137*, 3886. (b) Shi, K.; Zhang, F.; Di, C. A.; Yan, T. W.; Zou, Y.; Zhu, D.; Wang, J. Y.; Pei, J. *J. Am. Chem. Soc.* **2015**, *137*, 6979. (c) Hwang, Y. J.; Earmme, T.; Courtright, B. A. E.; Eberle, F. N.; Jenekhe, S. A. *J. Am. Chem. Soc.* **2015**, *137*, 4424. (d) Zhang, C.; Zang, Y.; Gann, E.; McNeill, C. R.; Zhu, X.; Di, C.; Zhu, D. *J. Am. Chem. Soc.* **2014**, *136*, 16176. (e) He, B.; Pun, A. B.; Zherebetskyy, D.; Liu, Y.; Liu, F.; Klivansky, L. M.; McGough, A. M.; Zhang, B. A.; Lo. K.; Russell, T. P.; Wang, L.; Liu, Y. *J. Am. Chem. Soc.* **2015**, *136,* 15093. For a recent review, see: (f) Guo, X.; Facchetti, A.; Marks, T. J. *Chem. Rev.* **2014**, *114*, 8943.

(2) Theoretical and experimental studies revealed a significant decrease of the energy gap between the highest occupied molecular orbital (HOMO) and the LUMO, as well as stronger π-π interactions upon substitution of the carbonyl oxygen with sulfur; see: (a) Lévesque, S.; David, G.; Bérubé, N.; Grenier, F.; Lecterc, M.; Côté, M. *J. Phys. Chem. C* **2014**, *118*, 3953. (b) Bérube, N.; Gaudreau, J.; Côté, M. *Macromolecules* **2013**, *46*, 6873. (c) Mizuguchi, J. *J. Phys. Chem. A* **2001**, *105,* 1125.

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(4) (a) Izuhara, D.; Swager, T. M. *Macromolecules* **2011**, *44*, 2678. (b) Wen. S.; Wang, C.; Ma, P.; Zhao, Y. X.; Li, C. *J. Mater. Chem. A* **2015**, *3*, 13794. (c) Fuji, K; Tamba, S.; Shono, K.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2013**, *135*, 12208.

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(12) The oxidative addition of aryl iodide to Pd(II) complexes with thioamide-based ligands to give Pd(IV) species has been reported; see: Liu, J.; Deng, Y.; Lin, C.; Lei, A. *Chem. Sci.* **2012**, *3*, 1211.

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Chapter 5

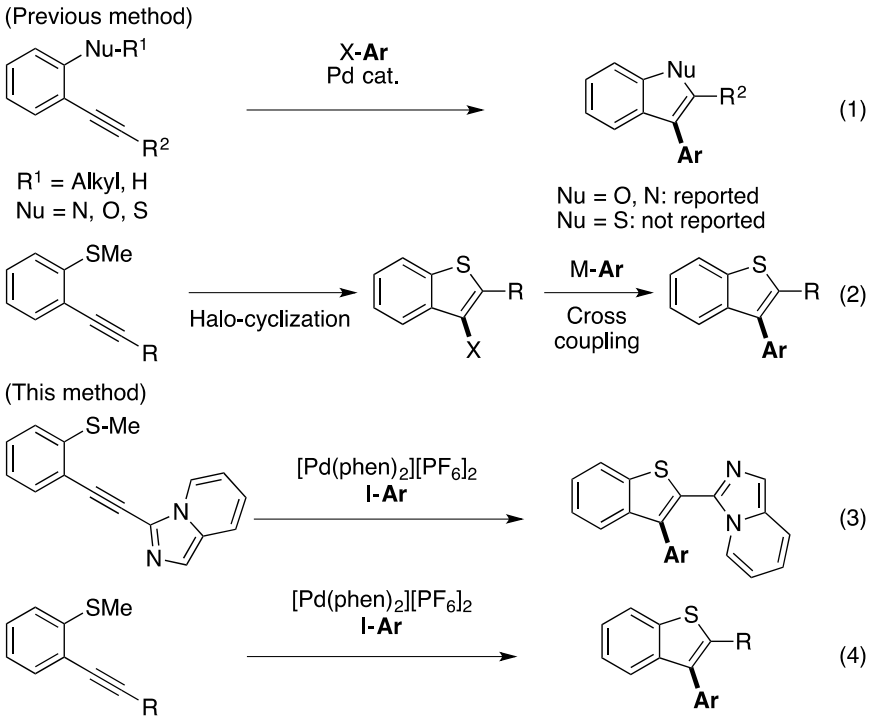
Arylative Cyclization of 2-Alkynylthioanisole by Using Pd-phenanthroline Complexes

The arylative cyclization of *o*-(1-alkynyl)thioanisoles with aryl iodides in the presence of catalytic amounts of $[Pd(phen)_2][PF_6]_2$ resulted in the efficient formation of 3-arylated benzo[*b*]thiophenes, and a range of aryl iodides with electron-donating or –withdrawing groups could be used. While this reaction proceeded in the presence of aromatic and aliphatic groups on the terminal alkynyl carbon atom, silyl and alkoxycarbonyl groups hampered the reaction. Furthermore, this method could be extended to the synthesis of 3-arylated indoles from *N,N*-dimethyl-*o*-(1-alkynyl)aniline. All these reactions proceeded smoothly via cleavage of the carbon-heteroatom bond. In addition to the desired cyclization products, the use of a *o*-(hydroxypropyl)phenylmethyl substituent on the sulfur atom afforded isochroman, which should be formed by the intramolecular attack of a hydroxy group onto the benzylic carbon atom.

5.1. Introduction

For the construction of benzazoles, π-acidic transition metal-mediated intramolecular cyclizations of 1-alkynylarenes with tethered heteroatom nucleophiles at the *o*-position proved to be very efficient.[1] In the context of these cyclization reactions, Cacchi *et al.*, Larock *et al.*, and others reported that Pd-catalyzed arylative cyclizations of alkynylarenes, containing nucleophilic groups in close proximity with e.g. nitrogen and oxygen atoms, represent powerful tools for the formation of 3-arylated benzazoles (eq. 1).[2] These reactions can be carried out using readily available *o*-alkynylarenes as starting materials in the presence of a wide variety of Pd catalysts. As these reactions are widely applicable and compatible with a broad range of functional groups, a wide variety of substituted benzazoles can thus be obtained. However, this method is not suitable for the synthesis of 3-arylated benzo[*b*]thiophenes, as sulfur atoms often deactivate transition metal catalysts.[3] Therefore, a two step synthesis of 3-arylated benzo[*b*]thiophenes, including halo-cyclization of *o*-(1-alkynyl)thioanisoles and a cross-coupling reaction of 3-halogenated benzothio[*b*]phenes with metalated arenes is utilized (eq. 2).[4] During the course of his study, 3-arylated benzo[*b*]thiophenes were obtained unexpectedly from the reaction of heteroaryl-substituted *o*-(1-alkynyl)thioanisole and aryl halides under direct arylation conditions using $[Pd(phen)_2][PF_6]_2$ (eq. 3). This reaction proceeded via an arylative cyclization involving the cleavage of the C-S bond. The author envisioned that such arylative cyclizations should represent a more efficient synthetic route to 3-arylated benzo[*b*]thiophenes compared to the corresponding halo-cyclization/cross-coupling

methods, and consequently carried out further investigations. Below, he describs the first examples for a Pd/phenanthroline-catalyzed arylative cyclization of *o*-(1-alkynyl)thioanisoles and aryl iodides to afford 3-arylated benzo[*b*]thiophenes (eq. 4).



