Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2022, **13**, 10095

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 13th June 2022
Accepted 9th August 2022

DOI: 10.1039/d2sc03294e

rsc.li/chemical-science

Palladium-catalyzed nucleomethylation of alkynes for synthesis of methylated heteroaromatic compounds†

Xi Yang, Gang Wang and Zhi-Shi Ye *

Herein, we disclosed a novel and efficient palladium-catalyzed nucleomethylation of alkynes for the simultaneous construction of the heteroaromatic ring and methyl group. The 3-methylindoles, 3-methylbenzofurans and 4-methylisoquinolines were obtained in moderate to excellent yields. Notably, this methodology was employed as a key step for synthesis of a pregnane X receptor antagonist, zindoxifene, bazedoxifene and AFN-1252. The kinetic studies revealed that reductive elimination might be the rate-determining step.

Introduction

In medicinal chemistry, numerous studies have demonstrated that installation of a methyl group on an aromatic ring can significantly improve the biological activity and pharmacokinetic profile, which is described as the "magic methyl" effect.[1] For instance, thiophene PTP1B inhibitor **II**, in which a methyl group was installed at the 4-position of the thiophene ring, displayed a 2135-fold boost in potency compared with its precursor **I** (Fig. 1A).[2] Additionally, the methylated aromatic ring as a ubiquitous structural unit is widely present in pharmaceuticals, natural products and biological molecules (Fig. 1B).[3] Bazedoxifene is a selective estrogen receptor modulator in clinical development for the prevention of postmenopausal osteoporosis.[3b] AFN-1252 is a potent inhibitor of enoyl-acyl carrier protein reductase (FabI).[3f] Dehydrocorydalin, which is an alkaloid isolated from traditional Chinese herb *Corydalis yanhusuo*, regulates protein expression of Bax and Bcl-2.[3h] As a result, development of an efficient and general strategy for the rapid construction of methylated aromatic compounds would substantially motivate medicinal chemists to explore the "magic methyl" effect in drugs and accelerate the discovery of new drugs.

Transition-metal-catalyzed methylation of (hetero)aromatic compounds is undoubtedly a straightforward and powerful strategy for the construction of methylated (hetero)aromatic compounds, and has received considerable attention from the synthetic community in the past few decades.[4] Various aromatic compounds assembled with leaving groups, including magnesium,[5] zinc,[6] tin,[7] boron,[8] halides,[9] and so on,[10] have successfully achieved methylation through a transmetalation and oxidative addition process (Scheme 1A). Additionally, in view of the atom-economic and eco-friendly process, transition-metal-catalyzed C–H methylation of (hetero)aromatic compounds has witnessed explosive development (Scheme 1A).[4,11] Despite these impressive advances, they have mainly focused on the direct introduction of the methyl group into aromatic rings, while the transformation for simultaneous construction of the (hetero)aromatic ring and methyl group remains unknown.

The transition-metal-catalyzed intramolecular nucleophilic cyclization of alkynes has emerged as an attractive and powerful tool for the construction of heteroaromatic rings including indoles, benzofurans and isoquinolines.[12] Consequently, we envisioned that simultaneous construction of the heteroaromatic ring and methyl group could be achieved through nucleometalation/methylation of alkynes (Scheme 1B). To realize this proposal, we had to overcome the following

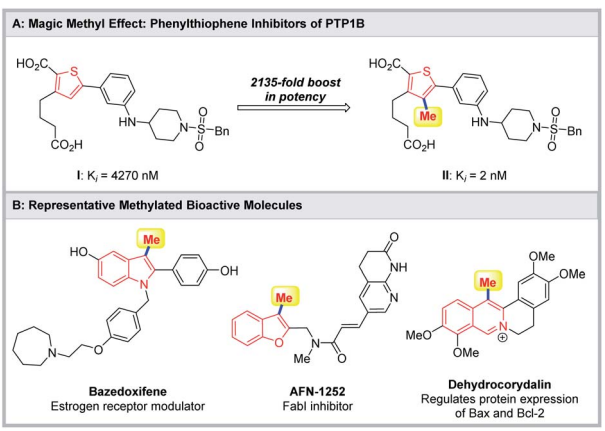
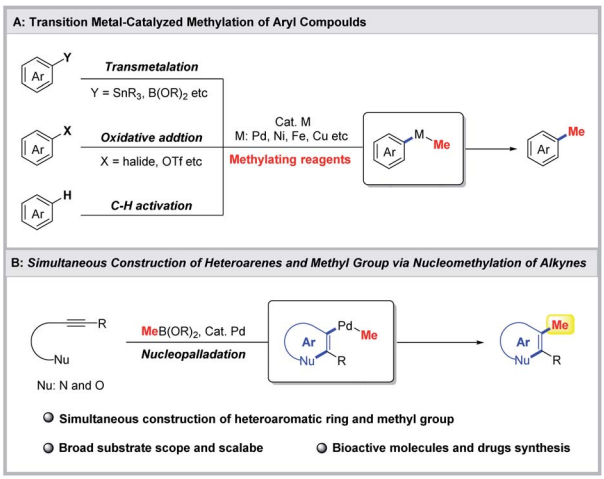


Fig. 1 Importance of methylated aromatic compounds.

Zhang Dayu School of Chemistry, Dalian University of Technology, Dalian 116024, P. R. China. E-mail: yzhsh1984@dlut.edu.cn

† Electronic supplementary information (ESI) available. See https://doi.org/10.1039/d2sc03294e



Scheme 1 Construction of the methylated aromatic ring *via* transition-metal-catalyzed methylation.

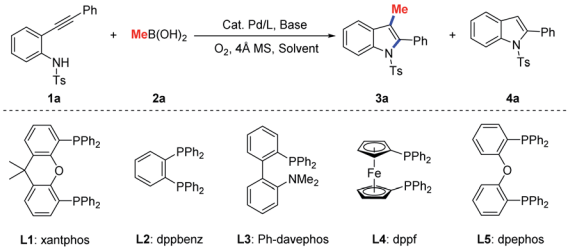
challenges: (1) the transition-metal catalyst promoted the successive nucleophilic cyclization and methylation; (2) competitive protonolysis for the nucleometalation intermediate of alkynes would impede the methylation.[13] Herein, we describe a palladium-catalyzed nucleomethylation of alkynes for the simultaneous construction of a heteroaromatic ring and methyl group. The present protocol features mild reaction conditions, broad substrate scope and scalability. Moreover, the method has been used in the synthesis of a pregnane X receptor antagonist, zindoxifene, bazedoxifene and AFN-1252.

