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Synthesis of stereodefined 1-aryl(heteroaryl) substituted 1,2-bis(2-bromopyridin-3-yl)ethenes by selective tandem Suzuki–Miyaura cross-coupling reactions

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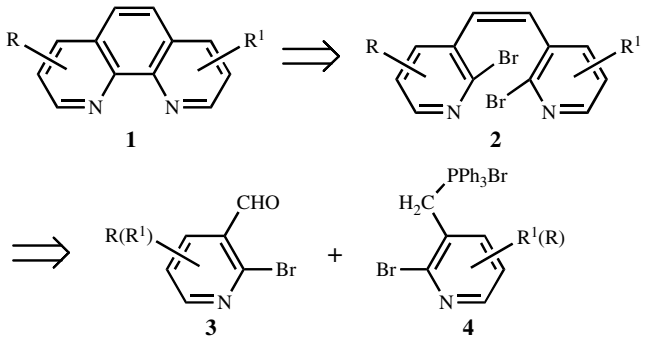
Abstract

A protocol for the synthesis of stereodefined 1-aryl(heteroaryl) substituted 1,2-bis(2-bromopyridin-3-yl)ethenes by tandem Suzuki–Miyaura cross-coupling reactions and an example of convention into 5-phenyl-1,10-phenanthroline are described.

Keywords: Alkenes; Nitrogen heterocycles; Suzuki–Miyaura reaction; Palladium catalysts

We have recently reported a protocol for the synthesis of substituted 1,10-phenanthrolines **1** hinged upon the Ullmann intramolecular coupling of *cis*-1,2-bis(2-bromopyridin-3-yl)ethenes **2**, which were in turn obtained by Wittig reaction of 2-bromonicotinaldehydes **3** with phosphonium salts **4** (Scheme 1).[1] The Wittig reaction allows the synthesis of *cis*-1,2-disubstituted alkenes such as **2** with satisfactory cis/trans stereoselectivity, but suffers from poor stereocontrol of the double bond when phosphonium salts are reacted with ketones in order to obtain trisubstituted olefins with the required geometry. Since the obtainment of 1-substituted *cis*-1,2-bis(2-bromopyridin-3-yl)ethenes **5** (Scheme 2) could allow a new access to 5-substituted 1,10-phenantrolines, we have now devoted our attention to find a valuable method for their preparation. Herein, we show the preparation of stereodefined trisubstituted alkenes **5** that can be achieved by sequential selective Suzuki–Miyaura reactions of 2-bromo-3-(2,2-dibromovinyl)pyridines **7** (Scheme 2). The potentiality of this strategy to obtain 5-aryl-1,10-phenanthrolines is also demonstrated.



Scheme 1.

We sought to realize the synthesis of **5** via sequential selective palladium-catalyzed arylation–arylation of **7** with organometal reagents (Scheme 2). While selective Pd-catalyzed trans-monoarylation of 1,1-dibromo-1-alkenes gives (*Z*)-1-bromo-1-arylethenes, which has been achieved with a variety of arylmetals containing Zn,[2] Sn[3] and B[4]; the scope of the second substitution to produce stereodefined trisubstituted alkenes had been essentially limited to some cases. In particular, to the best of our knowledge, only one example of Pd-catalyzed arylation in the second step of the disubstitution has been reported, and this process has been accomplished using organostannanes as the coupling partners.[3]

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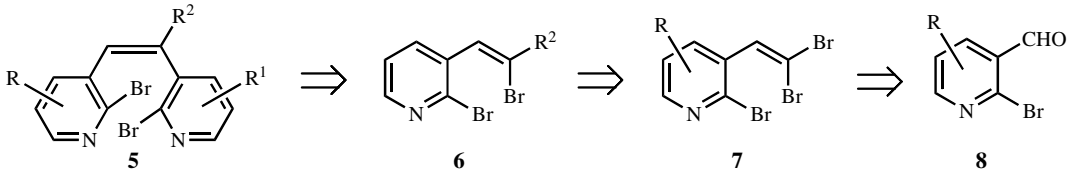


Scheme 2.