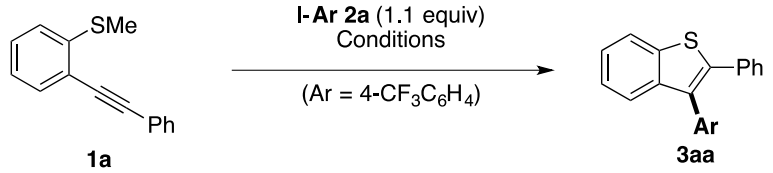
5.2. Results and Discussions

5.2.1. Optimization of Arylative Cyclization

Initially, the author treated *o*-(1-alkynyl)thioanisole **1a** with aryl iodide **2a** using the arylative cyclization conditions reported for *N,N*-dialkyl-*o*-(1-alkynyl)anilines[2c-d,] and *o*-(1-alkynyl)anisoles.[5] However, these conditions did not furnish the desired product (**3**) (Table 1, entries 1 and 2). In contrast, the use of $[Pd(phen)_2][PF_6]_2$ (5 mol%) as a catalyst yielded the desired product **3aa**, which was confirmed by GC-MS, albeit in fairly low yield (entry 2). The addition of Na_2CO_3 furnished **3aa** in higher yield (entry

4), and further tests of other inorganic salts revealed that Cs_2CO_3 provided the best results (entry 6).

Table 1. Arylative cyclization of *o*-(1-alkynyl)thioanisoles **1a**

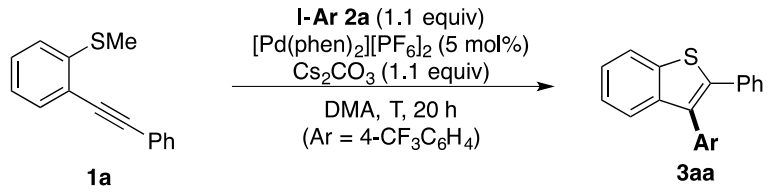


entry	conditions	yield
1	$Pd(PPh)_2Cl_2$ (10 mol%), *n*-Bu_4NI (10 mol%) CH_3CN, 90 ºC (MW), 1 h	n.d.
2[b]	$Cu(OTf)_2$ (10 mol%), DCE, 60 ºC, 10 h	n.d.
3	$[Pd(phen)_2][PF_6]_2$ (5 mol%), DMA, 150 ºC, 20 h	trace
4	$[Pd(phen)_2][PF_6]_2$ (5 mol%), Na_2CO_3 (1.1 equiv), DMA, 150 ºC, 20 h	24%
5	$[Pd(phen)_2][PF_6]_2$ (5 mol%), K_2CO_3 (1.1 equiv), DMA, 150 ºC, 20 h	24%
6	$[Pd(phen)_2][PF_6]_2$ (5 mol%), Cs_2CO_3 (1.1 equiv), DMA, 150 ºC, 20 h	46%[c]

[a] Yields determined by GC analysis using *n*-heptadecane as an internal standard; [b] Ph_2IPF_6 was used instead of I-Ar; [c] isolated yield; [d] n.d. = not detected.

Subsequently, the author tried to optimize the reaction temperature, as starting material **1a** was completely consumed at 150 ºC, but the yield of **3aa** was only moderate (Table 2, entry 1). Decreasing the reaction temperature to 120 ºC increased the yield of **3aa** to 66% (entry 2), whereas lower yields were obtained at 110 ºC (entry 3) and 70 ºC (entry 4). Prolonging the reaction time did not increase the yield of **3aa** (entry 5).

Table 2. Optimization of reaction conditions



entry	T (ºC)	yield[a]	conv.	entry	T (ºC)	yield[a]	conv.
1	150	46%[b]	100%	4	90	5%	7%
2	120	78%(66%[b])	72%	5[c]	120	60%	89%
3	110	33%	33%				

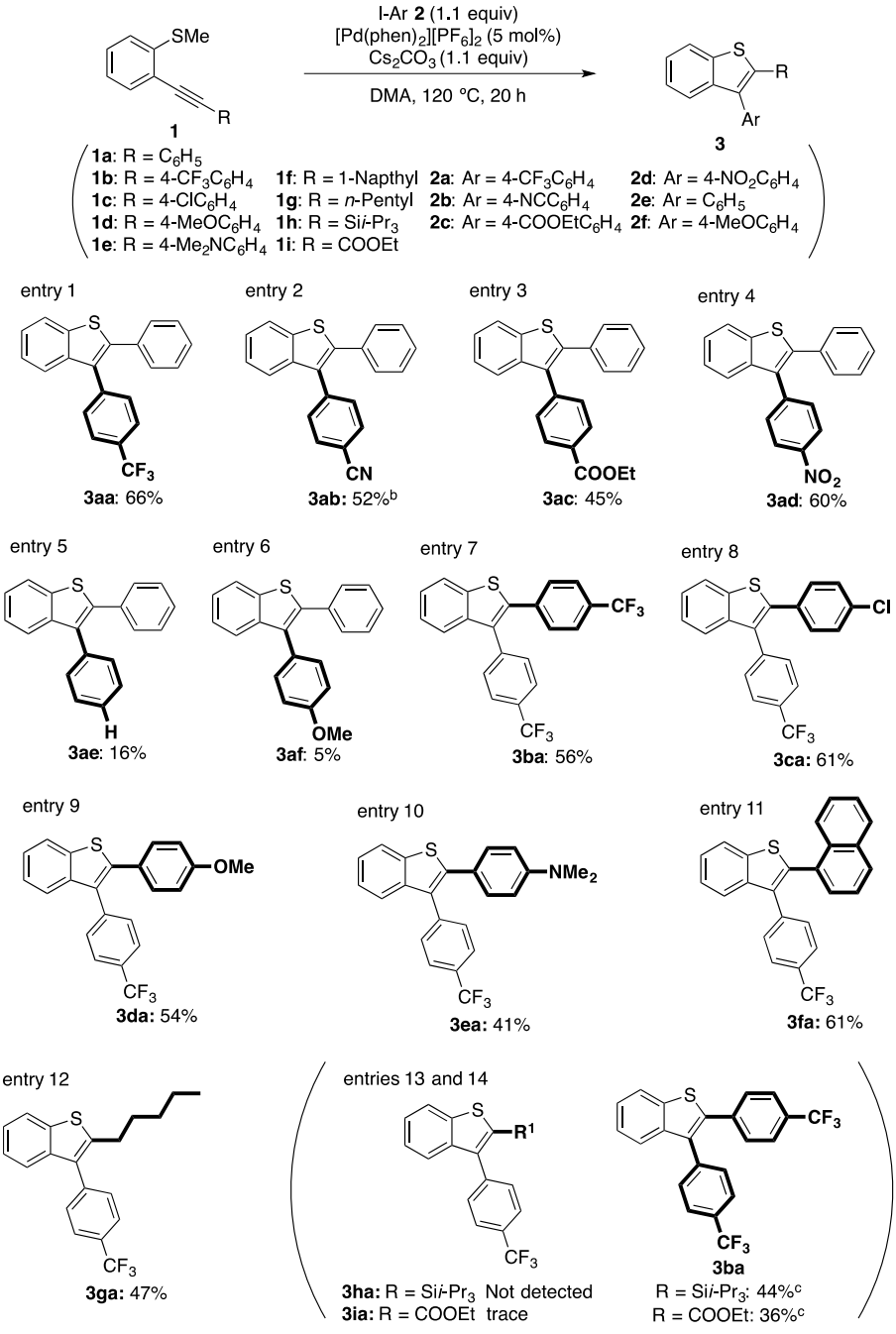
[a] Yields determined by GC analysis using *n*-heptadecane as an internal standard; [b] isolated yield; [c] t = 31 h.