Results and discussion

Initially, 2-alkynylanilide **1a** and methylboronic acid **2a** were chosen as the model substrates to evaluate the feasibility of our hypothesis. Various bases were first examined using $Pd(OAc)_2$ and xantphos (**L1**) as the catalyst combo (entries 1–4, Table 1). The results showed that the base played a crucial role in the reaction. Using 4-dimethylaminopyridine (DMAP) as base, the competitive protonolysis completely suppressed the methylation (entry 1, Table 1). Delightfully, K_2CO_3 and K_3PO_4 successfully promoted the aminopalladation/methylation, affording the desired product 3-methylindole **3a** in 81% and 84% yield, respectively (entries 2 and 3, Table 1). Replacement of THF with toluene as solvent resulted in poor reactivity (entry 5, Table 1). The transformation failed when DCM and DMSO were employed as the reaction medium. The further assessment of palladium precursors revealed that $Pd(TFA)_2$ is the best choice and the desired product **3a** was isolated in 95% yield (entry 10, Table 1). Additionally, although $PdCl_2$ showed an excellent ratio of **3a**/**4a**, the yield was disappointing (entry 9, Table 1).[14] It is worth noting that a significant ligand effect was observed. When Ph-davephos (**L3**) was employed for this transformation, only 4% yield of the desired product **3a** was obtained (entry 12, Table 1). dpephos (**L5**) also exhibited excellent reactivity with 92% yield (entry 14, Table 1). Moreover, the other methylating reagents, including $MeBF_3K$, trimethylboroxine and MeB(pin), did not show better reactivity than methylboronic acid **2a** (entries 15–17, Table 1). Remarkably, the reactivity was maintained very well when the amount of catalyst was reduced to 5 mol% (entry 18, Table 1).

Having identified the optimum conditions, the substrate scope for construction of 3-methylindoles *via* aminopalladation/methylation of 2-alkynylanilides was evaluated. As illustrated in Table 2, various 2-alkynylanilides **1** reacted smoothly with methylboronic acid **2a** to provide the desired 3-methylindoles **3** in moderate to excellent yields. Within the aryl unit of substrate **1**, the electronic properties of the substituent at the 4-position had a dramatic effect on the reactivity. For example, the 5-methoxy-3-methylindole **3c** was delivered in 96% yield, whereas only 50% yield of 5-chloro-3-methylindole **3d** was observed. It is noted that substrate **1** possessing the chloro group at the 6-position of the phenyl ring displayed high reactivity, giving product **3k** in 92% yield. When R^1 was an aryl group, the 2-alkynylanilides containing methoxy (**1l** and **1u**), methyl (**1m** and **1s**), fluoro (**1o** and **1v**), chloro (**1p** and **1t**), acetyl (**1q**), and nitro (**1r**) functional groups were

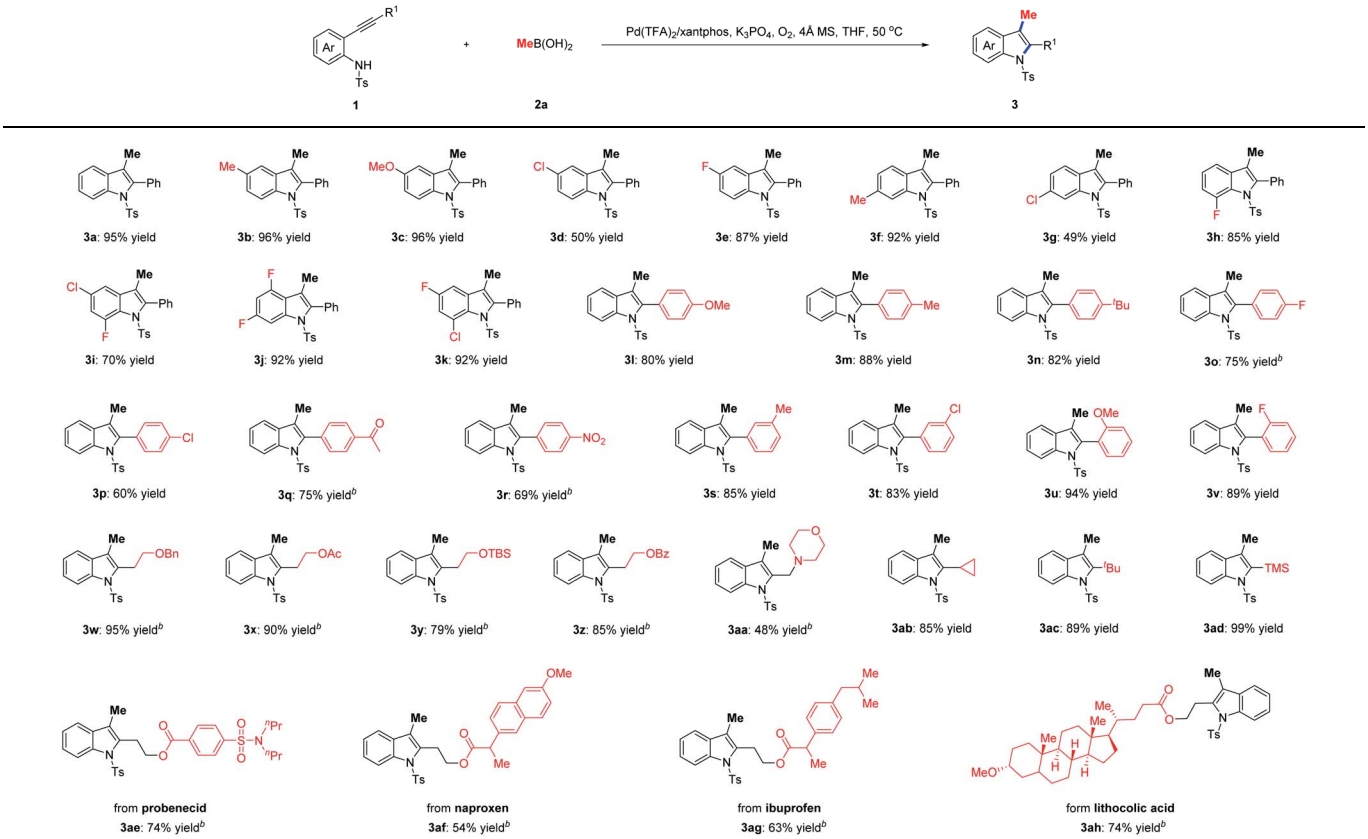
Table 1 Optimization of the reaction conditions[a]