Organoboron compounds used in the Suzuki–Miyaura cross-coupling[5] represent a valuable alternative to the use of organostannanes utilized in the Stille coupling.[6] Moreover, a number of organoboron compounds are now commercially available or readily prepared from a variety of starting points via transmetallation or hydroboration reactions.[5] Since the Suzuki–Miyaura reaction has proven to be successful for the selective trans-monoarylation and the symmetrical diarylation of 1,1-dibromo-1-alkenes to (*Z*)-1-bromo-1-alkenes[4] and tri- or tetrasubstituted alkenes,[3,7] respectively, it was of interest to explore this reaction to obtain the stereodefined trisubstituted alkene **5**.

Starting our investigation, we were aware of the fact that **7** contains not only two *gem*-dibromomides with different reactivity, but also the highly electrophilic Br–pyridine bond. Although it is known that the rate of palladium-catalyzed cross-coupling reaction of the (*E*)-bromide of 1,1-dibromo-1-alkenes is higher than that of the related (*Z*)-bromide, there are no data about their reactivity in the presence, in the molecule, of additional reactive halogen–carbon bonds.

With this considerations in mind, 1,1-dibromoalkene **10**, obtained from aldehyde **9** according to Corey and Fuchs procedure[8] (CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 1 h, 85%), was reacted with 1.05 mol equiv of phenylboronic acid in the presence of 2.5 mol % of Pd_2dba_3, 15.0 mol % of tri(2-furyl)phosphine (TFP) and 2.0 equiv of Cs_2CO_3 in 1,4-dioxane/H_2O (5 + 2 mL) at 65 °C for 14 h to afford the expected (*Z*)-2-bromo-3-(2-bromo-2-phenylvinyl)pyridine **11** in 87% yield (Scheme 3). Considering the good results obtained in this way,[4] no other catalysts or reaction conditions were further explored. Then, to assess the relative reactivity of the two remaining bromides, alkene **11** was submitted to a second coupling with phenylboronic acid using 5.0 mol % of Pd_2dba_3 (TFP (30.0 mol %), Cs_2CO_3 (2.0 equiv) in 1,4-dioxane/H_2O (5 + 2 mL)) (Scheme 3). We were gratified to find that the trisubstituted alkene **12** was formed in 74% yield after 14 h. Established the greater reactivity of the two *gem*-dibromides with respect to the pyridine bromide, the stereoselectivity of the reaction was examined by reacting **11** with 4-methoxy-3-methylphenylboronic acid and pyridylboronate **17** (Scheme 3). In both the cases, the coupling occurred with the retention of configuration, and the stereodefined tri-substituted alkenes **13** and **14** were isolated in 85% and 70% yield, respectively. Finally, the target 1,2-bis(2-bromopyridin-3-yl)-1-phenylethene **15** was obtained in good yield (77%) by cross-coupling of **11** with pyridylboronate **18** (Scheme 3).

These results demonstrate clearly that in tribromide **10** the insertion of the Pd(0)-complex into the (*E*)-bromoalkene bond is faster than that into the (*Z*)-bromoalkene bond that is in turn faster than that into the Br–pyridine bond (Fig. 1). That should be of interest since contrast with the products obtained in the Pd(0)-catalyzed coupling reactions of (*Z*)-2-bromo-5-(2-bromovinyl)furan **19** in which the initial Pd-attack onto the Br–furan bond is followed by that on the Br–alkene bond[9] (Fig. 1). In fact, since the Br–pyridine bond is more electrophilic than the Br–furan bond, it should be expected that in the coupling of **11**, which is formed after the first coupling of **10** with phenylboronic acid, the oxidative addition of Pd(0) onto the Br–pyridine bond should be faster than that onto the (*Z*)-bromoalkene bond.

On the basis of these findings, the synthetic scope of the Pd-catalyzed synthesis of 1-aryl(heteroaryl) substituted 1,2-bis(2-bromopyridin-3-yl)ethenes **5** was explored using a variety of boronic acids or boronate esters. The results are summarized in Table 1. Uniformly, satisfactory results were obtained in the monoarylation of **10** with organoboron derivatives with both electron deficient (entries 2 and 3) and electron rich (entry 4) groups to give the corresponding (*Z*)-1-bromo-1-aryl(eteroaryl)-1-alkenes in

