Accepted Manuscript

$PtCl_4$-Catalyzed cyclization of *N*-acetyl-2-alkynylanilines: a mild and efficient synthesis of *N*-acetyl-2-substituted indoles

Nattawadee Chaisan, Wilailak Kaewsri, Charnsak Thongsornkleeb, Jumreang Tummatorn, Somsak Ruchirawat

PII: S0040-4039(18)30026-1
DOI: https://doi.org/10.1016/j.tetlet.2018.01.014
Reference: TETL 49601

To appear in: *Tetrahedron Letters*

Received Date: 15 November 2017
Revised Date: 25 December 2017
Accepted Date: 5 January 2018

Please cite this article as: Chaisan, N., Kaewsri, W., Thongsornkleeb, C., Tummatorn, J., Ruchirawat, S., $PtCl_4$-Catalyzed cyclization of *N*-acetyl-2-alkynylanilines: a mild and efficient synthesis of *N*-acetyl-2-substituted indoles, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.01.014

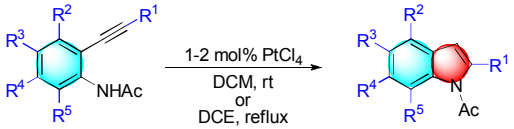
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

$PtCl_4$-Catalyzed cyclization of *N*-acetyl-2-alkynylanilines: a mild and efficient synthesis of *N*-acetyl-2-substituted indoles

Leave this area blank for abstract info.

Nattawadee Chaisan, Wilailak Kaewsri, Charnsak Thongsornkleeb, Jumreang Tummatorn, Somsak Ruchirawat



23 examples
56% to quantitative yields
amenable to gram-scale synthesis

Tetrahedron Letters
journal homepage: www.elsevier.com

$PtCl_4$-Catalyzed cyclization of *N*-acetyl-2-alkynylanilines: a mild and efficient synthesis of *N*-acetyl-2-substituted indoles

Nattawadee Chaisan,[a] Wilailak Kaewsri,[a] Charnsak Thongsornkleeb,[a,b,*] Jumreang Tummatorn,[a,c] and Somsak Ruchirawat[a,c]

[a] *Program on Chemical Biology, Chulabhorn Graduate Institute, Center of Excellence on Environmental Health and Toxicology (EHT), Ministry of Education, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.*
[b] *Laboratory of Organic Synthesis, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.*
[c] *Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Indoles
2-Alkynylanilines
Catalysis
Hydroamination
Cyclization

ABSTRACT

An efficient synthesis of *N*-acetyl-2-substituted indole derivatives *via* direct intramolecular hydroamination of *N*-acetyl-2-alkynylaniline derivatives was developed. The reaction could be applied to a wide range of substrates employing only 1-2 mol% of $PtCl_4$ as the catalyst to furnish the desired indole products in moderate to excellent yields. The current protocol is efficient, reliable and scalable, and could serve as an important tool for convenient and rapid access to this important class of *N*-heterocyclic skeleton from readily available substrates.

Introduction

It would be very difficult to overemphasize the importance of indoles in compounds of biological, pharmacological and medicinal significance. The realm of natural products, marketed drugs and compounds in clinical trials is filled with molecules containing indole nucleus in their structures as exemplified in Figure 1.[1] In fact, indole can be referred as a privileged structure of significant medicinal values. As a result, many chemists are still actively investigating strategies and methods for efficient generation of this essential nucleus as evidenced in the literature.[2]

Several strategies and methods for the preparation of indole derivatives have been described starting from a variety of substrates.[2b,c] One of the most common and reliable strategies focuses on the direct intramolecular hydroamination of 2-alkynylaniline derivatives employing bases,[3a,b] electrochemical method,[3c] and a wide variety of transition metal catalysts.[4] In addition, 2-alkynylaniline derivatives have also been employed in tandem intramolecular cyclization-functionalization to provide indole scaffold with the incorporation of different functional handles.[5] For the method employing transition metal catalysts, the most prevalent catalysts utilized were based on palladium,[4a,b] indium[4e] and gold complexes.[4d,f,h] However, some of the reactions carried out using these catalysts suffer from high catalyst loading (5-10 mol%), high reaction temperatures (50-110 °C), and/or long reaction time (up to 24 h in some systems).[4] In addition, most of these methods seemed to work well only with the 2-alkynylaniline substrates containing free amino group (-NH_2)

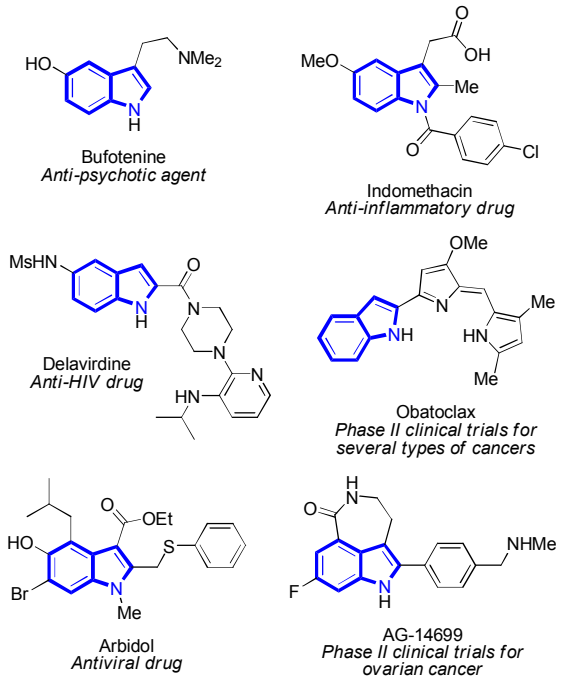
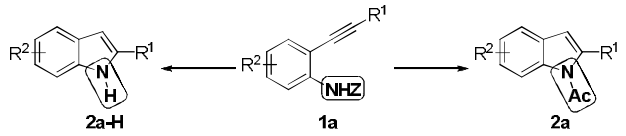


