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A General Modular Method of Azaindole and Thienopyrrole Synthesis *via* Pd-Catalyzed Tandem Couplings of *gem*-Dichloroolefins

Yuan-Qing Fang, Josephine Yuen, and Mark Lautens*

Davenport Chemistry Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, M5S 3H6, Canada

mlautens@chem.utoronto.ca

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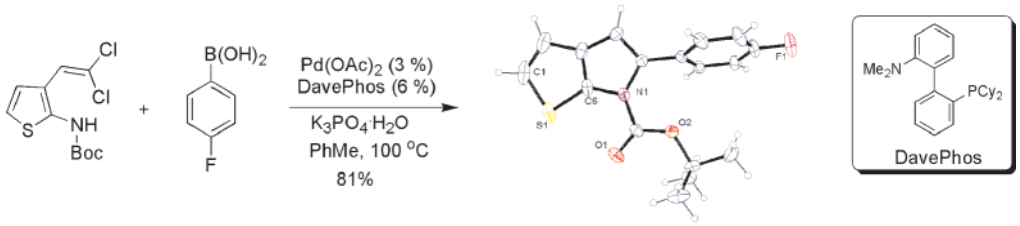

A palladium-catalyzed reaction of *gem*-dichloroolefins and a boronic acid via a tandem intramolecular C−N and intermolecular Suzuki coupling process gave corresponding substituted azaindoles or thienopyrroles. This method is a very modular protocol to synthesize all four isomers of azaindole and two isomers of thienopyrroles in good to excellent yield.

Introduction

Azaindoles and thienopyrroles are two very important families of drug-like heteroaromatic structures that show diverse biological activity.[1] Compared to their bioisosteric indole structure, they feature unique electronic properties. Moreover, the variable position of the heteroatom existing in the four azaindole and two stable thienopyrrole isomers increases the chance of suitable binding in biological systems, increasing selectivity,[2] as well as improving bioavailability.[3] For example, azaindole compounds exhibit a broad spectrum of activity including tubulin-inhibitory properties, antimitotic activity,[4] protein kinase inhibition and antiproliferative behavior,[5] selective potent dopamine D_4 antagonism,[2] transforming growth factor (TGF)-β1 antagonism,[6] antithrombotic and anticoagulant activity,[7] NK1 receptor antagonism,[8] and MAP kinase p38 inhibition.[9] Similarly, thienopyrroles are biologically active as sPLA2 inhibitors,[10] MCP-1 inhibitors,[11] glycogen phosphorylase inhibitors,[12] gonadotropin releasing hormone antagonists,[13] and antiviral agents.[14]

* Author to whom correspondence should be addressed. Phone: 416-978-6083. Fax: 416-946-8185.

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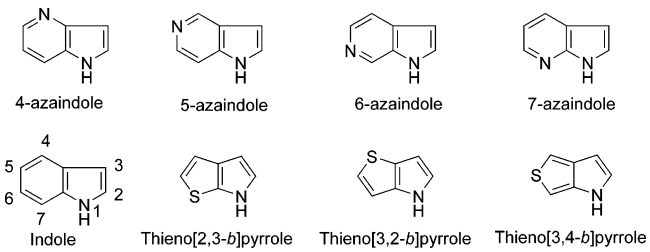

Synthetic routes to azaindoles or thienopyrroles are not always straightforward since the most general and effective processes, such as the Fischer indole method, often fail to give azaindoles and thienopyrroles.[15] Typical methods of azaindole synthesis are Madelung-type cyclization,[16] Gassman-type cyclization,[17] Bartoli-type cyclization,[18] intramolecular nitrene C−H insertion cyclization,[16a] ketone amine condensation,[19] electrophilic cyclization *via* a Pictet−Spengler reaction,[20] and Friedel−Crafts type cyclization followed by dehydration.[21] These traditional methods suffer from low yields, limited reaction scope, and harsh reaction conditions; hence, very few functional groups are compatible.[22] More recently, Pd-catalyzed alkynyl amine formation/cyclization,[23] Heck reaction,[24] Larock-type annulation,[25] Ar−Pd−X-mediated cyclization of alkynyl amines,[26] ring-opening of a spiro pyridone-cyclopropane followed by cross-couplings,[27] and a double Buchwald−Hartwig C−N coupling[28] show very attractive features which overcome the shortcomings of traditional methods owing to the mild reaction conditions and high functional group compatibility of Pd chemistry. Compared to azaindoles, synthetic methods for thienopyrroles are much more limited and include Friedel−Crafts acylation followed by aromatization,[29] reductive ketone amine condensation,[30] and aldol condensation,[31] nitrene C−H insertion cyclization using azides[32] or nitrothiophene,[33] intramolecular Heck reaction,[34] and a Rh(II)-mediated-Wolff rearrangement-cyclization sequence.[35] Again, these methods mostly suffer from drawbacks including low yields or difficult access to the starting materials. There are no previous reports of a single, general method to produce all the possible isomers of azaindoles and thienopyrroles.

In the context of developing rapid and efficient access to a diverse family of indole compounds via a tandem Pd-catalyzed C−N/C−C coupling or Cu-catalyzed double amidation of *gem*-dihalovinylaniline systems,[36] we sought to extend our methodology to the synthesis of azaindoles and thienopyrroles. We report herein our success in this endeavor leading to these important families of molecules.

Results and Discussion

Solution for Catalyst Poisoning. Initial experiments showed that the conditions we developed for indole synthesis (eq 1 in Scheme 1) via a tandem C−N/Suzuki coupling of *gem*-dibromovinylaniline **2** failed to give the desired 7-azaindole product **3** (eq 2 in Scheme 1). Not only did the starting material decompose under the reaction conditions, the starting material (or the decomposed products) poisoned the catalyst in a control experiment (eq 3 in Scheme 1). Attempts to synthesize 6-, 5-, or 4-azaindoles under these conditions all failed to result in the desired products.