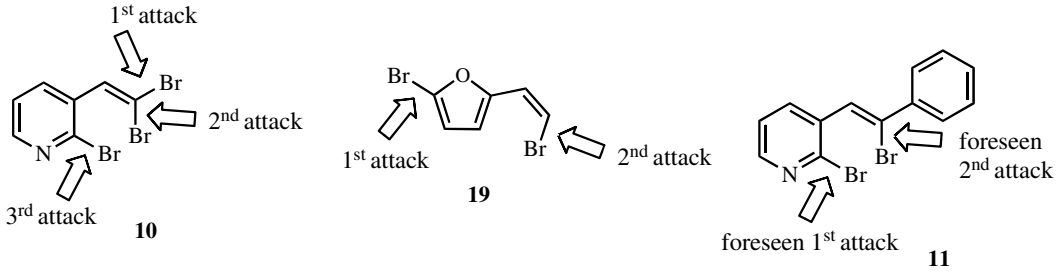
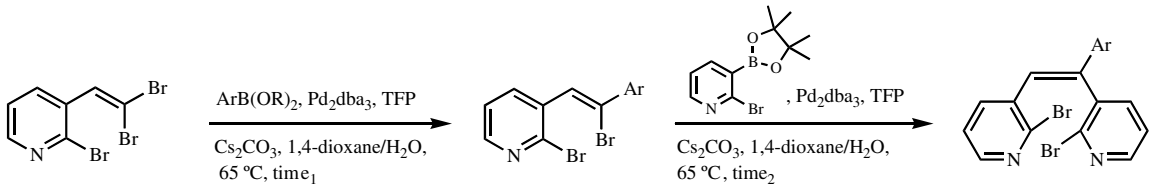


Fig. 1.

Table 1
Synthesis of 1-aryl(heteroaryl) substituted 1,2-bis(2-bromopyridin-3-yl)ethenes



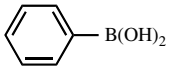
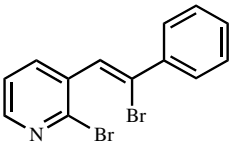
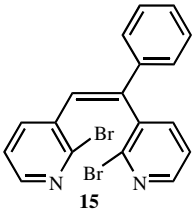
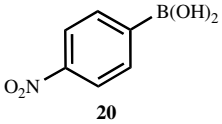
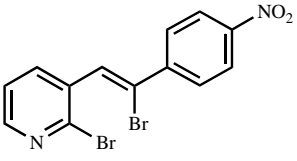
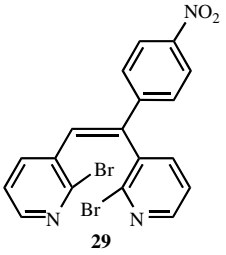
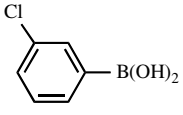
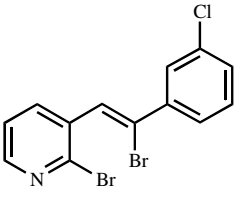
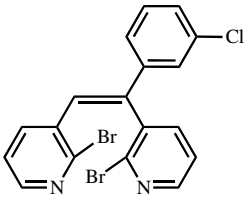
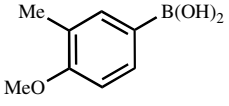
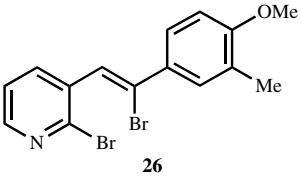
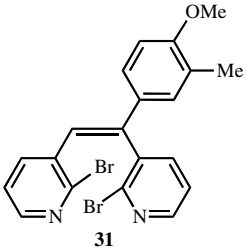
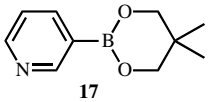
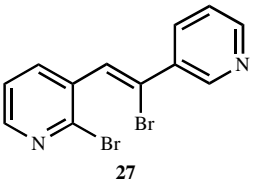
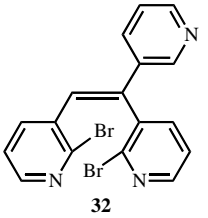
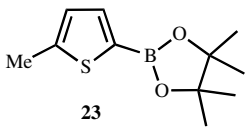
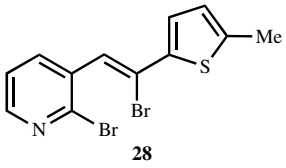
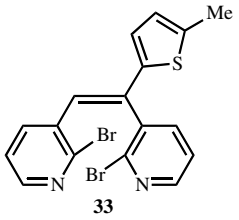
Entry	$ArB(OR)_2$	Bromoalkene[a]	$Time_1$ (h)	Yield[b] (%)	Tri-substituted[c] alkene	$Time_2$ (h)	Yield[b] (%)
1	 **16**	 **11**	14	87	 **15**	30	77
2	 **20**	 **24**	15	68	 **29**	30	53
3	 **21**	 **25**	15	80	 **30**	30	66
4	 **22**	 **26**	10	84	 **31**	30	71
5	 **17**	 **27**	14	70	 **32**	40	63