Entry	Pd cat.	L	Solvent	Base	3a/4a	3a yield (%)
1	$Pd(OAc)_2$	**L1**	THF	DMAP	0 : 1	0
2	$Pd(OAc)_2$	**L1**	THF	K_2CO_3	1 : 0.05	81
3	$Pd(OAc)_2$	**L1**	THF	K_3PO_4	1 : 0.12	84
4	$Pd(OAc)_2$	**L1**	THF	KOAc	1 : 0.66	60
5	$Pd(OAc)_2$	**L1**	PhMe	K_3PO_4	1 : 4.6	18
6	$Pd(OAc)_2$	**L1**	DCM	K_3PO_4	N. D.	<5
7	$Pd(OAc)_2$	**L1**	DMSO	K_3PO_4	N. D.	<5
8	$Pd(OAc)_2$	**L1**	1,4-Dioxane	K_3PO_4	1 : 0.27	78
9	$PdCl_2$	**L1**	THF	K_3PO_4	1 : 0.03	33
10	**$Pd(TFA)_2$**	**L1**	**THF**	**K_3PO_4**	**1 : 0.03**	**97/95[b]**
11	$Pd(TFA)_2$	**L2**	THF	K_3PO_4	1 : 1.1	20
12	$Pd(TFA)_2$	**L3**	THF	K_3PO_4	1 : 19.0	4
13	$Pd(TFA)_2$	**L4**	THF	K_3PO_4	1 : 0.37	46
14	$Pd(TFA)_2$	**L5**	THF	K_3PO_4	1 : 0.08	92
15[c]	$Pd(TFA)_2$	**L1**	THF	K_3PO_4	1 : 0.08	56
16[d]	$Pd(TFA)_2$	**L1**	THF	K_3PO_4	1 : 0.04	60
17[e]	$Pd(TFA)_2$	**L1**	THF	K_3PO_4	—	—
18[f]	**$Pd(TFA)_2$**	**L1**	**THF**	**K_3PO_4**	**1 : 0.05**	**95[b]**

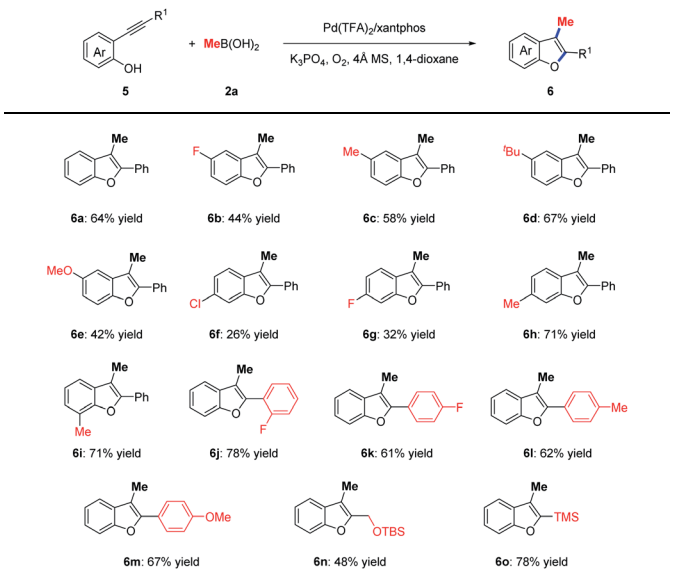
[a] **1a** (0.10 mmol), **2a** (0.30 mmol), Pd cat. (10 mol%), **L** (11 mol%), K_3PO_4 (1.5 eq.), solvent (2.0 mL), 4 Å MS (100 mg), O_2 balloon, 50 °C, 10 h. Yields of **3a** and ratios of **3a** : **4a** were determined by ^{1}H NMR (with 1,3,5-trimethoxybenzene as internal standard). [b] Isolated yield. [c] $MeB(OH)_2$ was replaced by $MeBF_3K$. [d] $MeB(OH)_2$ was replaced by trimethylboroxine. [e] $MeB(OH)_2$ was replaced by MeB(pin). [f] $Pd(TFA)_2$ (5 mol%), **L1** (5.5 mol%).

Table 2 Scope for synthesis of 3-methylindoles[a,b]



[a] **1** (0.10 mmol), **2a** (0.30 mmol), $Pd(TFA)_2$ (5 mol%), xantphos (5.5 mol%), K_3PO_4 (1.5 eq.), THF (2.0 mL), 4 Å MS (100 mg), O_2 balloon, 50 °C, 10 h, isolated yield. [b] $Pd(TFA)_2$ (10 mol%), xantphos (11 mol%).

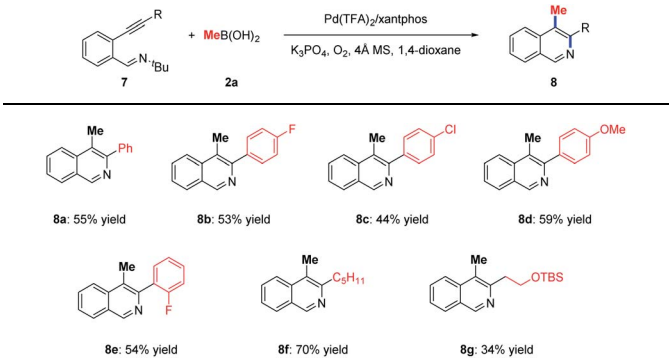
Table 3 Scope for synthesis of 3-methylbenzofurans[a]



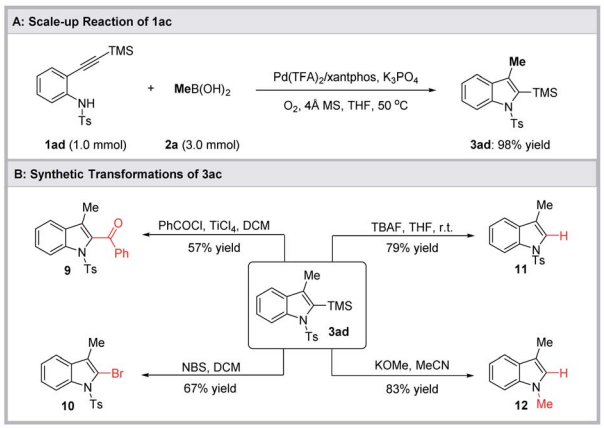
[a] **5** (0.1 mmol), **2a** (0.3 mmol), $Pd(TFA)_2$ (10 mol%), xantphos (11 mol%), K_3PO_4 (1.5 eq.), 1,4-dioxane (2.0 mL), 4 Å MS (100 mg), O_2 balloon, 50 °C, 10 h, isolated yields.