5.2.2. Scope of Substrates

With optimized conditions in hand, the author examined the scope of this arylative cyclization with respect to *o*-(1-alkynyl)thioanisoles **1** and aryl iodides **2** (Scheme 1). The author observed that the electronic properties of the aromatic rings in **2** had a strong impact on the yield of **3** (entries 1-6). For instance, reactions with **2a-d**, which contain electron-withdrawing -CF_3, -CN, -COOEt, and -NO_2 groups, afforded the arylative cyclization products **3aa-3ad** in good yield (entries 1-4). In contrast, low yields were obtained when 4-iodoanisole (**2e**) and iodobenzene (**2f**) were used (entries 5 and 6). The reaction of various *o*-(1-alkynyl)thioanisoles **1a-f** with **2a** furnished the corresponding benzo[*b*]thiophenes **3ba-3fa** in good yield, regardless of the electronic character and steric hindrance of the aromatic groups (R) attached to the alkynyl carbon atoms (entries 7-11). Substrate **1g**, which carried an alkyl group on the alkynyl carbon atom, also afforded the arylative cyclization product **3ga** in 47% yield (entry 12). Silyl **1h** and alkoxycarbonyl groups **1i** were not compatible with these arylative cyclization

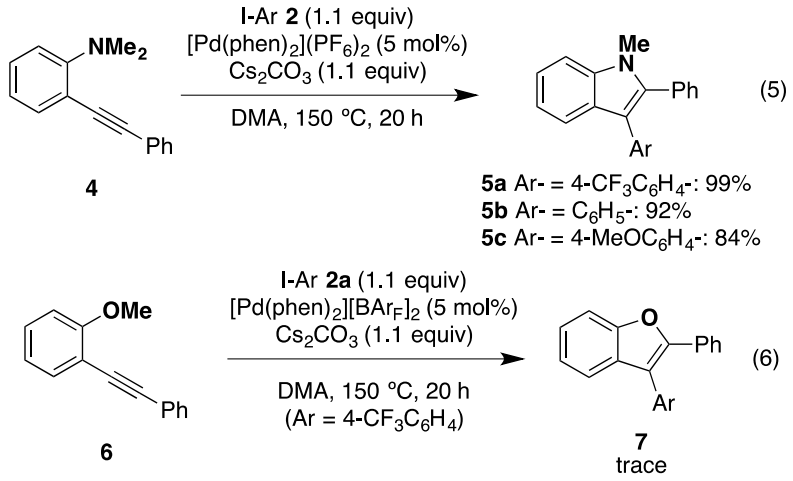
conditions, and yielded 2,3-diarylated benzo[*b*]thiophene **3ba** in 44% and 39%, respectively (entries 13 and 14).

Scheme 1. Substrate scope of the arylative cyclization of *o*-(1-alkynyl)thioanisoles **1** and I-Ar **2**



[a] Isolated yield; [b] K_2CO_3 was used instead of Cs_2CO_3; [c] relative to the amount of I-Ar.

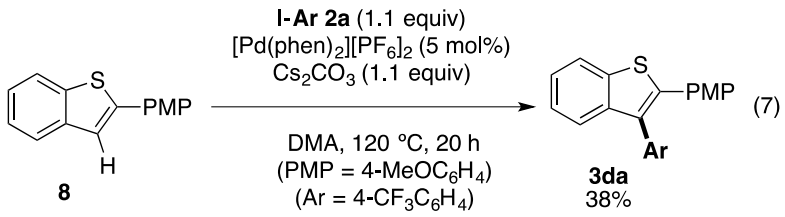
The author then turned his attention to the reaction of other nucleophilic heteroatom-containing *o*-(1-alkynyl)arenes. Initially, the arylative cyclization of *N,N*-dimethyl-*o*-(1-alkynyl)aniline **4** proceeded smoothly to afford the corresponding 3-arylated indoles **5** in excellent yield, regardless of the electronic character of the aryl iodides **2**, albeit that higher reaction temperatures were required (eq. 5). However, when [Pd(phen)][BAr_F]$_2$ (BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenylborate]) was used as a catalyst, a reaction using *o*-(1-alkynyl)anisole **6** produced merely trace amounts of 3-arylated benzofuran **7** (eq. 6).



5.2.3. Mechanistic Studies

It became clear that the following question requires answering: does the intramolecular cyclization of *o*-(1-alkynyl)thioanisoles **1** initially generates a 3-unsubstituted benzo[*b*]thiophene, which is subsequently transformed into 3-arylated benzo[*b*]thiophene **3** via C-H bond arylation. When the preformed 3-unsubstituted benzo[*b*]thiophene **8** was treated with aryl iodide **2a** under arylative cyclization conditions, 3-arylated benzo[*b*]thiophene **3da** was obtained (eq. 7). However, the yield was substantially lower than in the reaction with the corresponding alkyne **1d** (*cf.*

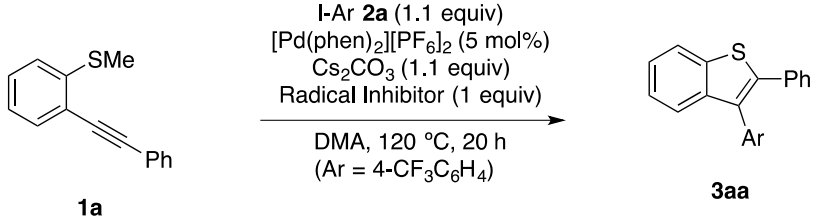
Scheme 1, entry 9). Furthermore, the reaction of *o*-(1-alkynyl)thioanisoles **1** in the absence of aryl iodides **2** under arylative cyclization conditions did not proceed at all. These results indicate that the present reaction should be a tandem, rather than a one-pot reaction.



(7)

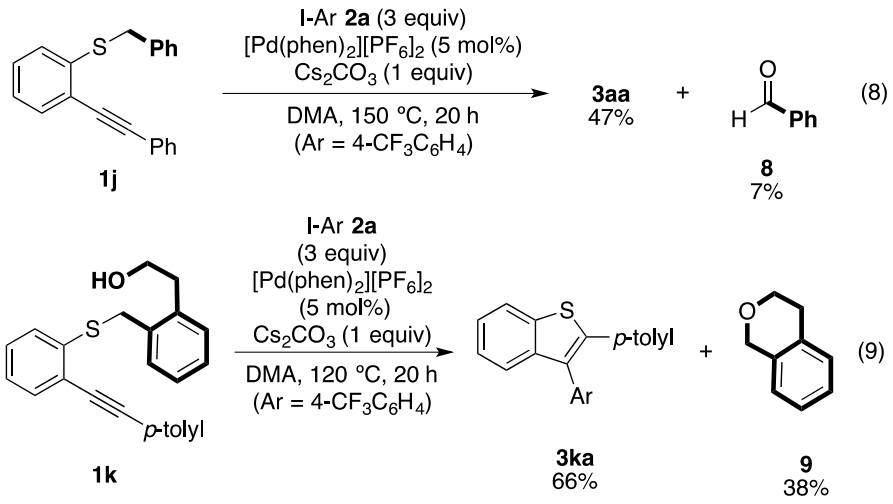
In order to gain insight into the reaction mechanism of the cleavage of the C-S bond during the arylative cyclization of **1**, further examinations were carried out. For similar transition metal-catalyzed intramolecular cyclizations of *o*-(1-alkynyl)arenes, usually an S_N2-type cleavage of the carbon-heteroatom bond is proposed.[6] Alternatively, the involvement of radical species is conceivable.[7] However, the addition of radical inhibitors such as Galvinoxyl, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), or dibutylhydroxytoluene (BHT) did not hamper the arylative cyclization (Table 3).

Table 3. Effect on addition of radical inhibitors



entry	Radical inhibitor	**3aa**	conv.
1	Galvinoxyl	63%	75%
2	TEMPO	53%	71%
3	BHT	60%	81%
4	-	66%	72%

In order to capture the substituents eliminated from the sulfur atom, we prepared a substrate with a bulky substituent on the sulfur atom, and treated it with aryl iodide **2a** under identical cyclization conditions. Using (*o*-alkynylphenyl)sulfide **1j** as a substrate furnished, in addition to the arylative cyclization product **3aa**, benzaldehyde (**8**) in 7% yield, even though the mass balance of the reaction was low (eq. 8). The low yield of the products derived from the benzyl group on the sulfur atom may be due to several follow-up reactions of the initially formed products. To efficiently trap the substituents of the sulfur atom, we envisioned an approach, in which the substituents within the starting material trap themselves. Accordingly, we carried out the $[Pd(phen)_2][PF_6]_2$-catalyzed reaction between **1k** and **2a** (eq. 9). In this case, the intramolecular S_N2 cyclization of the substituent on the sulfur atom occurred readily and generated isochroman (**9**) in 38% yield in addition to **3ka** (66%).