Table 1 (*continued*)

Entry	$ArB(OR)_2$	Bromoalkene[a]	$Time_1$ (h)	Yield[b] (%)	Tri-substituted[c] alkene	$Time_2$ (h)	Yield[b] (%)
6	 **23**	 **28**	17	65	 **33**	30	52

[a] Reaction conditions: 1,1-dibromoalkene (1.0 mmol), boronic acid or ester (1.05 equiv), Pd_2dba_3 (2.5 mol %), TFP (15.0 mol %), Cs_2CO_3 (1.0 M in H_2O, 2.0 mL, 2.0 equiv), 1,4-dioxane (5 mL), 65 °C.

[b] Isolated yields after flash chromatography.

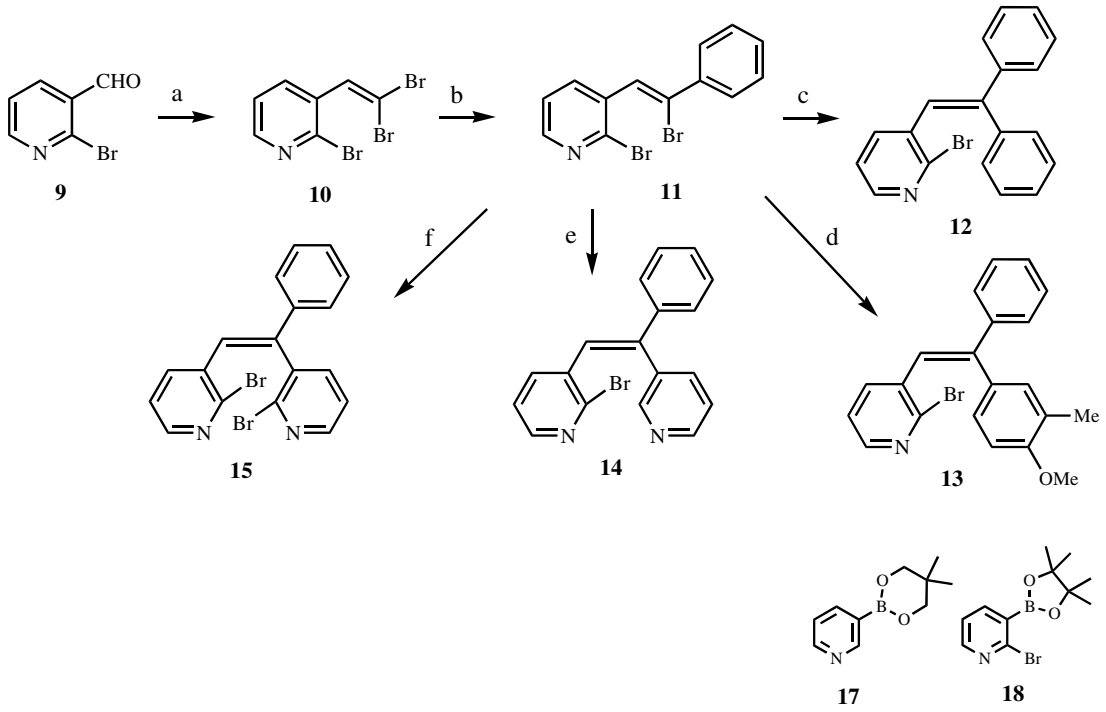
[c] Reaction conditions: **12**, **24**–**28** (1.0 mmol), **18** (1.05 equiv), Pd_2dba_3 (5.0 mol %), TFP (30.0 mol %), Cs_2CO_3 (1.0 M in H_2O, 2.0 mL, 2.0 equiv), 1,4-dioxane (5 mL), 65 °C.

satisfactory yields (68–84%). These results did not change substantially when both π-deficient and π-excessive heteroaromatic organoboron reagents (entries 5 and 6) were used (64–70% yield). The successive cross-coupling of alkenes **24**–**28** with the boronate ester **18** afforded adequate yields (52–77%) of the stererodefined trisubstituted alkenes **29**–**33**.