perfectly compatible with the standard conditions, furnishing the desired 3-methylindoles **3l–3v** in 60–94% yields. Notably, the effect of steric hindrance had only a marginal influence on the reactivity. For example, the hindered 2-(2-methoxyphenyl)-3-

Table 4 Synthesis of 4-methylisoquinolines[a]



[a] **7** (0.1 mmol), **2a** (0.3 mmol), $Pd(TFA)_2$ (10 mol%), xantphos (11 mol%), K_3PO_4 (1.5 eq.), 1,4-dioxane (2.0 mL), 4 Å MS (100 mg), O_2 balloon, 50 °C, 10 h, isolated yields.



Scheme 2 Scale-up experiment and synthetic transformations.

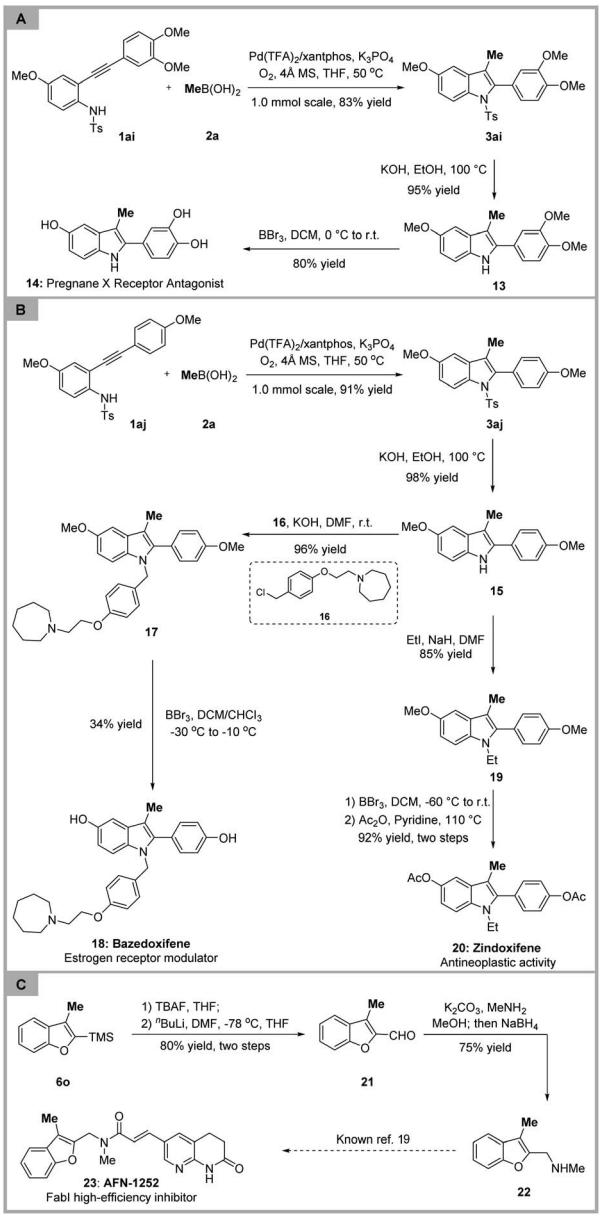
methylindole **3u** was afforded in 94% yield. Additionally, when R^1 was an alkyl group, the transformation still proceeded smoothly to afford the corresponding products **3w–3ac** in satisfactory yield. It is remarkable that the 3-methyl-2-trimethylsilylindole **3ad** was achieved in quantitative yield.

Encouraged by the above results, we further applied this aminopalladation/methylation to late-stage modification of medicinal agents. The 2-alkynylanilides obtained from probenecid, naproxen, ibuprofen and lithocholic acid proceeded smoothly to construct the desired products **3ae–3ah** in satisfactory yield.[15]

Subsequently, synthesis of the 3-methylbenzofurans through oxypalladation/methylation was explored, and the results are summarized in Table 3. As expected, numerous 2-alkynylphenols **5** successfully underwent oxypalladation/methylation, affording the 3-methylbenzofurans **6** in moderate to good yields. Probably due to the electron effects, introducing the fluoro (**6b**) and methoxy (**6e**) groups at the 4-position of the phenyl ring resulted in a diminished yield. Meanwhile, the oxypalladation/methylation of compounds **5h** and **5i** smoothly occurred to deliver target 3-methylbenzofurans **6h** and **6i** in 71 and 71% yields, respectively. When R^1 was an aryl group, the electron-donating group could improve the reactivity. For instance, 3-methylbenzofuran **6m** was furnished in 67% yield. Moreover, substrate **5o** bearing the trimethylsilyl group could be successfully converted to the desired product **6o** with 78% yield.

Furthermore, aminopalladation/methylation was conducted to construct 4-methylisoquinolines (Table 4), which are prevalent structural motifs in numerous bioactive molecules and natural products.[3g,h,16] Subjecting substrate **7a** and methylboronic acid **2a** to the standard conditions furnished the desired product **8a** in 55% yield. It is noteworthy that halides including F and Cl remained intact under this protocol. Moreover, pentyl-substituted substrate **7f** showed good reactivity and 70% yield was achieved. The substrate containing the OTBS group was also a good reaction partner.