5.3. Conclusion

In conclusion, the author developed an arylative cyclization between *o*-(1-alkynyl)thioanisoles (**1**) and aryl iodides (**2**), involving a demethylation and subsequent coupling reaction with aryl halides. To the best of his knowledge, this study presents the first examples of arylative cyclizations via the cleavage of the C-S bonds in *o*-(1-alkynyl)thioanisoles. The addition of inorganic salts such as Cs_2CO_3 was essential for this arylative cyclization, although its role in the reaction still remains to be ascertained. Nevertheless, a range of aromatic substituents could be incorporated into the products **3**.

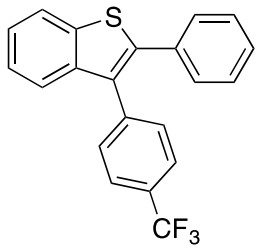
5.4. Experimental

General procedure for arylative cyclization of *o*-(1-alkynyl)thioanisoles 1

$[Pd(phen)_2][PF_6]_2$ (5 mol%, 10 mg), *o*-(1-alkynyl)thioanisoles **1** (0.25 mmol), aryl iodides **2** (1.1 equiv), and DMA (0.5 M, 0.50 ml) were added to a screw-capped test tube under an argon atmosphere. After completion of the reaction, the mixture was cooled to room temperature, and filtered through a pad of celite, before being concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give **3**.

Spectroscopic data for 3

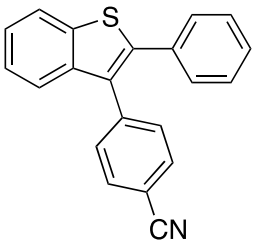
2-Phenyl-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene[8] (3aa)



Chemical Formula: $C_{21}H_{13}F_3S$
Exact Mass: 354.0690
Molecular Weight: 354.3902

66% yield (58 mg), colorless solid, Rf = 0.80 (*n*-hexane). ^{1}H NMR ($CDCl_3$) δ 7.26-7.29 (m, 5H), 7.33-7.40 (m, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.54-7.56 (m, 1H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.87-7.90 (m, 1H).

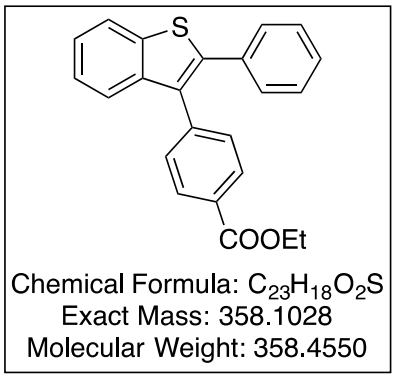
2-Phenyl-3-(4-cyanophenyl)benzo[*b*]thiophene (3ab)



Chemical Formula: $C_{21}H_{13}NS$
Exact Mass: 311.0769
Molecular Weight: 311.4020

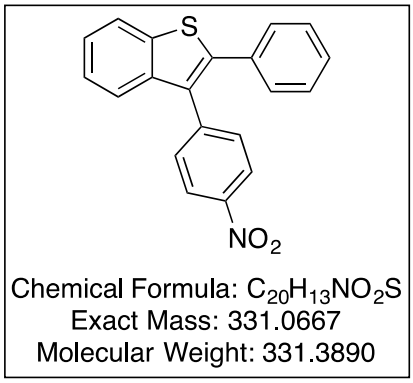
52% yield (40 mg), colorless solid, mp 138.9-139.8 ºC. Rf = 0.59 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 2227, 1604, 1430, 854, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.24-7.29 (m, 5H), 7.34-7.41 (m, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.53-7.56 (m, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.88-7.90 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 112.2, 119.0, 122.4, 122.8, 125.0, 125.0, 128.4, 128.8, 129.8, 131.2, 131.3, 132.6, 133.5, 139.1, 139.9, 140.7, 141.5. MS (EI) m/z: 311 (100, M^+), 296 (9, M^+–N–H). HRMS (EI): Exact mass calcd for $C_{21}H_{13}NS$ (M^+); 311.0769, Found: 311.0744.

2-Phenyl-3-(4-ethoxycarbonylphenyl)benzo[*b*]thiophene (3ac)



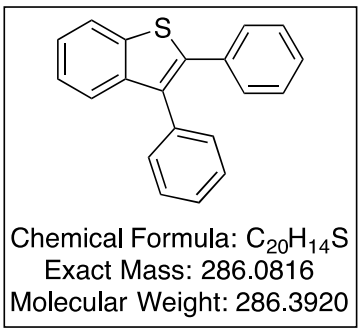
31% yield (40 mg), colorless solid, mp 127.8-132.8 ºC. Rf = 0.42 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 1715, 1270, 1110, 1096, 1020, 757, 737, 691 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.22-7.29 (m, 5H), 7.31-7.38 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.54-7.57 (m, 1H), 7.85-7.87 (m, 1H), 8.06 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.5, 61.1, 122.3, 123.1, 124.8, 124.8, 128.1, 128.6, 129.5, 129.8, 130.0, 130.6, 132.2, 133.9, 139.1, 140.4, 140.5, 140.6, 166.6. MS (EI) m/z: 358 (M^+), 285 (33, M^+–COOEt). HRMS (EI); Exact mass calcd for $C_{23}H_{18}O_2S$ (M^+); 358.1028, Found 358.1030.

2-Phenyl-3-(4-nitrophenyl)benzo[*b*]thiophene (3ad)



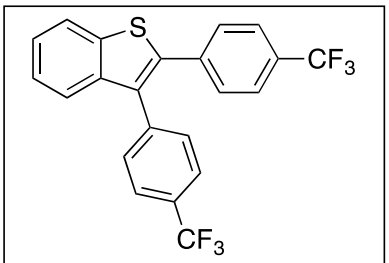
60% yield (50 mg), yellow solid, mp 88.0-90.8 ºC. Rf = 0.50 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 1521, 1483, 1347, 856, 708 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.26-7.30 (m, 5H), 7.36-7.42 (m, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.56-7.58 (m, 1H), 7.89-7.91 (m, 1H), 8.25 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 114.1, 122.5, 122.7, 125.1, 125.1, 126.0, 128.5, 128.8, 129.8, 130.9, 131.5, 139.2, 139.8, 141.8, 142.8, 147.1. MS (EI) m/z: 331 (M^+). HRMS (EI): Exact mass calcd for $C_{20}H_{13}NO_2S$ (M^+); 331.0667, Found 331.0663.

2,3-Disphenylbenzo[*b*]thiophene[9] (3ae)



15% yield (11 mg), colorless solid, Rf = 0.68 (*n*-hexane). ^1H NMR ($CDCl_3$) δ 7.23-7.25 (m, 3H), 7.30-7.39 (m, 9H), 7.57-7.60 (m, 1H,), 7.86-7.88 (m, 1H).

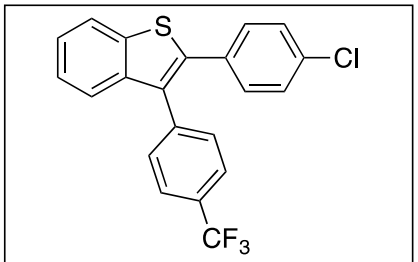
2,3-Bis(4-trifluoromethylphenyl)benzo[*b*]thiophene (3ba)



Chemical Formula: $C_{22}H_{12}F_6S$
Exact Mass: 422.0564
Molecular Weight: 422.3884

56% yield (59 mg), colorless solid, mp 127.3-131.8 ºC. Rf = 0.48 (*n*-hexane). IR (KBr) 1615, 1324, 1169, 1121, 1066, 1018, 818 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36-7.42 (m, 4H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.54-7.57 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.89-7.91 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 122.5, 123.3, 124.0 (q, *J* = 272.5 Hz), 124.2 (q, *J* = 271.6 Hz), 125.1, 125.4, 125.6 (q, *J* = 3.7 Hz), 126.0 (q, *J* = 3.8 Hz), 129.9, 130.0 (q, *J* = 32.9 Hz), 130.1 (q, *J* = 32.8 Hz), 130.8, 133.0, 137.5, 138.8, 138.9, 139.2, 140.2. ^{19}F NMR ($CDCl_3$) δ –58.9, –59.1. MS (EI) m/z: 422 (100, M^+), 353 (13, $M^+–CF_3$), 284 (27, $M^+–2CF_3$). HRMS (EI); Exact mass calcd for $C_{22}H_{12}F_6S$ (M^+); 422.0564, Found 422.0564.