There are only a few cases of C−N coupling between free aminopyridines and aryl halides employing bidentate phosphine ligands.[37] Moreover, it is well-established that the free NH_2 group in aminopyridines retards the Pd-catalytic cycle.[38] Early studies on Pd-catalyzed C−N coupling reactions using a monodentate phosphine ligand showed that primary amines are generally poor substrates due to formation of the aryl palladium bis-amine complex, which failed to undergo reductive elimination.[39] Therefore, formation of complex **4** from the *gem*-

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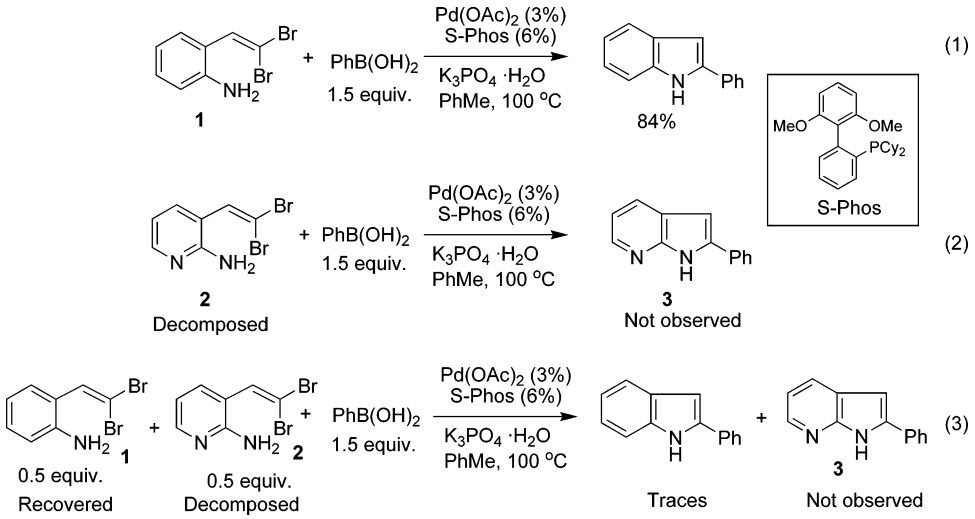
SCHEME 1



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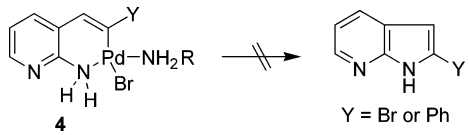

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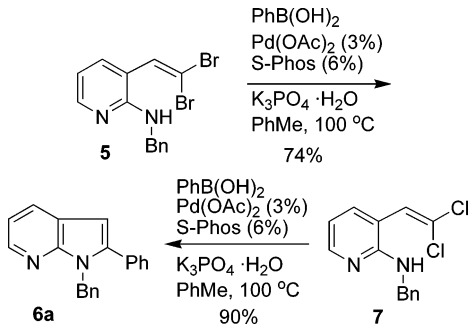
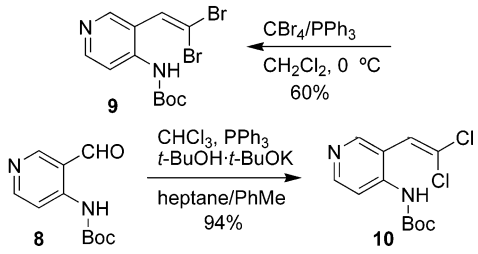


dibromovinyl aminopyridine substrate **2** is presumably the cause of catalyst poisoning (Scheme 2).

To avoid catalyst poisoning through bis-amine coordination to palladium, we chose to introduce a substituent on the nitrogen. In the event, the *N*-benzyl substrate **5** gave the desired *N*-benzyl-7-azaindole **6** in good yield (74%) in the presence of phenylboronic acid (1.5 equiv) under our previously described conditions [($Pd(OAc)_2$ (3 mol %), S-Phos (6 mol %), $K_3PO_4 \cdot H_2O$ (3−5 equiv) in toluene at 100 °C] (Scheme 3). More interestingly, further investigation revealed that the *gem*-dichloroolefin substrate **7** gave a significantly improved yield (90%). Therefore, we explored the scope of this reaction in the synthesis of azaindole isomers using *gem*-dichlorovinyl substrates.

Substrate Synthesis. The Ramirez olefination[40] of aldehydes which also bear an N−H group in the molecule (e.g., **8**) typically afforded *gem*-dibromovinyl products in moderate yield presumably due to the interference of the amide NH group (Scheme 4). Conversely, preparation of *gem*-dichlorovinyl substrates can be achieved with much better functional group compatibility by reacting aldehydes or ketones with the ylid,

SCHEME 4



CCl_2PPh_3, generated from the reaction of PPh_3 and dichlorocarbene (generated *in situ* from the reaction of KO*t*Bu and chloroform).[41] Although the literature protocol was effective, the need to use freshly prepared KO*t*Bu makes it less attractive. Fortunately, freshly prepared KO*t*Bu can be substituted by a KO*t*Bu·HO*t*Bu adduct, which was prepared by simply heating commercially available *t*-BuOK in anhydrous *t*-BuOH followed by removal of excess *t*-BuOH under vacuum. This white solid adduct was stable at −20 °C for long periods of time without deterioration in yield of the olefination.

Preparation of a variety of these substrates consisting of different azaindole and thienopyrrole isomers following this procedure is shown in Table 1. Alkylation of the BocNH substrate (e.g., **11**) followed by deprotection of the Boc group gave the *N*-alkyl substrate.[42]

Synthesis of 7-Azaindole Derivatives. A range of 7-azaindoles were prepared as shown in Table 2. Substrates with alkyl substituents on the nitrogen produced successful reactions, with the least bulky methylamine **19** being the most efficient (Table 2, entry 2 vs 4). The Boc-protected amino substrate also gave the desired product, albeit in lower yield (Table 2, entry 7). Both electron-rich and electron-poor boronic acids were tolerated under these conditions. More interestingly, reaction of the tetrasubstituted olefin substrate **20** gave the 2,3-disubstituted 7-azaindole in excellent yield, although prolonged heating was required, which caused partial loss of the Boc group.