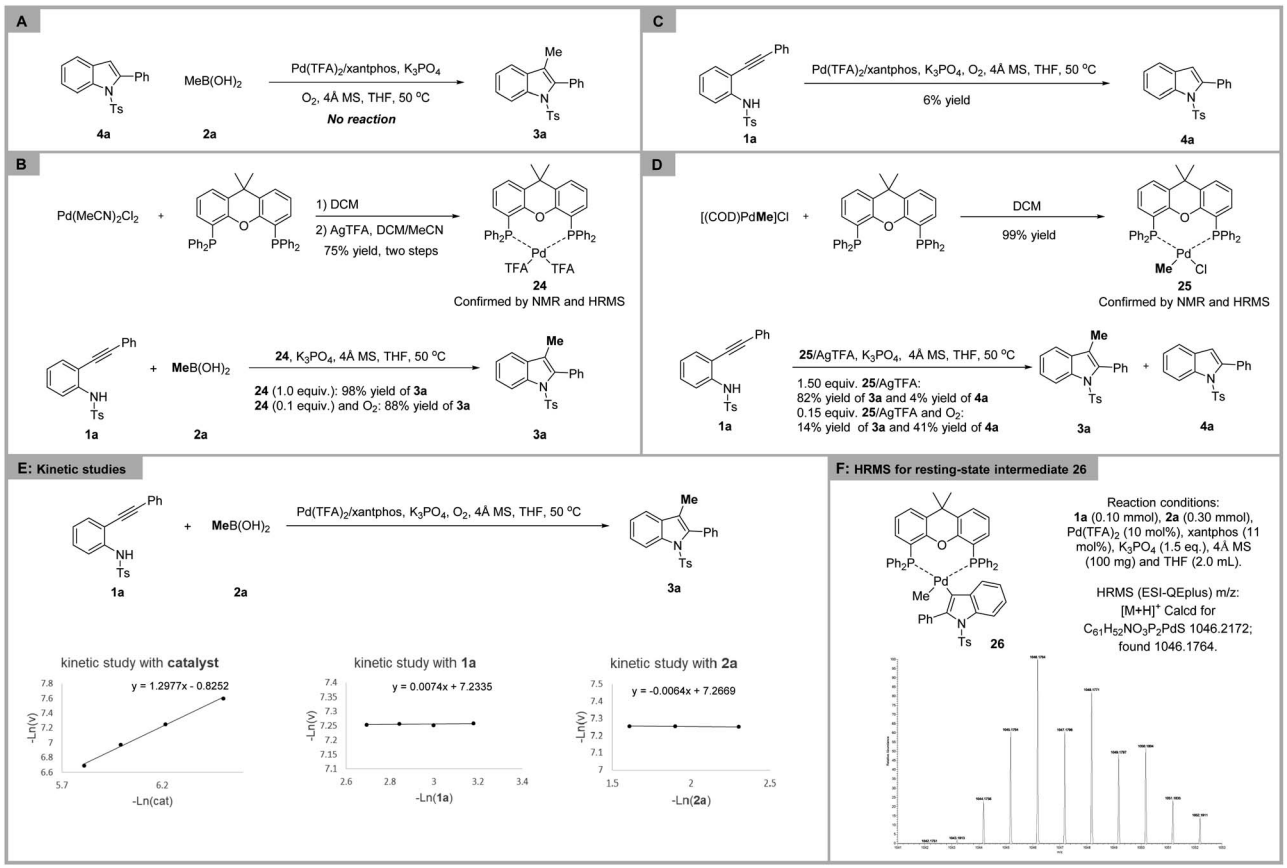
To verify the practical utility of the current protocol, a scale-up experiment and synthetic transformations were carried out



Scheme 3 Synthesis of bioactive molecules and drugs.

(Scheme 2). The aminopalladation/methylation of 2-alkynylanilide **1ad** proceeded smoothly to deliver the target 3-methylindole **3ad** in 98% yield, demonstrating that the reactivity was perfectly maintained in the scale-up reaction. Besides, titanium promoted the cross-coupling reaction of **3ad** with benzoyl chloride affording ketone **9** in 57% yield. Treatment of **3ad** with NBS furnished 2-bromoindole **10** in 67% yield. The TMS group of **3ad** was removed in the presence of TBAF. Compound **12** was constructed through Ts group deprotection/*N*-methylation and removal of the TMS group.

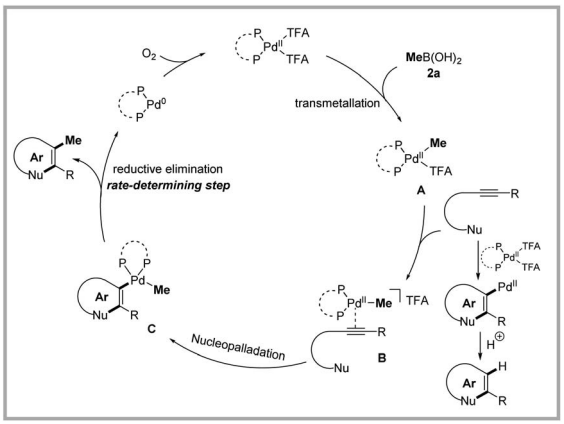
Next, we were keen to perform the synthesis of bioactive molecules and pharmaceutical molecules to further broaden the application of our protocol (Scheme 3). The aminopalladation/methylation of 2-alkynylanilide **1ai** and methylboronic acid **2a** provided the desired 3-methylindole **3ai**



Scheme 4 Mechanism study.

in 83% yield, and subsequent deprotection of the Ts group and demethylation of the methoxy group gave compound **14**, which is a potent pregnane X receptor antagonist.[17] The subjection of **1aj** and methylboronic acid to the standard conditions furnished the corresponding product **3aj** in 91% yield. The deprotection of the Ts group and *N*-alkylation with substituted benzyl chloride **16** afforded compound **17**. Treatment of compound **17** with BBr_3 generated bazedoxifene **18**. Additionally, the anti-oestrogen zindoxifene **20**, which was identified as a drug for the treatment of hormone-dependent mammary carcinomas,[18] could be conveniently constructed from intermediate **15** through *N*-ethylation, demethylation of the methoxy group and esterification. Besides, the TMS group removal of **6o** was followed by formylation and reductive amination to generate compound **22**, which was the key intermediate for the construction of AFN-1252 reported in the literature.[19]

To unveil the mechanistic details of palladium-catalyzed nucleomethylation of alkynes, several control experiments were performed. Treatment of indole **4a** with methylboronic acid **2a** under the standard conditions failed to achieve 3-methylindole **3a**, suggesting that the possibility of palladium-catalyzed C–H methylation of indoles should be ruled out (Scheme 4A). In order to identify the active catalyst, the complex Pd(xantphos)$(TFA)_2$ was synthesized and characterized by NMR and HRMS.[20] The palladium complex **24** was found to catalyze the aminopalladation/methylation of 2-alkynylanilide as efficiently as under the standard conditions (Scheme 4B). The subjection of 2-alkynylanilide **1a** to the standard conditions without methylboronic acid afforded **4a** in only 6% yield, which indicated that the aminopalladation rate of the Pd$(TFA)_2$/xantphos complex might be slow (Scheme 4C). Based on the above results and previous reports,[21] we speculated that transmetallation of the Pd$(TFA)_2$/xantphos catalyst and methylboronic acid might take precedence over aminopalladation of 2-alkynylanilide. To further document the above speculation, the



Scheme 5 Proposed catalytic cycle.