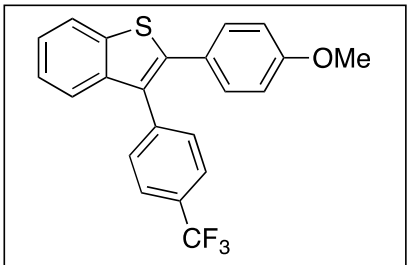
2-(4-Chlorophenyl)-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene (3ca)



Chemical Formula: $C_{21}H_{12}ClF_3S$
Exact Mass: 388.0300
Molecular Weight: 388.8322

61% yield (59 mg), colorless solid, mp 165.6-166.5 ºC. Rf = 0.68 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 1327, 1157, 1124, 1066, 833 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.34-7.41 (m, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.53-7.55 (m, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.87-7.89 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 123.3, 123.1, 124.2 (q, *J* = 272.2 Hz), 125.9, 125.2, 125.9 (q, *J* = 3.8 Hz), 128.9, 129.8 (q, *J* = 32.6 Hz), 130.9, 130.9, 132.2, 132.3, 134.3, 139.0, 139.1, 139.4, 140.2. MS (EI) m/z: 388 (100, M^+), 390 (36, M^++2), 284 (10, $M^+–Cl–CF_3$). HRMS (EI): Exact mass calcd for $C_{21}H_{12}ClF_3S$ (M^+); 388.0300, Found: 388.0295.

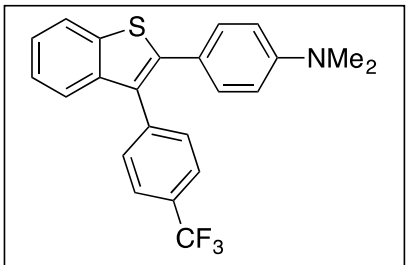
2-(4-Methoxyphenyl)-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene[9] (3da)



Chemical Formula: $C_{22}H_{15}F_3OS$
Exact Mass: 384.0796
Molecular Weight: 384.4162

54% yield (52 mg), colorless solid, Rf = 0.60 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 6.80 (d, *J* = 8.9 Hz, 2H), 7.20 (d, *J* = 8.9 Hz, 2H), 7.31-7.38 (m, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.51-7.55 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.85-7.88 (m, 1H).

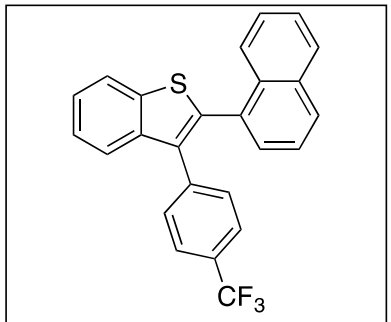
2-(4-Dimethylaminophenyl)-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene (3ea)



Chemical Formula: $C_{23}H_{18}F_3NS$
Exact Mass: 397.1112
Molecular Weight: 397.4592

41% yield (41 mg), colorless solid, mp 198.1-199.9 ºC. Rf = 0.47 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 1602, 1326, 1155, 1112, 1064 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.95 (s, 6H), 6.61 (br, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.30-7.33 (m, 2H), 7.47-7.49 (m, 3H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.83-7.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 40.3, 112.0, 121.2, 122.2, 122.4, 124.2, 124.6, 124.5 (q, *J* = 271.1 Hz), 125.7 (q, *J* = 125.7), 129.2 (q, *J* = 32.6 Hz), 129.5, 13.5, 131.0, 138.5, 140.2, 140.8, 141.9, 150.1. MS (EI) *m/z*: 397 (100, M^+), 284 (12, M^+–CF_3–NMe_2). HRMS (EI): Exact mass calcd for $C_{23}H_{18}F_3NS$ (M^+); 397.1112, Found: 397.1096.

2-(1-Napthyl)-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene (3fa)

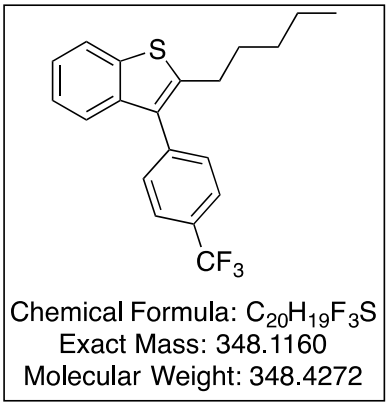


Chemical Formula: $C_{25}H_{15}F_3S$
Exact Mass: 404.0847
Molecular Weight: 404.4502

61% yield (61 mg), colorless solid, mp 143.5-144.4 ºC. Rf = 0.30 (*n*-hexane). IR (KBr) 1616, 1323, 1018, 1119, 1065 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.40-7.47 (m, 8H), 7.73-7.74 (m, 1H), 7.85-7.87 (m, 3H), 7.94-7.95 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 122.3, 123.1, 123.9 (q, *J* = 272.2 Hz), 124.9, 125.0, 125.1, 125.3 (q, *J* = 3.8 Hz), 125.9, 126.2, 126.6, 128.4, 129.1 (q, *J* = 32.6 Hz), 129.3, 129.7, 130.1, 131.2, 132.6, 133.5, 134.4, 139.0, 139.1, 130.3, 140.0. ^{19}F NMR ($CDCl_3$) δ –62.5. MS (EI) *m/z*: 404 (100, M^+), 335 (6, M^+–CF_3). HRMS (EI): Exact

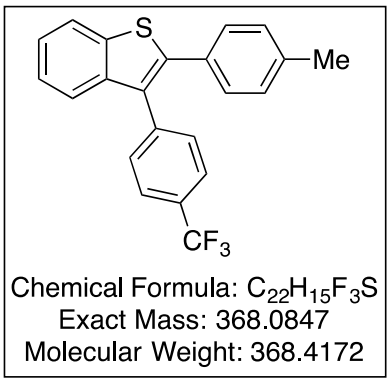
mass calcd for $C_{25}H_{15}F_3S$ (M^+); 404.0847, Found: 404.0858.

2-*n*-Pentyl-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene (3ga)



47% yield (41 mg), colorless oil, Rf = 0.58 (*n*-hexane). IR (KBr) 2957, 2928, 2857, 1325, 1167, 1126, 1106, 1065 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.25-1.31 (m, 4H), 1.63-1.71 (t, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 7.38-7.41 (m, 1H), 7.26-7.32 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.80-7.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.4, 28.8, 31.4, 31.5, 122.2, 122.3, 124.1, 124.3 (q, *J* = 272.5 Hz), 124.4, 125.6 (q, *J* = 3.8 Hz), 129.5 (q, *J* = 32.0 Hz), 130.5, 132.1, 138.3, 139.5, 140.0, 143.7. ^{19}F NMR ($CDCl_3$) δ –58.8. MS (EI) m/z: 348 (84, M^+), 291 (100, M^+–C_4H_9), 222 (45, M^+–C_4H_9–CF_3). HRMS (EI): Exact mass calcd for $C_{20}H_{19}F_3S$; 348.1160, Found: 348.1162.