Compound **6b** was subsequently converted into a transforming growth factor (TGF)-β1 antagonist SIS3 (**21**), which was

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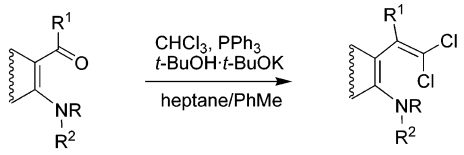
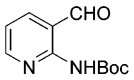
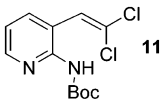
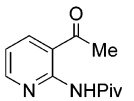
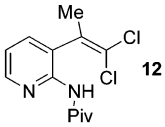
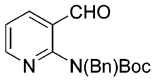
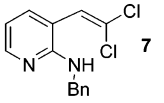
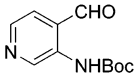
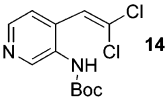
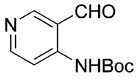
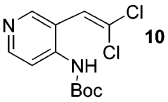
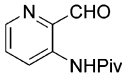
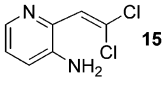
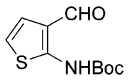
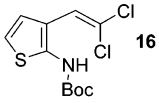
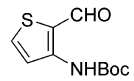
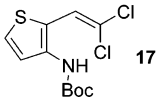
TABLE 1. Preparation of *gem*-Dichloroolefins Using the Wittig Reaction



entry	aldehyde/ketone	product	yield (%)[a]
1		 **11**	86
2		 **12**	89
3		 **7**	93[b]
4		 **14**	60
5		 **10**	94
6		 **15**	77[b]
7		 **16**	76
8		 **17**	80

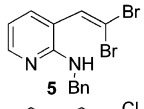
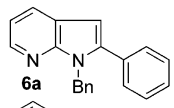
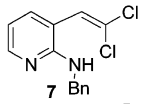
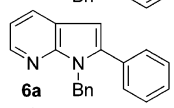
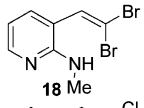
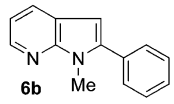
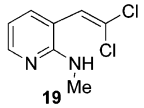
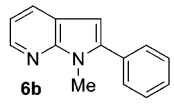
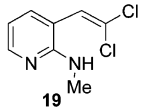
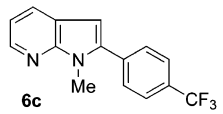
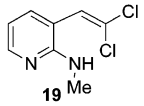
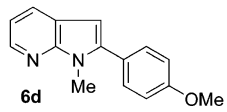
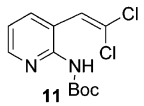
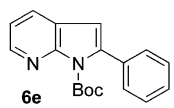
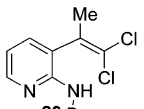
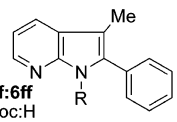
[a] Isolated yield. [b] After HCl treatment.

identified as a drug candidate for the treatment of systematic sclerosis or scleroderma (Scheme 5).[6] Iodination of 7-azaindole **6b** using NIS afforded the 3-iodo-7-azaindole **22** in excellent yield (95%), and Heck reaction between **22** and the acrylamide **23** under microwave irradiation gave the desired product **21** in excellent yield (90%).

Synthesis of 6-Azaindole Derivatives. We next examined the efficiency of 6-azaindole formation using the Boc-protected chloro substrate **14** and various boronic acids. Under these conditions, aryl boronic acids with electron-donating, electron-withdrawing groups, or ortho substituents were tolerated. A 2-pentenyl azaindole **24g**, which can be further functionalized, was prepared using an alkenyl boronic acid in good yield (Table 3, entry 7). Heteroaryl boronic acids such as 3-thienyl boronic and quinolinyl boronic acid were also successfully applied to the synthesis of 6-azaindoles (Table 3, entries 6 and 8).

The Boc-protected azaindole can be deprotected under acidic conditions, for example treatment of **24d** with TFA gave **25** in good yield (Scheme 6). Both Boc and methyl groups in **24h** were removed upon treatment with HCl, affording the 6-azaindole analogue **26** in quantitative yield, which was reported by Merck as a KDR kinase inhibitor.

TABLE 2. Synthesis of 7-Azaindoles

entry	substrate	$ArB(OH)_2$	product	yield (%)[a]
1	 **5**	$PhB(OH)_2$	 **6a**	74
2	 **7**	$PhB(OH)_2$	 **6a**	90
3	 **18**	$PhB(OH)_2$	 **6b**	84
4	 **19**	$PhB(OH)_2$	 **6b**	96
5	 **19**	4-CF_3PhB(OH)$_2$	 **6c**	87
6	 **19**	4-MeOPhB(OH)$_2$	 **6d**	83
7	 **11**	$PhB(OH)_2$	 **6e**	62
8	 **20**	$PhB(OH)_2$	 **6f:6ff** R= Boc:H 40:57	97

[a] Isolated yield.

Synthesis of 5-Azaindoles. Initial attempts to form the 5-azaindole **27a** using substrate **10** and 1.5 equiv of $PhB(OH)_2$ were rather disappointing, giving a mixture of bis-Suzuki coupling product **28** and the desired product **27a** (Scheme 7). We have not previously obtained the bis-coupled product and speculate this reaction is due to the unique electron-withdrawing character of the 4-pyridylamide **10**.

In order to solve this problem, the first strategy was to protect the pyridyl group as an *N*-oxide, thereby reversing the electronic properties of the 4-pyridyl amide. After N-oxidation of the substrate **10** using *m*CPBA, the tandem coupling reaction of **29** proceeded very well, giving the 5-azaindole **30** in good yield (Scheme 8).

While this approach solved the problem of reactivity, it added extra N-oxidation and deoxygenation steps if the azaindole is the desired product. Our second approach was to reduce the number of equivalents of the arylboronic acid from 1.5 to 1.2 and also to investigate the use of other phosphine ligands to slow down the rate of the Suzuki step. Buchwald's family of biphenyl phosphine ligands allow for fine-tuning by varying the substituent on the second phenyl ring, which may help to facilitate C−N bond formation.