Me–Pd complex **25** was synthesized *via* a method reported in the literature and used for this transformation.[22] When the 2-alkynylanilide **1a** was treated with 1.50 and 0.15 equivalents of Me–Pd complex **25,** 82% and 14% yield of the desired product **3a** was obtained, respectively (Scheme 4D).

Kinetic studies were conducted to investigate the rate-determining step (Scheme 4E). The experimental results showed that the reaction order of 2-alkynylanilide **1a** and methylboronic acid **2a** is zero, indicating that the rate-determining step occurs after the transmetallation of methylboronic acid and aminopalladation of 2-alkynylanilides. According to literature reports, oxidation of Pd(0) to Pd(II) is a kinetically fast process.[23] Therefore, the first-order dependence on the catalyst evidenced that reductive elimination might be the rate-determining step. Additionally, the resting-state intermediate **26** was detected by HRMS (Scheme 4F), which further confirmed the above speculation.

Based on these results, the catalytic cycle was proposed in Scheme 5. Transmetallation of the $Pd(TFA)_2$/xantphos catalyst and methylboronic acid gave Me–Pd complex **A**. Coordination of Me–Pd complex **A** with the triple bond of the substrate was followed by nucleopalladation to deliver intermediate **C**, which underwent reductive elimination to deliver the desired product. The palladium(II) catalyst was regenerated by oxidation with O_2. Although the transmetallation of the $Pd(TFA)_2$/xantphos catalyst and methylboronic acid as the initial step seems more reasonable, the pathway of nucleopalladation followed by transmetallation should not be entirely dismissed.[24]

Conclusions

In conclusion, we have successfully developed a palladium-catalyzed nucleomethylation of alkynes, affording a general and facile approach for the construction of 3-methylindoles, 3-methylbenzofurans and 4-methylisoquinolines in moderate to excellent yields. The late-stage modification of bioactive molecules, scaled up reaction and divergent derivatization have been performed to demonstrate the potentially broad applicability of this protocol. It is worth noting that this methodology was employed for synthesis of a pregnane X receptor antagonist, zindoxifene, bazedoxifene and AFN-1252. Preliminary mechanistic studies suggested that reductive elimination might be the rate-determining step. The reaction represents a new strategy for efficient construction of methylated heteroaromatic compounds, which might be potentially useful for organic synthesis and medicinal chemistry.

Data availability

All experimental data, and detailed experimental procedures are available in the ESI.†

Author contributions

Z.-S. Y. designed the project and directed the study. X. Y. and G. W. carried out the experiments. X. Y., G. W. and Z.-S. Y. analyzed the data and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Natural Science Foundation of China (22071014 and 21801036), Liaoning Revitalization Talents Program (XLYC1907036), and the Fundamental Research Funds for the Central Universities (DUT19TD28) is acknowledged. We thank Bo Wu (DICP) for helpful discussions and manuscript revisions.

References

1 (*a*) S. Sun and J. Fu, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 3283–3289; (*b*) H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256–12267; (*c*) C. S. Leung, S. S. F. Leung, J. Tirado-Rives and W. L. Jorgensen, *J. Med. Chem.*, 2012, **55**, 4489–4500; (*d*) E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga, *Chem. Rev.*, 2011, **111**, 5215–5246.

2 D. P. Wilson, Z.-K. Wan, W.-X. Xu, S. J. Kinincich, B. C. Follows, D. Joseph-McCarthy, K. Foreman, A. Moretto, J. Wu, M. Zhu, E. Binnun, Y.-L. Zhang, M. Tam, D. V. Erbe, J. Tobin, X. Xu, L. Leung, A. Shilling, S. Y. Tam, T. S. Mansour and J. Lee, *J. Med. Chem.*, 2007, **50**, 4681–4698.

3 (*a*) Y.-J. Wu, in *Heterocyclic scaffolds II: Reactions and applications of indoles*, ed. G. W. Gribble, Springer-Verlag Berlin Heidelberg, Berlin, 2010, pp. 1–29; (*b*) C. P. Miller, M. D. Collini, B. D. Tran, H. A. Harris, Y. P. Kharode, J. T. Marzolf, R. A. Moran, R. A. Henderson, R. H. W. Bender, R. J. Unwalla, L. M. Greenberger, J. P. Yardley, M. A. Abou-Gharbia, C. R. Lyttle and B. S. Komm, *J. Med. Chem.*, 2001, **44**, 1654–1657; (*c*) E. von Angerer, *Cancer Treat. Rev.*, 1984, **11**, 147–153; (*d*) H. K. Shamsuzzaman, *Eur. J. Med. Chem.*, 2015, **97**, 483–504; (*e*) R. J. Nevagi, S. N. Dighe and S. N. Dighe, *Eur. J. Med. Chem.*, 2015, **97**, 561–581; (*f*) J. A. Karlowsky, N. Kaplan, B. Hafkin, D. J. Hoban and G. G. Zhanel, *Antimicrob. Agents Chemother.*, 2009, **53**, 3544–3548; (*g*) K. W. Bentley, in *The Isoquinoline Alkaloids*, Hardwood Academic, Amsterdam, 1998; (*h*) J. Lee, E. J. Sohn, S. W. Yoon, C. G. Kim, S. Lee, J. Y. Kim, N. Baek and S. H. Kim, *Phytother. Res.*, 2017, **31**, 441–448; (*i*) S. Lal and T. J. Snap, *Curr. Med. Chem.*, 2012, **19**, 4828–4837; (*j*) E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390–2402; (*k*) J. Mao, Z. Wang, X. Xu, G. Liu, R. Jiang, H. Guan, Z. Zheng and P. J. Walsh, *Angew. Chem., Int. Ed.*, 2019, **58**, 11033–11038; (*l*) X. Xu, M. Ou, Y.-E. Wang, T. Lin, D. Xiong, F. Xue, P. J. Walsh and J. Mao, *Org. Chem. Front.*, 2022, **9**, 2541–2548.