2-(4-Methylphenyl)-3-(4-trifluoromethylphenyl)benzo[*b*]thiophene (3ka)



66% yield (61 mg), colorless solid, mp 131.6-132.0 ºC. Rf = 0.50 (*n*-hexane). IR (KBr) 1330, 1159, 1119, 1066 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.32-7.39 (m, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.52-7.55 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.86-7.88 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.3, 122.3, 122.9, 124.3 (q, *J* = 272.2 Hz), 124.7, 125.7 (q, *J* = 125.7 Hz), 129.4 (q, *J* = 32.6 Hz), 129.4, 129.6, 130.8, 130.9, 131.3, 138.2, 138.9, 139.6, 140.4, 141.1 (Two peaks are overlapped). MS (EI) *m/z*: 368 (100, M^+), 352 (12, M^+–Me), 284 (20, M^+–Me–CF_3). HRMS (EI): Exact mass calcd for $C_{22}H_{15}F_3S$ (M^+); 368.0847, Found: 368.0850.

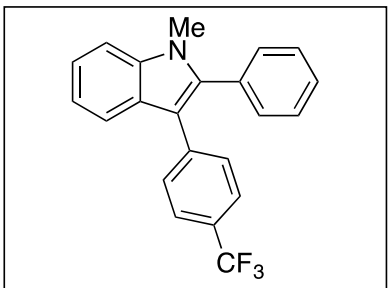
General procedure for arylative cyclization of *N,N*-dimethyl-2-alkynylanilines

$[Pd(phen)_2][PF_6]_2$ (5 mol%, 10 mg), Cs_2CO_3 (1.1 equiv, 85 mg), *N,N*-dimethyl-*o*-(1-alkynyl)aniline **4** (0.25 mmol, 55 mg), aryl iodides **2** (1.1 equiv), and DMA (0.5 M, 0.5 ml) were added to a screw-capped test tube. The reaction mixture was

stirred for 20 h at 150 °C. After completion of the reaction, the mixture was cooled to room temperature, and filtered through a pad of celite, before being concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel.

Spectroscopic data for 5

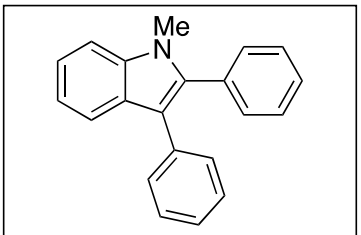
1-Methyl-2-phenyl-3-(4-(trifluoromethyl)phenyl)-*1H*-indole[10] (5a)。



Chemical Formula: $C_{22}H_{16}F_3N$
Exact Mass: 351.1235
Molecular Weight: 351.3722

99% yield (87 mg), colorless solid, Rf = 0.53 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3H), 7.01 (t, *J* = 7.5 Hz, 1H), 7.11-7.15 (m, 5H), 7.20-7.26 (m, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H).

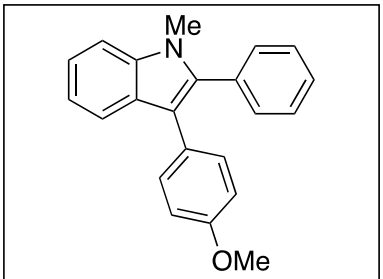
1-Methyl-2,3-diphenyl-*1H*-indole[9] (5b)



Chemical Formula: $C_{21}H_{17}N$
Exact Mass: 283.1361
Molecular Weight: 283.3740

92% yield (65 mg), yellow solid, Rf = 0.54 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 7.15-7.21 (m, 2H), 7.24-7.26 (m, 2H), 7.27-7.34 (m, 5H), 7.36-7.39 (m, 3H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H).

1-Methyl-2-phenyl-3-(4-methoxyphenyl)-*1H*-indole[11] (5c)



Chemical Formula: $C_{22}H_{19}NO$
Exact Mass: 313.1467
Molecular Weight: 313.4000

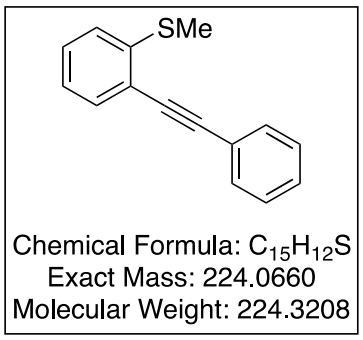
84% yield (66 mg), yellow solid, Rf = 0.40 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.80 (s, 3H), 6.83 (d, *J* = 8.1 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.26-7.41 (m, 3H), 7.54-7.56 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 1H).

General procedure for synthesis of *o*-(1-alkynyl)arenes 1a-i, 4, 6

To a solution of *2*-iodothioanisole (5.0 mmol, 1.3 g), $PdCl_2(PPh_3)_2$ (2.0 mol%, 70 mg), and CuI (1.0 mol%, 10 mg) in Et_3N (20 mL) (stirring for 5 min) was added dropwise terminal alkyne (1.2 equiv) in 5.0 mL of Et_3N over 10 min. The reaction flask was flushed with Ar and the mixture was stirred at room temperature for 2 h. The resulting solution was diluted with EtOAc, filtered through a pad of celite. The solution was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give *o*-(1-alkynyl)arenes **1**.

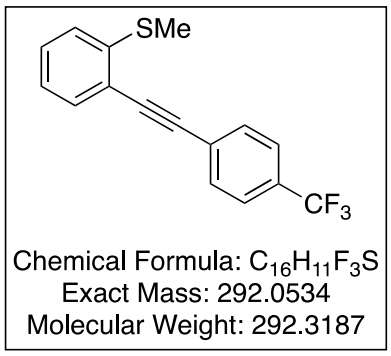
Spectroscopic data for 1a-i, 4, and 6

***o*-(1-Alkynylphenyl)thioanisole[12] (1a)**



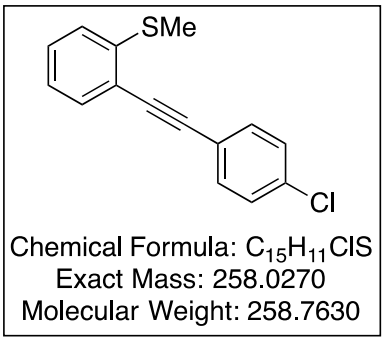
100% yield (1.1 g), yellow oil, Rf = 0.33 (*n*-hexane). ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.27-7.36 (m, 5H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.56-7.58 (m, 2H).

2-(4-Trifluoromethylphenylethynyl)thioanisole (1b)



58% yield (847 mg), yellow oil, Rf = 0.38 (*n*-hexane). IR (KBr) 2923, 2217, 1614, 1463, 1436, 1323, 1168, 1125, 1064, 842, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H). 7.48 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 15.1, 89.3, 94.4, 120.6, 124.0 (q, *J* = 271.5 Hz), 124.2, 124.4, 125.4 (q, *J* = 3.8 Hz), 127.1, 129.4, 130.1 (q, *J* = 32.6 Hz), 131.9, 132.5, 142.2. ^{19}F NMR ($CDCl_3$) δ –59.2. MS (EI) m/z: 292 (100, M^+), 147 (62, M^+–$CF_3C_6H_4$). HRMS (EI): Exact mass calcd for $C_{16}H_{11}F_3S$ (M^+); 292.0534, Found 292.0536.

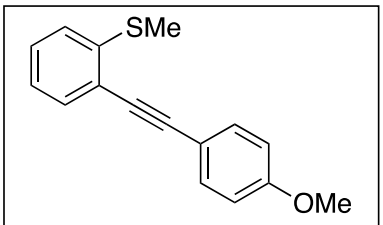
2-(4-Chlorophenylethynyl)thioanisole[13] (1c)



Chemical Formula: $C_{15}H_{11}ClS$
Exact Mass: 258.0270
Molecular Weight: 258.7630

86% yield (1.1 g), yellow oil, Rf = 0.61 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.45-7.51 (m, 1H), 7.50 (d, *J* = 8.6 Hz, 2H).