Indeed, the reaction was much cleaner with 1.2 equiv of $PhB(OH)_2$ (Table 4, entry 1). All the ligands shown in Figure 1

SCHEME 5. Synthesis of a SIS3 Inhibitor

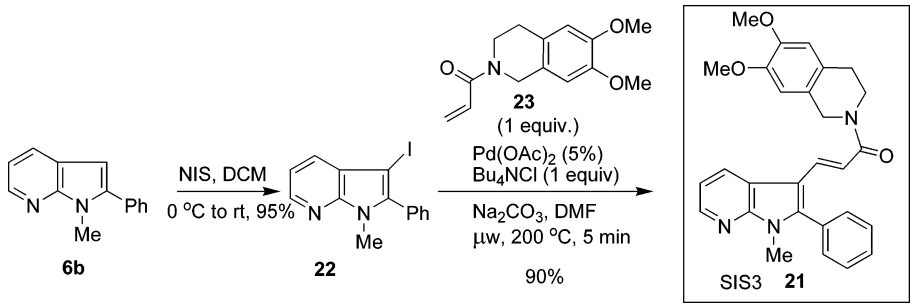
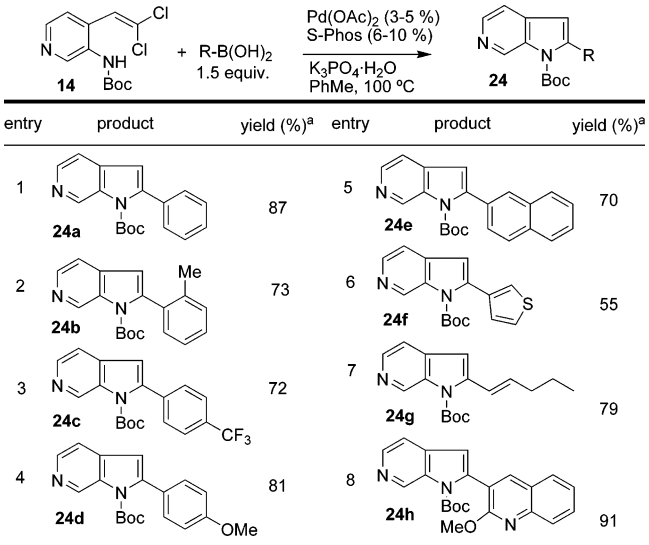


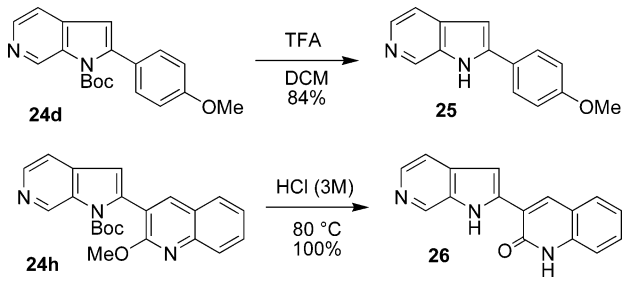
TABLE 3. The Scope of 6-Azaindole Synthesis



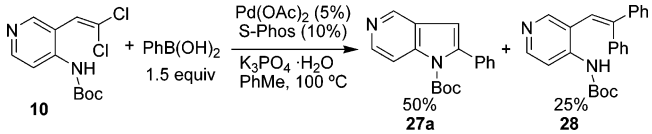
entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	**24a**	87	5	**24e**	70
2	**24b**	73	6	**24f**	55
3	**24c**	72	7	**24g**	79
4	**24d**	81	8	**24h**	91

[a] Isolated yield.

SCHEME 6

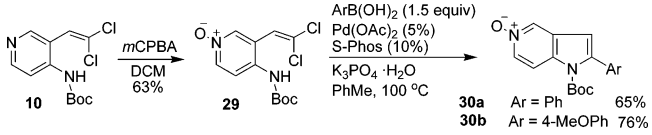


SCHEME 7

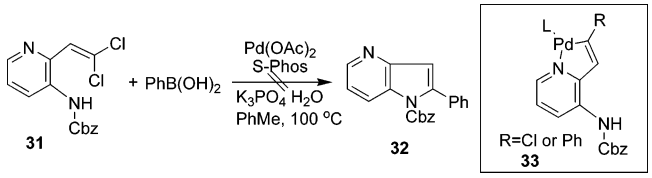


were effective and X-Phos was the best, affording the desired product **27a** in 87% yield. Evaluation of a number of electron-poor, electron-rich, hindered, and heterocyclic arylboronic acids showed that this strategy is effective for a wide range of boronic acids (Table 4, entries 5−8). It was found that electron-rich boronic acids (Table 4, entry 6) were less effective than electron poor boronic acids (Table 4, entry 5), because rapid Suzuki coupling in the former case resulted in bis-arylated coupling product. In some cases, the original S-Phos ligand was more effective than X-Phos (Table 4, entry 8).

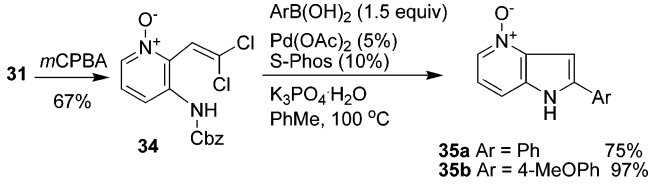
SCHEME 8



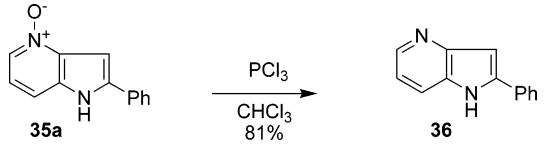
SCHEME 9



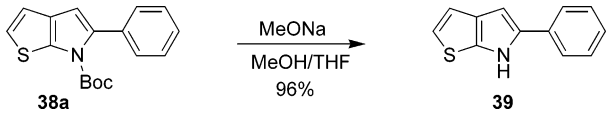
SCHEME 10



SCHEME 11



SCHEME 12



Synthesis of 4-Azaindoles. Attempts to synthesize 4-azaindole **32** from substrate **31** were plagued by formation of a complex mixture of products (Scheme 9), probably due to formation of the vinylpalladium species **33** wherein coordination to the pyridyl nitrogen retards the C−N bond formation. Variation in ligand and other conditions failed to reverse this behavior.