4 (*a*) D. Aynetdinova, M. C. Callens, H. B. Hicks, C. Y. X. Poh, B. D. A. Shennan, A. M. Boyd, Z. H. Lim, J. A. Leitch and D. J. Dixon, *Chem. Soc. Rev.*, 2021, **50**, 5517–5563; (*b*) N.-D. Mao, Y. Ye, X.-T. Zhuo, X.-Y. Ye and T. Xie, *Tetrahedron*, 2021, **96**, 132402; (*c*) J. Huang, Z. Chen and J. Wu, *ACS Catal.*, 2021, **11**, 10713–10732; (*d*) G. Yan,

A. J. Borah, L. Wang and M. Yang, *Adv. Synth. Catal.*, 2015, **357**, 1333–1350; (*e*) Y. Chen, *Chem. - Eur. J.*, 2019, **25**, 3405–3439; (*f*) L. Hu, Y. A. Liu and X. Liao, *Synlett*, 2018, **29**, 375–382.

5 (*a*) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158–163; (*b*) P. L. Castle and D. A. Widdowson, *Tetrahedron Lett.*, 1986, **27**, 6013–6016.

6 K. M. Hossain and K. Takagi, *Chem. Lett.*, 1999, **28**, 1241–1242.

7 (*a*) Y. Andersson, A. P. Cheng and B. Långström, *Acta Chem. Scand.*, 1995, **49**, 683–688; (*b*) M. Suzuki, H. Doi, M. Bjorkman, Y. Andersson, B. Långström, Y. Watanabe and R. Noyori, *Chem.–Eur. J.*, 1997, **3**, 2039–2042.

8 (*a*) L. J. Goossen, *Appl. Organomet. Chem.*, 2004, **18**, 602–604; (*b*) S. Nakajima, H. Takaya and M. Nakamura, *Chem. Lett.*, 2017, **46**, 711–714; (*c*) Z.-T. He, H. Li, A. M. Haydl, G. T. Whiteker and J. F. Hartwig, *J. Am. Chem. Soc.*, 2018, **140**, 17197–17202; (*d*) A. M. Haydl and J. F. Hartwig, *Org. Lett.*, 2019, **21**, 1337–1341.

9 (*a*) J. Blum, D. Gelman, W. Baidossi, E. Shakh, A. Rosenfeld, Z. Aizenshtat, B. C. Wassermann, M. Frick, B. Heymer, S. Schutte, S. Wernik and H. Schumann, *J. Org. Chem.*, 1997, **62**, 8681–8686; (*b*) D. Gelman, H. Schumann and J. Blum, *Tetrahedron Lett.*, 2000, **41**, 7555–7558; (*c*) M. Gray, I. P. Andrews, D. F. Hook, J. Kitteringham and M. Voyle, *Tetrahedron Lett.*, 2000, **41**, 6237–6240; (*d*) T. Wang, B. J. Alfonso and J. A. Love, *Org. Lett.*, 2007, **9**, 5629–5631; (*e*) Y. Nakamura, N. Yoshikai, L. Ilies and E. Nakamura, *Org. Lett.*, 2012, **14**, 3316–3319; (*f*) L. Hu, X. Liu and X. Liao, *Angew. Chem., Int. Ed.*, 2016, **55**, 9743–9747; (*g*) Q. Wu, S. Han, X. Ren, H. Lu, J. Li, D. Zou, Y. Wu and Y. Wu, *Org. Lett.*, 2018, **20**, 6345–6348; (*h*) N. R. Lee, R. T. H. Linstadt, D. J. Gloisten, F. Gallou and B. H. Lipshutz, *Org. Lett.*, 2018, **20**, 2902–2905; (*i*) S. K. Kariofillis, B. J. Shields, M. A. Tekle-Smith, M. J. Zacuto and A. G. Doyle, *J. Am. Chem. Soc.*, 2020, **142**, 7683–7689; (*j*) S. K. Kariofillis, S. Jiang, A. M. Żurański, S. S. Gandhi, J. I. M. Alvarado and A. G. Doyle, *J. Am. Chem. Soc.*, 2022, **144**, 1045–1055; (*k*) Z. Wu, F. Wei, B. Wan and Y. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 4524–4530; (*l*) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman and D. J. Weix, *J. Am. Chem. Soc.*, 2016, **138**, 5016–5019; (*m*) P. Zhang, C. Le and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2016, **138**, 8084–8087.

10 (*a*) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao and Z.-J. Shi, *Chem. Commun.*, 2008, 1437–1439; (*b*) J. Wang, J. Zhao and H. Gong, *Chem. Commun.*, 2017, **53**, 10180–10183; (*c*) D. Heijnen, F. Tosi, C. Vila, M. C. A. Stuart, P. H. Elsinga, W. Szymanski and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2017, **56**, 3354–3359; (*d*) T. Agrawal and S. P. Cook, *Org. Lett.*, 2014, **16**, 5080–5083; (*e*) M. Tobisu, T. Takahira and N. Chatani, *Org. Lett.*, 2015, **17**, 4352–4355; (*f*) T. Okita, K. Muto and J. Yamaguchi, *Org. Lett.*, 2018, **20**, 3132–3135; (*g*) B. Y. Feng, Y. D. Yang and J. S. You, *Chem. Sci.*, 2020, **11**, 6031–6035.

11 (*a*) S. J. Tremont and H. U. Rahman, *J. Am. Chem. Soc.*, 1984, **106**, 5759–5760; (*b*) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634–12635; (*c*) Y. Zhang, J. Feng and C.-J. Li, *J. Am. Chem. Soc.*, 2008, **130**, 2900–2901; (*d*) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1109–1113; (*e*) H. Wang, S. Yu, Z. Qi and X. Li, *Org. Lett.*, 2015, **17**, 2812–2815; (*f*) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2015, **137**, 7660–7663; (*g*) S.-J. Chen, G.-P. Lu and C. Cai, *RSC Adv.*, 2015, **5**, 70329–70332; (*h*) T. Uemura, M. Yamaguchi and N. Chatani, *Angew. Chem., Int. Ed.*, 2016, **55**, 3162–3165; (*i*) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2016, **138**, 10132–10135; (*j*) G. Cera, T. Haven and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 1484–1488; (*k*) T. Sato, T. Yoshida, H. H. Al Mamari, L. Ilies and E. Nakamura, *Org. Lett.*, 2017, **19**, 5458–5461; (*l*) K. Polidano, B. D. W. Allen, J. M. J. Williams and L. C. Morrill, *ACS Catal.*, 2018, **8**, 6440–6445; (*m*) Q. Gao, Y. Shang, F. Song, J. Ye, Z.-S. Liu, L. Li, H.-G. Cheng and Q. Zhou, *J. Am. Chem. Soc.*, 2019, **141**, 15986–15993; (*n*) S. D. Friis, M. J. Johansson and L. Ackermann, *Nat. Chem.*, 2020, **12**, 511–519; (*o*) B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, D. D. Dixon, J.-Q. Yu and P. S. Baran, *Angew. Chem., Int. Ed.*, 2013, **52**, 7317–7320; (*p*) W. Liu, X. Yang, Z.-Z. Zhou and C.-J. Li, *Chem*, 2017, **2**, 688–702; (*q*) J. Jin and D. W. C. MacMillan, *Nature*, 2015, **525**, 87–90; (*r*) H. Wang, S. Zhang, Z. Wang, M. He and K. Xu, *Org. Lett.*, 2016, **18**, 5628–5631.