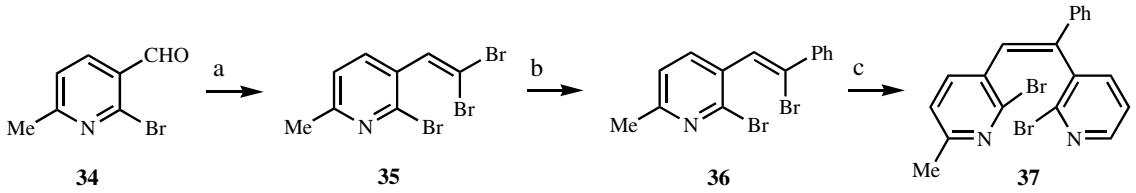
Next, in order to extend the scope of this method to provide alkenes **5** with additional substituents on the pyridine ring, 2-bromo-3-(2,2-dibromovinyl)-6-methylpyridine **35**, prepared from pyridinecarboxaldehyde **34**,[10] was cross-coupled with phenylboronic acid to give **36** in high yield (86%) (Scheme 4). Subsequent reaction of **36** with **18** afforded *cis*-1,2-dipyridylethene derivative **37** in 51% yield.

Moreover, the feasibility to accomplish the preparation of alkenes **5** by an one-pot process of sequential coupling of **10** with two different organoboron compounds was shortly examined. Thus, the reaction of **10** with phenylboronic acid in the presence of 2.5 mol % of Pd_2dba_3 was first carried out in the usual way and then 1.05 equiv of pyridylboronate **18** and 5.0 mol % of Pd_2dba_3 [TFP (30.0 mol %), Cs_2CO_3 (2.0 equiv) in 1,4-dioxane/H_2O (5 + 2 mL)] were added to the reaction vessel and heating was continued for 24 h (Scheme 3).[11] The expected *cis*-1,2-dipyridylethene **15** was isolated in 65% yield that is very close to that obtained in the two-step protocol (67% overall).

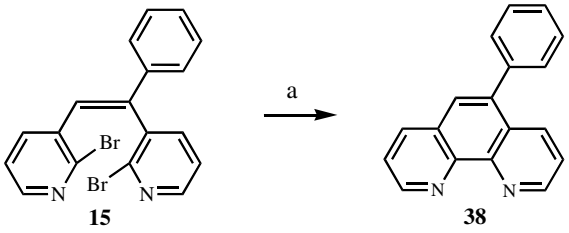
Finally, in order to demonstrate the potentiality of this protocol to obtain 5-substituted 1,10-phenanthrolines, the



Scheme 3. Reagents and conditions: (a) CBr_3, PPh_3, CH_2Cl_2, 0 °C to rt 85%; (b) $PhB(OH)_2$ (**16**), Pd_2dba_3 (2.5%), TFP (15%), 1,4-dioxane, Cs_2CO_3 (2.0 equiv), H_2O, 65 °C, 14 h, 87%; (c) $PhB(OH)_2$, Pd_2dba_3 (5%), TFP (30%), 1,4-dioxane, Cs_2CO_3 (2.0 equiv), H_2O, 65 °C, 24 h, 74%; (d) conditions in (c), 3-Me-4-$MeOC_6H_3B(OH)_2$, 14 h, 85%; (e) conditions in (c), **17**, 24 h, 70%; (f) conditions in (c), **18** 24 h, 77%.



Scheme 4. Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 85%; (b) $PhB(OH)_2$, Pd_2dba_3 (2.5%), TFP (15%), 1,4-dioxane, Na_2CO_3 (2.0 equiv), H_2O, 65 °C, 14 h, 87%; (c) **18**, Pd_2dba_3 (5%), TFP (30%), 1,4-dioxane, Na_2CO_3 (2.0 equiv), H_2O, 65 °C, 24 h, 51%.