Under these circumstances, it was necessary to protect the pyridyl nitrogen as the *N*-oxide, and following oxidation of **31** with *m*CPBA, **34** successfully underwent a tandem coupling to afford the desired *N*-oxy-4-azaindole **35a** and **35b** in good to excellent yield (Scheme 10). In addition, the Cbz group was completely deprotected under the reaction conditions. Deoxygenation of *N*-oxy-4-azaindole **35a** to give 2-phenyl

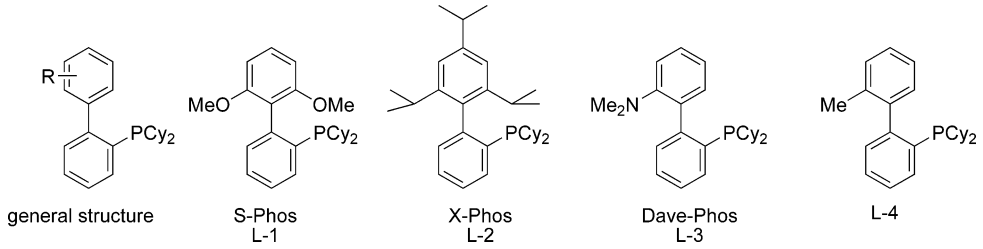
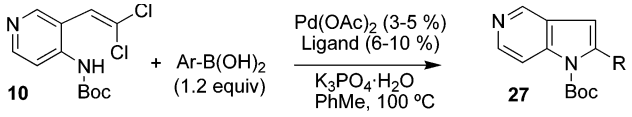
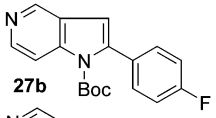
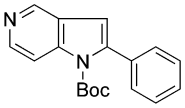
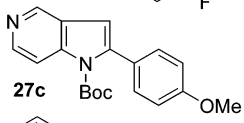
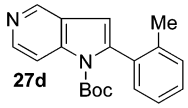
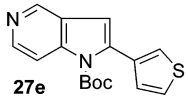


FIGURE 1. Buchwald's biphenylphosphine ligands.

TABLE 4. Synthesis of 5-Azaindoles



entry	product	Ligand	yield (%)[a]	entry	product	Ligand	yield (%)[a]
1		L-1	79	5	 **27b**	L-2	88
2	 **27a**	L-2	87	6	 **27c**	L-2	68
3		L-3	80	7	 **27d**	L-2	75
4		L-4	81	8	 **27e**	L-1	80

[a] Isolated yield.

4-azaindole (**36**) was performed in good yield using PCl_3 (Scheme 11).

Synthesis of Thienopyrroles. Subjecting Boc-protected aminothiophene **16** or **17** to the reaction conditions afforded the Boc-protected thienopyrrole **37** or **38** (Table 5). Thiophene substrates with either a free NH_2 or *N*-alkyl failed to give the desired thienopyrroles due to the instability of these substrates. In general, electron-poor boronic acids worked well, while electron-rich boronic acids often gave mixtures of the desired product and bis-arylated byproduct. The reaction with hindered boronic acids such as *o*-tolyl boronic acid resulted in a very low yield. Depending on the boronic acid, some fine-tuning using Buchwald's biphenyl family of phosphine ligands (Figure 1) was required to obtain good yields (Table 5, entry 7−9). The easiest and cleanest way of removing the Boc-protecting group is by using NaOMe in anhydrous methanol and THF (Scheme 12).

Mechanism of Tandem Reactions in Azaindole and Thienopyrrole Syntheses. Our mechanistic studies for indole synthesis revealed that intramolecular C−N bond formation is faster than C−C bond formation for *gem*-dibromovinylaniline **1**.[43] However, the formation of bis-arylated product **28** in the 5-azaindole series (Scheme 7) suggests that in these circumstances, the Suzuki reaction is faster than the C−N bond formation.

(43) Fang, Y.; Lautens, M. Unpublished results.

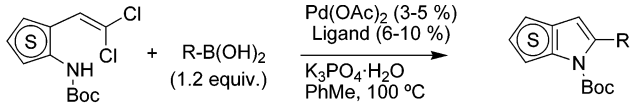
Additional support for the relative rates was obtained by isolation of the monoaryl intermediate **40**, which was possible since the C−N coupling was very slow when X-Phos was used as the ligand. (Scheme 13). Subjecting **40** to the reaction conditions using S-Phos for a longer period of time in the absence of boronic acid gave the desired azaindole **27e** in high yield (Scheme 13). It is also possible that the change in ligand may lead to a change in the relative rates of the two steps (Suzuki versus C−N coupling).

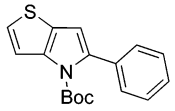
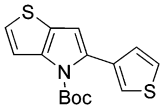
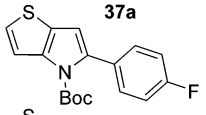
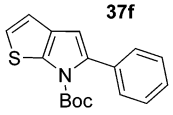
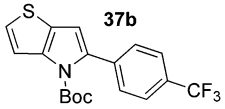
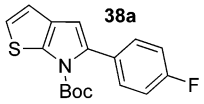
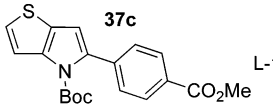
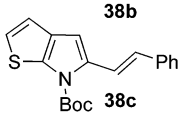
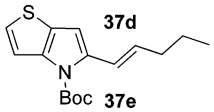
The mechanism of thienopyrrole synthesis from substrate **16** or **17** is consistent with our results with azaindoles. The reaction between **16** and hindered *o*-tolyl boronic acid at 100 °C for 18 h gave only 6% of the desired thieno[2,3-*b*]pyrrole **38d** (Scheme 14). The major product formed was a mono arylated intermediate **41**. Subjecting the isolated intermediate **41** to a higher catalyst loading (7%) and in the presence of stronger base Cs_2CO_3 gave 2-*o*-tolyl thienopyrrole **38d** in good yield.