12 (*a*) J. S. S. Neto and G. Zeni, *Org. Chem. Front.*, 2020, **7**, 155–210; (*b*) J. Li, S. Yang, W. Wu and H. Jiang, *Chem.–Asian J.*, 2019, **14**, 4114–4128; (*c*) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev.*, 2012, **41**, 3929–3968; (*d*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215–PR283; (*e*) K. Krüger, A. Tillack and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2153–2167; (*f*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911; (*g*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920; (*h*) Z.-S. Ye, J.-C. Li and G. Wang, *Synthesis*, 2022, **54**, 2133–2147; (*i*) M. Yamaguchi and K. Manabe, *Heterocycles*, 2022, **104**, 3–26; (*j*) A. A. Abu-Hashem, H. A. R. Hussein, A. S. Aly and M. A. Gouda, *Synth. Commun.*, 2014, **44**, 2285–2312; (*k*) L. De Luca, G. Nieddu, A. Porcheddu and G. Giacomelli, *Curr. Med. Chem.*, 2009, **16**, 1–20; (*l*) K. C. Majumdar, P. Debnath, N. De and B. Roy, *Curr. Org. Chem.*, 2011, **15**, 1760–1801; (*m*) Y. Yamamoto, I. D. Gridnev, N. T. Patil and T. Jin, *Chem. Commun.*, 2009, **34**, 5075–5087; (*n*) H. Cedric, D. Etelinda, D. D. Laetitia and B. Tyler, *ChemCatChem*, 2016, **8**, 2912–2915.

13 (*a*) A. Bruneau, K. P. J. Gustafson, N. Yuan, C.-W. Tai, I. Persson, X. Zou and J.-E. Bäckvall, *Chem.–Eur. J.*, 2017, **23**, 12886–12891; (*b*) M. Yamaguchi and K. Manabe, *Org. Lett.*, 2014, **16**, 2386–2389; (*c*) B. W. Priv.-Doz, C. Alayrac and L. Tevzadze-Saeftel, *Angew. Chem., Int. Ed.*, 2003, **42**, 4257–4260; (*d*) K. Dooleweerdt, T. Ruhland and

T. Skrydstrup, *Org. Lett.*, 2009, **11**, 221–224; (*e*) N. Ototake, Y. Morimoto, A. Mokuya, H. Fukaya, Y. Shida and O. Kitagawa, *Chem.–Eur. J.*, 2010, **16**, 6752–6755; (*f*) E. C. Taylor, A. H. Katz, H. Salgado-Zamora and A. McKillop, *Tetrahedron Lett.*, 1985, **26**, 5963–5966; (*g*) G. Wang, J.-C. Li, Y.-G. Zhou and Z.-S. Ye, *Org. Lett.*, 2021, **23**, 802–807.

14 The starting material 2-alkynylanilide **1a** was recovered in 37% yield. Additionally, 2,2′-diphenyl-1,1′-ditosyl-1*H*,1′*H*-3,3′-biindole was isolated in 6% yield.

15 (*a*) Y. L. Chow, M. Sogame and F. Sato, *Sci. Rep.*, 2016, **6**, 38129; (*b*) Z.-Z. Ma, W. Xu, N. H. Jensen, B. L. Roth, L.-Y. Liu-Chen and D. Y. W. Lee, *Molecules*, 2008, **13**, 2303–2312; (*c*) Z.-H. Zhang, Y. Yan, A.-J. Deng, H.-J. Zhang, Z.-H. Li, T.-Y. Yuan, L.-H. Fang, L.-Q. Wu, G.-H. Du and H.-L. Qin, *Chin. Chem. Lett.*, 2018, **29**, 131–135.

16 When ethylboronic acid was employed for the reaction, trace amounts of the desired product were observed.

17 Ž. Hodnik, L. Peterlin Mašič, T. Tomašić, D. Smodiš, C. D'Amore, S. Fiorucci and D. Kikelj, *J. Med. Chem.*, 2014, **57**, 4819–4833.

18 R. Stein, M. Dowsett, D. Cunningham, J. Davenport, H. Ford, J.-C. Gazet, E. von. Angerer and R. Coombes, *Br. J. Cancer*, 1990, **61**, 451–453.

19 P. J. Hergenrother, E. J. Geddes, B. S. Drown, S. E. Motika and E. N. Parker, PCT Int. Appl., WO 2019177975 A1, 2019.

20 G. Qin, L. Li, J. Li and H. Huang, *J. Am. Chem. Soc.*, 2015, **137**, 12490–12493.

21 (*a*) M. Tian, D. Bai, G. Zheng, J. Chang and X. Li, *J. Am. Chem. Soc.*, 2019, **141**, 9527–9532; (*b*) Y.-P. He, H. Wu, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2020, **59**, 2105–2109.

22 The transmetallation experiment of $Pd(TFA)_2$/xantphos and methylboronic acid was conducted, and the Me–Pd(xantphos)–TFA complex was observed by HRMS (see the details in the ESI†), which clarified that transmetallation of complex **24** with methylboronic acid can occur. Additionally, the stable Me–Pd(xantphos)–Cl complex **25** was synthesized *via* a method reported in the literature: T. L. Andersen, P. Nordeman, H. F. Christoffersen, H. Audrain, G. Antoni and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2017, **56**, 4549–4553.

23 C. Adamo, C. Amatore, I. Ciofini, A. Jutand and H. Lakmini, *J. Am. Chem. Soc.*, 2006, **128**, 6829–6836.

24 A. Arcadi, S. Cacchi, G. Fabrizi, A. Goggiamani, A. lazzetti and F. Marinelli, *Org. Biomol. Chem.*, 2013, **11**, 545–548.