Scheme 5. Reagents and conditions: (a) Cu, DMF, reflux, 2 h, 72%.

1,2-dipyridylethene derivative **15** was submitted to Ullmann intramolecular coupling (Scheme 5). Thus, by heating under reflux a DMF solution of **15** in the presence of copper powder,[1] 5-phenylphenanthroline **38** was formed in 72% yield.

In conclusion, we have reported the first example of stereoselective tandem arylation–arylation of 1,1-dihalo-1-alkenes to give trisubstituted alkenes under Suzuki–Miyaura cross-coupling reactions. The new protocol has been exploited to obtain stereodefined 1-aryl(heteroaryl) substituted *cis*-1,2-bis(2-bromopyridin-3-yl)ethenes. It is worthy to note in the sequential cross-coupling processes, the palladium insertion occurs selectively on the Br–C bond on the alkene moiety notwithstanding the high electrophilicity of the Br–pyridine bond. The value of this strategy to obtain a new entry to 5-aryl-1,10-phenanthrolines has also been demonstrated. Further studies on this subject are currently in progress.

Acknowledgements

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References and notes

1. Chelucci, G.; Addis, D.; Baldino, S. *Tetrahedron Lett.* **2007**, *48*, 3359.
2. Minato, A. *J. Org. Chem.* **1991**, *56*, 4052.
3. Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.
4. Shen, W. *Synlett* **2000**, 737.
5. (a) Some reviews *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Dennis, G. A., Ed.; Wiley-VCH: Weinheim, 2005; (b) Miyuaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (d) Kotha, S.; Lahitri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633; (e) Suzuki, A.; Brown, H. C. In *Organic Syntheses via Boranes*; Springer: London, 2003; Vol. 3.
6. Some reviews Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442; Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; Echvarrenm, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3962.
7. Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, 254; Li, Y.-H.; Zhao, X.-M.; Lu, L. *J. Fluorine Chem.* **2004**, *125*, 1821.
8. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
9. Thanh, D.; Tung, D. T.; Langer, P. *Synlett* **2006**, 2812.
10. New, J. S.; Yevich, J. P.; Temple, D. L., Jr.; New, K. B.; Gross, S. M.; Schelmmer, R. F.; Eison, M. S.; Taylor, D. P.; Riblet, L. A. *J. Med. Chem.* **1988**, *31*, 618.
11. *Illustrative experimental for the tandem one-pot diarylation of 1.1-dibromo-1-alkenes:* 2-bromo-3-(2,2-dibromovinyl)pyridine **10** (0.342 g, 1.0 mmol), phenylboronic acid (128.1 mg, 1.05 equiv), Pd_2dba_3 (23.0 mg, 0.025 mmol), tri(2-furyl)phosphine (TFP) (35.0 mg, 0.15 mmol) and Cs_2CO_3 in (1.0 M in H_2O, 2.0 mL) in 1,4-dioxane (5.0 mL) were heated under nitrogen at 65 °C. After 14 h, 2-bromopyridine-3-boronic acid pinacol ester 18 (298.2 mg, 1.05 mmol), Pd_2dba_3 (46.0 mg, 0.05 mmol), TFP (70 mg, 0.30 mmol) and Cs_2CO_3 in (1.0 M in H_2O, 2.0 mL) in 1,4-dioxane (5.0 mL) were added and heating (65 °C) was continued for 30 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with H_2O (10 mL) and brine (5 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 4/6) to afford *(Z)-2-bromo-3-(2-(2-bromopyridin-3-yl)-2-phenylvinyl)pyridine* **15**: 270.5 mg (65% yield); oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.69 (dd, 1H, $J = 4.8$, 1.8 Hz), 8.42 (dd, 1H, $J = 4.8$, 1.8 Hz), 8.17 (ddd, 1H, $J = 7.8$, 1.8, 0.9 Hz), 7.73 (dd, 1H, $J = 7.8$, 1.8 Hz), 7.49–7.40 (m, 3H), 7.39–7.28 (m, 4H), 6.94 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.5, 149.8, 148.6, 141.8, 139.5, 139.4, 137.9, 137.5, 132.3, 129.3, 128.8, 128.4, 127.6, 125.9, 123.0, 122.6.