The same product distribution was observed for the isomeric substrate **17** when treated with 4-methoxycarbonylphenylboronic acid (Scheme 15). With 3% catalyst loading, a mixture of **42** (57%) and the desired product **37d** (12%) was obtained even after prolonged heating, presumably due to deactivation of the catalyst. However, with 5% catalyst loading, both the intermediate **42** and the original substrate **17** underwent complete conversion to the desired product **37d**.

From these studies, it is most likely that 4-, 6-, and 7-azaindole formation may follow the same mechanism, in

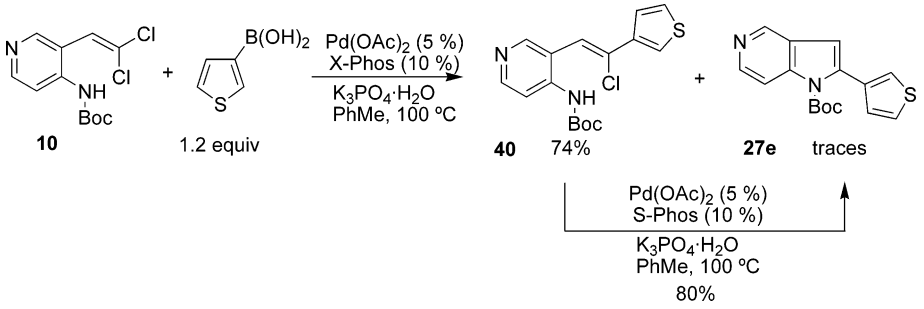
TABLE 5. The Scope of Thienopyrrole Synthesis



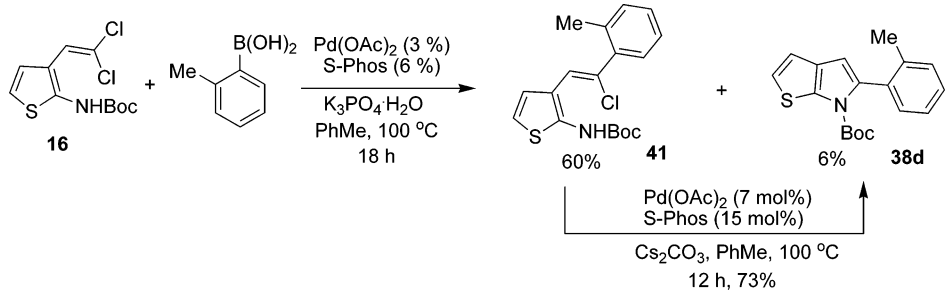
entry	product	ligand	yield (%)[a]	entry	product	ligand	yield (%)[a]
1	 **37a**	L1	73	6	 **37f**	L-1	73
2	 **37b**	L-1	74	7	 **38a**	L-1	76
3	 **37c**	L-1	66	8	 **38b**	L-3	81
4	 **37d**	L-1	74	9	 **38c**	L-3	71
5	 **37e**	L-1	80				

[a] Isolated yield.

SCHEME 13



SCHEME 14



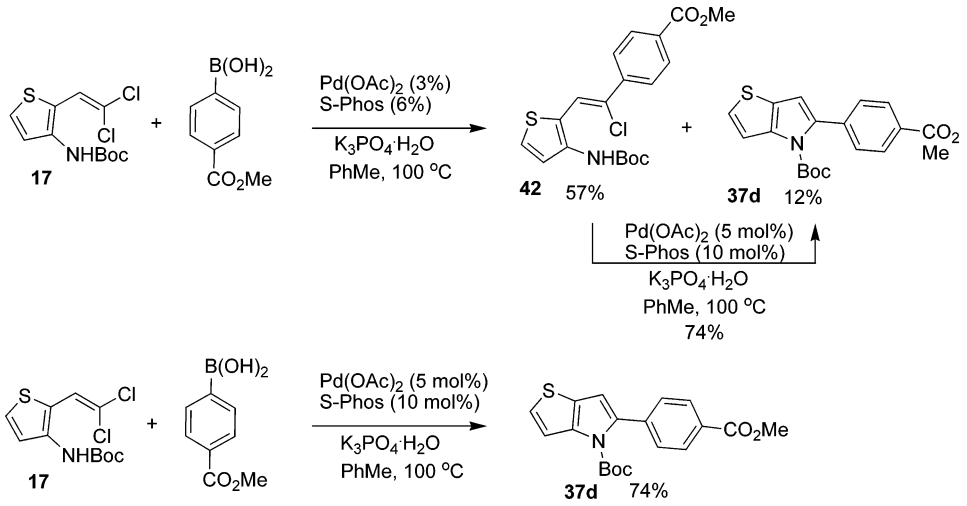
which Suzuki coupling occurs prior to C−N coupling. However, other possibilities such as initial C−N formation or competing mechanisms cannot be excluded.

Conclusion

We have extended the methodology of tandem C−N/Suzuki couplings toward the synthesis of azaindoles and thienopyrroles using *gem*-dichlororovinyl-pyridine or thiophene substrates. To the best of our knowledge, this is the first general method that is suitable for preparing all the stable azaindole and thienopyrrole isomers, which is potentially beneficial for the pharmaceutical industries since it can be applied to library synthesis owing to large numbers of commercially available boronic acids.[44]

(44) There were over 640 commercially available aryl boronic acids by early 2004.