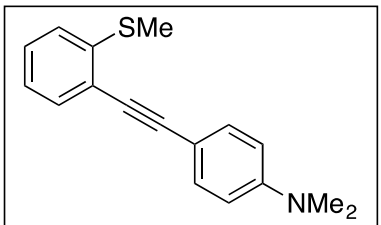
2-(4-Methoxyphenylethynyl)thioanisole[14] (1d)



Chemical Formula: $C_{16}H_{14}OS$
Exact Mass: 254.0765
Molecular Weight: 254.3468

100% yield (1.3 g), colorless solid, Rf = 0.15 (*n*-hexane). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 3.82 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H).

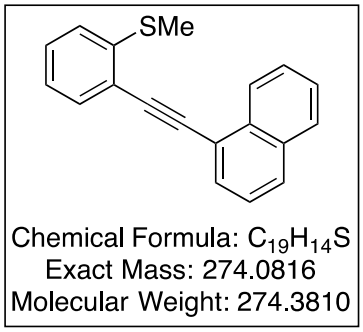
2-(4-Dimethylaminophenylethynyl)thioanisole (1e)



Chemical Formula: $C_{17}H_{17}NS$
Exact Mass: 267.1082
Molecular Weight: 267.3900

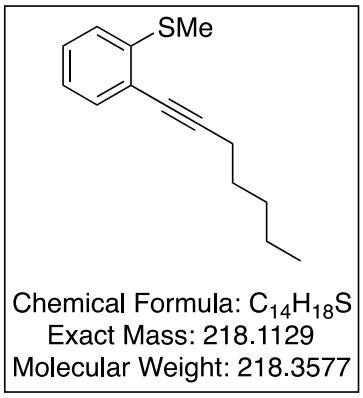
98% yield (1.3 g), brown solid, mp 75.6-76.5 ºC. Rf = 0.40 (*n*-hexane : EtOAc = 10 : 1). IR (KBr) 2204, 1604, 1519, 1358, 821, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.99 (s, 6H), 6.66 (brd, *J* = 8.2 Hz, 2H), 7.06-7.10 (m, 1H), 7.14-7.16 (m, 1H), 7.23-7.27 (m, 1H), 7.43-7.46 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 15.2, 40.4, 85.0, 97.4, 110.0, 111.9, 122.3, 124.1, 124.3, 128.1, 131.9, 132.8, 141.1, 150.3. MS (EI) *m/z*: 267 (100, M^+), 208 (4, M^+–NMe_2–Me). HRMS (EI): Exact mass calcd for $C_{17}H_{17}NS$ (M^+); 267.1082, Found: 267.1063.

2-(1-Napthylethnyl)thioanisole[15] (1f)



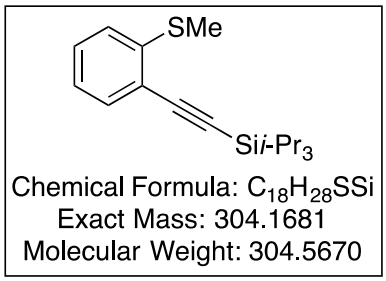
97% yield (1.3 g), brown solid. Rf = 0.53 (*n*-hexane : EtOAc = 10: 1). ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.22-7.25 (m, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.51-7.55 (m, 1H), 7.58-7.63 (m, 1H), 7.79-7.90 (m, 4H), 8.60 (d, *J* = 8.1 Hz, 1H).

2-(1-Heptyn-1-yl)thioanisole[12] (1g)



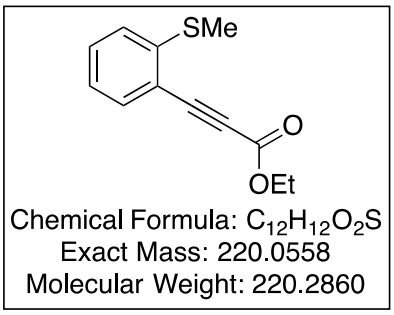
30% yield (327 mg), colorless oil, Rf = 0.43 (*n*-hexane). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.31-1.40 (m, 2H), 1.43-1.51 (m, 2H), 1.60-1.68 (m, 2H), 2.46 (s, 3H), 2.47 (t, *J* = 7.7 Hz, 2H), 7.04 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H, Ar), 7.22 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H).

2-(2-Triisopropylethynyl)thioanisole (1h)



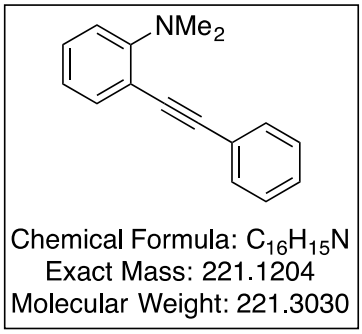
100% yield (1.5 g), colorless oil, Rf = 0.18 (*n*-hexane). IR (KBr) 2863, 2153, 1460, 883, 833, 748, 678 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.14 (br, 21H), 2.46 (s, 3H), 7.04 (t, *J* = 7.7 Hz, 1H), 7.10-7.12 (d, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 11.4, 15.1, 18.8, 97.9, 103.9, 121.5, 123.8, 124.0, 128.8, 133.0, 142.1. MS (EI) m/z: 304 (15, M^+), 289 (20, M^+–Me), 261 (100, M^+–*i*-Pr). HRMS (EI): Exact mass calcd for $C_{18}H_{28}SSi$; 304.1681, Found: 304.1680.

Ethyl-3-(2-(methylthio)phenyl)propiolate[16] (1i)



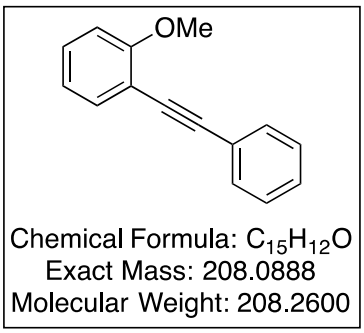
54% yield (599 mg), yellow oil, Rf = 0.38 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* = 7.3 Hz, 3H), 2.51 (s, 3H), 4.31 (q, *J* = 7.3 Hz, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H).

***N,N*-Dimethyl(phenylethynyl)thioanisole[17] (4)**



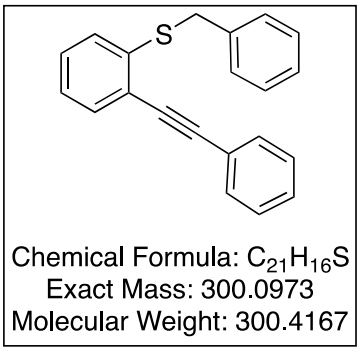
95 % yield (1.0 g), yellow oil, Rf = 0.55 (*n*-hexane : EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 6H), 6.87-6.93 (m, 2H), 7.26-7.25 (m, 1H), 7.32-.7.36 (m, 3H), 7.47-7.49 (m, 1H), 7.52-7.54 (m, 2H).

2-(Phenylethynyl)anisole[12] (6)



100% yield (1.1 g), yellow oil, Rf = 0.51 (*n*-hexane : EtOAc = 10: 1). ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.91 (t, *J* = 9.0 Hz, 1H), 6.89-6.95 (m, 2H), 7.28-7.34 (m, 4H), 7.48 (m, 1H), 7.54-7.56 (m, 1H).