SCHEME 15



Experimental Section

[3-(2,2-Dichlorovinyl)pyridin-2-yl]carbamic Acid *tert*-Butyl Ester (11). Preparation of KO*t*Bu·HO*t*Bu: A mixture of KO*t*Bu (56 g), HO*t*Bu (46 g), and anhydrous *n*-heptane (100 mL) was heated to 115 °C (reflux) for 1 h. *n*-Heptane was distilled off at a bath temperature of 115 °C. The mixture was cooled to rt, and the residual HO*t*Bu was removed under vacuum (0.3 mmHg) for 1 h to yield a white powder (90.5 g, 97%).

General Procedure for the Preparation of *gem*-Dichlorovinyl Substrates. To a round-bottomed flask was charged KO*t*Bu·HO*t*Bu (1.86 g, 10 mmol) and powdered PPh_3 (2.62 g, 10 mmol), and the flask was purged with argon for 10 min. After *n*-heptane (15 mL) was added, the mixture was cooled to 0 °C with an ice bath. To the vigorously stirred mixture, a solution of chloroform (1.19 g, 10 mmol) in *n*-heptane (5 mL) was added dropwise in such rate that the internal temperature was maintained under 3 °C. After addition, the mixture was stirred for an additional 30 min. The mixture was concentrated to about 10 mL under high vacuum at rt. To the mixture at 0 °C, 2-BocNH-3-pyridinecarboxaldehyde (1.11 g, 5 mmol) was added in one portion followed by dry benzene (3 mL), and the resulting mixture was stirred at 0 °C for 1 h and then at rt overnight. The reaction was quenched with NH_4Cl solution (20 mL), and extracted with DCM (3 × 20 mL). H_2O_2 (10%, 1 mL) was added to the combined organic layers, and the mixture was stirred for 30 min. After partition, the organic layer was washed with Na_2SO_3 (10 mL), H_2O (50 mL), brine (20 mL), and dried over $MgSO_4$. The crude material was further purified by flash chromatography on silica gel (33% EtOAc in hexanes) to afford the desired product as a white solid (1.24 g, 86%). mp 151−152 °C. IR ($CHCl_3$, cm^{-1}): 3415, 2981, 1731, 1576, 1489, 1438, 1369, 1154. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, dd, J = 4.9, 1.7 Hz), 7.94 (1H, ddd, J = 7.7, 1.8, 0.7 Hz), 7.71 (1H, br), 7.14 (1H, dd, J = 7.7, 4.8 Hz), 6.85 (1H, s), 1.51 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.1, 148.3, 138.5, 125.0, 123.9, 123.2, 120.4, 81.5, 28.3. HRMS (ESI) calcd for $C_{12}H_{14}N_2O_2NaCl_2$ ([M + Na]$^+$) 311.0324. Found: 311.0331.

[3-(2,2-Dibromovinyl)-pyridin-2-yl]methylamine (18). To a mixture of 2-BocNH-3-pyridinecarboxaldehyde (0.222 g, 1 mmol) and DMF (3 mL) was added MeI (0.178 g, 1.25 mmol) dropwise at 0 °C. NaH (0.052 g, 60% mineral oil, 1.35 mmol) was added in three portions over 15 min, and the resulting yellowish suspension was stirred for an additional 60 min. The mixture was warmed to rt, and quenched with $NaHCO_3$ (10 mL) and H_2O (10 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with H_2O (10 mL), $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. The crude material was further purified by flash chromatography using 25% EtOAc in hexanes to afford an oil (0.197 g, 84%), which was used directly in the next step. To a solution of the methylated aldehyde (0.183 g, 0.77 mmol) and CBr_4 (0.389 g, 1.17 mmol) was added a solution of PPh_3 (0.613 g, 2.34 mmol) in DCM (∼1 mL) at 0 °C for 15 min before warmed to rt. The mixture was poured into a Na_2CO_3 solution, extracted with Et_2O (2 × 5 mL), washed with brine (5 mL), dried over Na_2SO_4. After removal of solvent, the crude material was filtered through a short column, eluting with 33% EtOAc in hexane containing 1% Et_3N to afford a yellow oil. The oil was added into a solution of HCl (3 M, 10 mL), heated to 75 °C for 30 min, cooled to rt, then neutralized with solid K_2CO_3. After extraction with Et_2O, the organic layers were dried over Na_2SO_4, chromatographed with 20% EtOAc in hexane to afford **18** as a yellow oil (0.160 g, 71% in 2 steps). IR (neat, cm^{-1}): 3305, 2942, 1593, 1517, 1394, 1268. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, dm, J^d = 5.1 Hz), 7.49 (1H, dm, J^d = 7.5 Hz), 7.15 (1H, s), 6.62 (1H, dd, J = 7.5, 5.5 Hz), 4.42 (1H, br), 3.04 (3H, d, J = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 148.1, 137.1, 132.3, 116.9, 112.3, 95.0, 29.0 HRMS (ESI) calcd for $C_8H_9Br_2N_2$ ([M + H]$^+$) 290.9126. Found: 290.9126.

1-Methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (6b). General Procedure for the Tandem Coupling. To a mixture of the *gem*-dibromoolefin (87.6 mg, 0.30 mmol), phenylboronic acid (55 mg, 0.45 mmol) and $K_3PO_4·H_2O$ (350 mg, 0.15 mmol) was added a solution of $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and S-Phos (8.2 mg, 0.020 mmol) in toluene (3 mL). The resulting mixture was heated at 100 °C for 2 h and cooled to rt. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified using chromatography eluting with 25% EtOAc in hexane to afford the product as a white solid (52.6 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, dd, J = 4.8, 1.5 Hz), 7.90 (1H, dd, J = 7.7, 1.5 Hz), 7.56−7.54 (2H, m), 7.50−7.47 (2H, m), 7.45−7.40 (1H, m), 7.08 (1H, dd, J = 7.7, 4.6 Hz), 6.52 (1H, s), 3.88 (3H, s).

The general procedure for the tandem coupling was followed using **19** (63 mg, 0.31 mmol), phenylboronic acid (55 mg, 0.45 mmol), $K_3PO_4·H_2O$ (350 mg, 0.15 mmol), and a solution of $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and S-Phos (8.2 mg, 0.020 mmol) in PhMe (3 mL). The reaction mixture was heated at 100 °C for 3 h. The crude material was purified using chromatography eluting with 25% EtOAc in hexanes to afford the product as a white solid (62 mg, 96%).

2-Phenylpyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (24a). The general procedure for the tandem coupling was followed using **14** (86.7 mg, 0.30 mmol), 2-phenylboronic acid (55 mg, 0.45 mmol), $K_3PO_4·H_2O$ (350 mg, 0.15 mmol), and a

solution of $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and S-Phos (8.2 mg, 0.020 mmol) in PhMe (3 mL). The reaction mixture was heated at 100 °C for 3 h. The crude material was purified using chromatography eluting with 33% EtOAc in hexane to afford product as a white solid (77 mg, 87%). mp 108−109 °C. IR (neat, cm^{-1}): 2979, 1734, 1433, 1349, 1326, 1149. ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (1H, s), 8.42 (1H, d, $J = 5.3$ Hz), 7.45 (1H, dd, $J = 5.3$, 1.1 Hz), 7.43−7.40 (5H, m), 6.54 (1H, s), 1.36 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 144.0, 142.4, 137.8, 134.6, 134.3, 133.9, 129.0, 128.5, 128.1, 114.9, 108.8, 84.7, 27.7. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ ($[M + H]^+$) 295.1441. Found: 295.1450.

5-(4-Fluorophenyl)thieno[2,3-*b*]pyrrole-6-carboxylic Acid *tert*-Butyl Ester (38b). The general procedure for the tandem coupling was followed using **16** (58.9 mg, 0.20 mmol), 4-fluorophenylboronic acid (33.6 mg, 0.24 mmol), $K_3PO_4 \cdot H_2O$ (230 mg, 1.0 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), and DavePhos (7.9 mg, 0.02 mmol). The reaction mixture was heated in PhMe (2 mL) at 100 °C for 13.5 h. The crude material was purified using chromatography eluting with 3.5% EtOAc in hexanes to give the product as a white solid (51.4 mg, 81%). The single-crystal suitable for X-ray crystallographic determination was obtained by slow evaporation of an Et_2O solution in a freezer. mp 114−115 °C. IR (neat, cm^{-1}): 2980, 1753, 1724, 1504, 1369, 1316, 1161, 1140, 1123. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.37 (2H, m), 7.09−7.05 (2H, m), 7.02 (1H, AB, $J = 5.4$ Hz), 6.99 (1H, AB, $J = 5.4$ Hz), 6.45 (1H, s), 1.46 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 ($J_{C-F} = 247$ Hz), 149.0, 138.8, 136.2, 131.4 ($J_{C-F} = 8.2$ Hz), 130.5, 130.4 ($J_{C-F} = 3.4$ Hz), 121.8, 117.4, 114.8 ($J_{C-F} = 22$ Hz), 108.8, 84.9, 28.1. ^{19}F NMR (288 MHz, $CDCl_3$) δ −114.4. HRMS (EI): calcd for $C_{17}H_{16}NO_2SF$ ($[M]^+$) 317.0886. Found: 317.0878.

2-(4-Methoxyphenyl)-1*H*-pyrrolo[2,3-*c*]pyridine (25). Trifluoroacetic acid (0.1 mL) was added to a solution of **24d** (24 mg, 0.074 mmol) in DCM (0.5 mL) at rt. The reaction was stirred for 4 h at rt and then diluted with DCM and basified to pH 10 using 2 M NaOH. H_2O was added and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the product as a pale brown solid (14 mg, 84%). mp 222−225 °C. IR (neat, cm^{-1}): 1602, 1493, 1429, 1249. ^1H NMR (400 MHz, DMSO) δ 11.87 (1H, s), 8.68 (1H, s), 8.04 (1H, d, $J = 5.3$ Hz), 7.85 (1H, d, $J = 8.6$ Hz), 7.44 (1H, d, $J = 5.7$ Hz), 7.06 (1H, d, $J = 8.3$ Hz), 6.82 (1H, s), 3.80 (3H, s). ^{13}C NMR (100 MHz, DMSO) δ 159.6, 141.5, 138.2, 134.1, 133.8, 133.0, 127.2, 123.8, 114.5, 114.1, 96.6, 55.3, 55.2. HRMS (ESI): calcd for $C_{14}H_{13}N_2O$ ($[M + H]^+$) 225.1022. Found: 225.1013.

3-(1*H*-Pyrrolo[2,3-*c*]pyridin-2-yl)-1*H*-quinolin-2-one (26). 24h (30 mg, 0.08 mmol) was dissolved in a HCl solution (3 M, 2 mL) and heated to 80 °C for 13 h. The reaction was cooled to rt and basified to ∼pH 9 by the careful addition of solid K_2CO_3. The reaction was diluted with water then extracted using $CHCl_3$ (6 × 20 mL). The combined organic layers were concentrated and then purified using chromatography eluting with 10%→20% MeOH/EtOAc to give the product as a bright yellow solid (21 mg, 100%). mp >290 °C. IR (neat, cm^{-1}): 3256, 2355, 1667, 1157. ^1H NMR (400 MHz, DMSO) δ 12.29 (1H, s), 12.0 (1H, s), 8.89 (1H, s), 8.69 (1H, s), 8.09 (1H, d, $J = 4.9$ Hz), 7.77 (1H, d, $J = 7.7$ Hz), 7.57 (1H, tm, $J^t = 8.3$ Hz), 7.52 (1H, d, $J = 5.3$ Hz), 7.40 (1H, d, $J = 8.1$ Hz), 7.31 (1H, d, $J = 0.9$ Hz), 7.27 (1H, t, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, DMSO) δ 160.5, 138.0, 137.2, 136.5, 135.1, 133.5, 131.7, 130.9, 128.2, 122.5, 121.6, 119.2, 115.0, 114.2, 100.3, 100.3. HRMS (EI): calcd for $C_{16}H_{11}N_3O$ ($[M]^+$) 261.0902. Found: 261.0901.

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Supporting Information Available: Experimental procedure and characterization data for rest of the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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