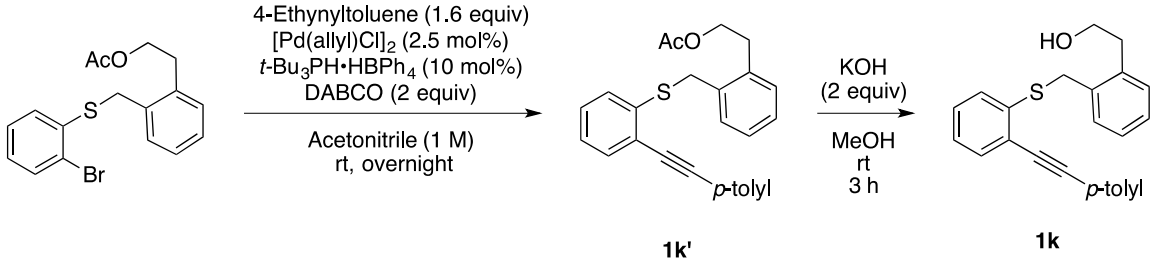
1-Benzylthio-2-phenylethynyenzen (1j)



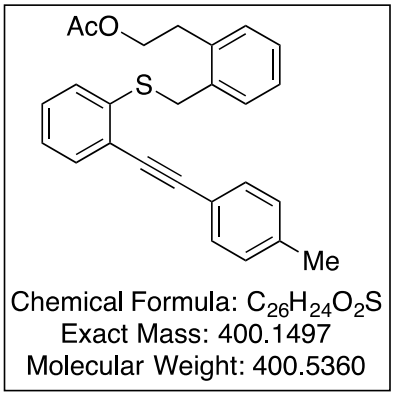
A solution of the 1-benzylthio-2-bromobenzene (4 mmol, 1.1 g) was treated with 1,4-diazabicyclo[2.2.2]octane (2 equiv, 896 mg), $[Pd(allyl)Cl]_2$ (2.5 mol%, 37 mg), *t*-Bu_3P (10 mol%, 94 μL) and phenylacetylene (1.6 equiv, 0.70 mL) in acetonitrile (1 M, 4 mL) under argon atmosphere. The reaction mixture was stirred overnight at room

temperature. The mixture was diluted with ether, filtered celite pad and concentrated *in vacuo*. The crude product was purified by flush column chromatography on silica gel (Rf = 0.36, *n*-hexane) and GPC ($CHCl_3$) to give **1j** in 75% yield (902 mg) as a yellow solid. mp 62.6-63.6 ºC, IR (KBr) 1491, 1456, 1065, 754, 714, 688 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.44 (s, 2H). 7.14 (td, *J* = 7.2, 1.8 Hz, 1H), 7.21 (td, *J* = 7.2, 1.8 Hz, 1H), 7.23-7.31 (m, 5H), 7.32-7.38 (m, 4H), 7.49-7.51 (m, 1H), 7.55-7.58 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 37.6, 87.3, 95.6, 123.2, 125.6, 127.3, 127.9, 128.4, 128.5, 128.6, 128.7, 129.0, 131.7, 132.7, 136.9, 139.6 (Two peaks are overlapped). MS (EI) m/z: 300 (49, M^+), 223 (98, $M^+–C_6H_5$), 91 (100, $M^+–C_{14}H_9S$). HRMS (EI): Exact mass calcd for $C_{21}H_{16}S$; 300.0973, Found: 300.0981.

Procedure for the synthesis of 1k



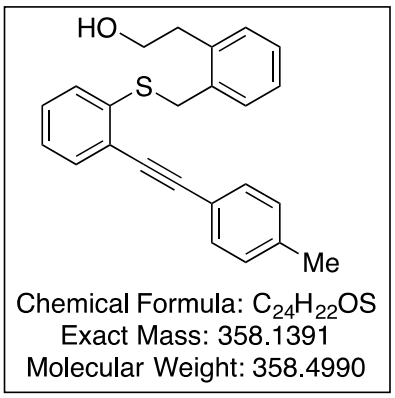
2-(2-(*p*-Tolylethynyl)benzyl)phenethyl acetate (1k´)



A solution of 2-(((2-bromophenyl)thio)methyl)phenylethnyl acetate (2.2 mmol, 800 mg) was treated with 4-ethynyltoluene (1.0 equiv, 240 μL), $[Pd(allyl)Cl]_2$ (2.5 mol%, 21 mg), *t*-$Bu_3PH·BPh_4$ (10 mol%, 116 mg) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 equiv, 560 mg) in acetonitrile (1 M, 2.2 mL) under argon atmosphere. The reaction mixture was stirred for 11 h at room temperature. The mixture filtered through short column (*n*-heaxane : EtOAc = 1 : 1) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Rf = 0.45, *n*-hexane : EtOAc = 4 : 1) to give **1k´** in 95% yield (768 mg) as a brown oil. IR (KBr) 2956, 1737, 1448, 1238, 1022, 744 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.34 (s, 3H), 3.07 (t, *J* = 7.2 Hz, 2H), 4.24 (s, 2H), 4.28 (t,

J = 7.2 Hz, 2H), 7.11-7.30 (m, 9H), 7.41-7.51 (m, 3H). ^{13}C NMR δ 21.1, 21.7, 31.7, 35.5, 64.7, 86.7, 95.7, 120.1, 123.9, 125.9, 127.1, 127.9, 128.5, 128.6, 129.2, 130.1, 130.8, 131.6, 132.7, 134.8, 136.6, 138.7, 139.3, 171.1. MS (EI) *m/z*: 400 (100, M^+), 341 (63, M^+–OAc). 326 (22, M^+–OAc–Me). HRMS (EI): Exact mass calcd for $C_{26}H_{24}O_2S$ (M^+); 400.1497, Found: 400.1492.

2-(2-(2-(*p*-tolylethynyl)benzyl)phenyl)ethan-1-ol (1k)



A solution of **1k´** (0.34 mmol, 135 mg) was treated with KOH (2.4 equiv, 46 mg) in MeOH (2 mL) under argon atmosphere. The reaction mixture was stirred for 3 h at room temeperature. The reaction mixture was quenched with 1M HCl, and stirred for 1 h. The solution was diluted with EtOAc, and washed with brine. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo.* The residue was purified by the short column chromatography on silica gel (Rf = 0.55, *n*-hexane : EtOAc = 1 : 1) to give **1k** in 89% yield (109 mg) as a yellow oil. IR (KBr) 3367, 1510, 1460, 1039, 816, 750, 521 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.02 (t, J = 6.4 Hz, 2H), 3.89 (q, J = 6.4 Hz, 2H), 4.25 (s, 2H), 7.12-1.62 (m, 1H), 7.15 (d, J = 8.2 Hz, 2H), 7.19 (dd, J = 7.7, 1.4 Hz, 1H), 7.22-7.34 (m, 6H), 7.43 (d, J = 8.2 Hz, 2H), 7.52 (dd, J = 7.7, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 21.6, 35.8, 63.5, 86.8, 95.7, 120.1, 124.1, 126.0, 126.9, 127.9, 128.6, 128.8, 129.0, 129.2, 130.3, 130.8, 131.6, 132.8, 134.9, 137.5, 138.8, 139.2. MS (EI) *m/z*: 358 (80, M^+), 357 (100, M^+–H). HRMS (EI): Exact mass calcd for $C_{24}H_{22}OS$ (M^+); 358.1391, Found: 358.1393.

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List of Publications

Parts of the present thesis have been, or are to be, published in the following journals

(1) "One-pot Sequential Direct C-H Bond Arylation of Azoles Catalyzed by [Pd(phen)-$_2$]$(PF_6)_2$: Synthetic Methods for Triarylated Azoles" Shibahara, F.; Yamauchi, T.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2012**, *77*, 8815.

(2) "Facile Synthetic Methods for Diverse Polyfunctionalized Imidazoles by Means of Pd-Catalyzed C-H Bond Arylation of *N*-Methyl-4,5-dibromoimidazole" Yamauchi, T.; Shibahara, F.; Murai, T. *J. Org. Chem.* **2014**, *79*, 7185.

(3) "Direct C-H Bond Arylation of Thienyl Thioamides Catalyzed by Pd-phenanthroline Complexes" Yamauchi, T.; Shibahara, F.; Murai, T. *Org. Lett.* **2015**, *17*, 5392.

(4) "Arylative Cyclization of 2-Alkynylthianisole by Using Pd-phenanthroline Complexes" to be submitted

Following publications are not included in this thesis.

(1) "Copper-Catalyzed C-H Bond Direct Chalecogenation of Aromatic Compounds Leading to Diaryl Sulfides, Selenides, and Diselenides by Using Elemental Sulfur and Selenium as Chalcogen Sources Under Oxidative Conditions" Shibahara, F.; Kanai, T, Yamaguchi, E.; Kamei, A.; Yamauchi, T.; Murai, T. *Chem. Asian. J.* **2014**, *9*, 237.

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March 2016

Takayuki Yamauchi