Figure 1. Examples of natural products, marketed drugs and compounds in clinical trials containing indole scaffolds.

while there were only few published methods of *N*-protected 2-alkynylaniline substrates undergoing the cyclization. For examples, $PdCl_2(CH_3CN)_2$ (13 mol%) in refluxing acetonitrile[4b] and $InBr_3$ (5 mol%) in refluxing toluene[4e] were utilized in the cyclization of *N*-acetyl-2-alkynyl anilines to provide the corresponding *N*-acetyl indole products in relatively moderate yields of 69% and 71%, respectively (Scheme 1). To expand the repertoire of methods available in the synthetic toolbox for the construction of this very important class of heterocyclic skeleton, we wish to report $PtCl_4$ as a mild and very efficient catalyst for the conversion of *N*-acetyl-2-alkynylanilines to *N*-acetyl-2-substituted indoles. The current procedure is highlighted by low catalyst loading, low reaction temperature, and applicability to a wide range of substrates.



Scheme 1. Methods for the construction of indole derivatives *via* hydroamination of 2-alkynylanilines.

Results and discussion

To commence the investigation, substrate **1a** was constructed[6] and employed in the optimization study. We subjected compound **1a** to conditions as summarized in Table 1. We focused on screening the reaction with platinum catalysts for the cyclization of substrate **1a**. As summarized in Table 1, when 10 mol% of K_2PtCl_6 was utilized in DCM, the conversion of alkynylaniline **1a** to the corresponding indole **2a** was effected in 86% yield after stirring the reaction mixture at room temperature overnight (entry 1). $PtCl_2$ was next investigated; at 10 mol% in DCM at room temperature overnight, compound **1a** was smoothly converted to indole **2a** with excellent efficiency (98%, entry 2). However, in an attempt to lower the catalyst loading to 2 mol% of $PtCl_2$, product **2a** was obtained in only 37% yield (entry 3). $PtCl_4$ was next investigated, first at 10 mol%. At this amount, the reaction was complete within 3 h and the desired product was obtained in 96% yield (entry 4). When the amount of $PtCl_4$ was lowered to 5 mol%, the reaction took longer to complete (5 h), however, the desired product **2a** was obtained with comparable efficiency (99%, entry 5). In an attempt to study the effect of different solvents, the cyclization was conducted with 5 mol% of $PtCl_4$ in acetonitrile and DMF at room temperature for 4h and 3h, respectively, to find that the reactions produced no product, but only recovered starting material **1a** (entries 6-7). This result was in a stark contrast to the previous report that $PdCl_2$ could effect the same conversion in refluxing acetonitrile,[4b] while $PtCl_4$ in our reaction seemed to be shut down in acetonitrile. From these results, it was sufficient to conclude that DCM was the solvent of choice for this transformation. In lowering the amount of $PtCl_4$ catalyst even further, it was found that 2 mol% of the catalyst could fully convert compound **1a** to the corresponding indole **2a** in excellent yield upon stirring at room temperature in DCM overnight (entry 8). A comparable yield (97%, entry 9) of product **2a** was obtained when the reaction was conducted with 1 mol% of $PtCl_4$. Finally, the reaction with the catalyst loading as low as 0.5 mol% was attempted (entry 10). Under these conditions, the reaction became significantly more sluggish and even after allowing the reaction to stir at room temperature overnight, only 8% yield of the desired indole product was obtained with the recovery of all remaining starting material. We suspected that at such extremely low catalyst loading, the reaction required much longer time to initiate and proceed. From these results, it was clear that $PtCl_4$ was superior to other platinum complexes for the cyclization of alkynylaniline **1a** to indole **2a** with excellent reaction efficiency at a very low loading of 1-2 mol% under mild conditions, in DCM at room temperature overnight.

With the optimal conditions in hands, the scope of the cyclization of 2-alkynylanilines **1** to indole derivatives **2** was next studied. The results of our study are shown in Table 2. For substrate **1a**, the reaction proceeded at room temperature to give the desired product **2a** in excellent yield (99%). When substrate **1a-Bz** (containing *N*-Bz) was employed, the reaction also proceeded excellently at ambient temperature to give the corresponding indole **2a-Bz** in 98% yield A sulfonamide substrate was next investigated with substrate **1a-Ts**, the reaction of which proceeded smoothly at room temperature to give the desired product **2a-Ts** in 98%. We next tested our conditions with *N*-Boc protected substrate (**1a-Boc**) which was found to be well susceptible under our conditions and provided the corresponding product **2a-Boc** in 98% yield. However, for substrate with free NH_2 group, the reaction was more sluggish at room temperature. In this case, the reaction was conducted in refluxing DCE instead and it underwent a very clean conversion to give the corresponding *N*-unprotected indole **2a-H** in 84% isolated yield.

The effects of R^1 group were next studied (R^2-R^5 = H). For substrate **1b** (R^1 = *para*-methoxyphenyl), the reaction again proceeded uneventfully to give the desired indole **2b** in quantitative yield. Next, the substrates with R^1 = *para*-fluorophenyl and *para*-chlorophenyl groups were attempted. The reactions were very clean and could afford the desired indoles **2c**

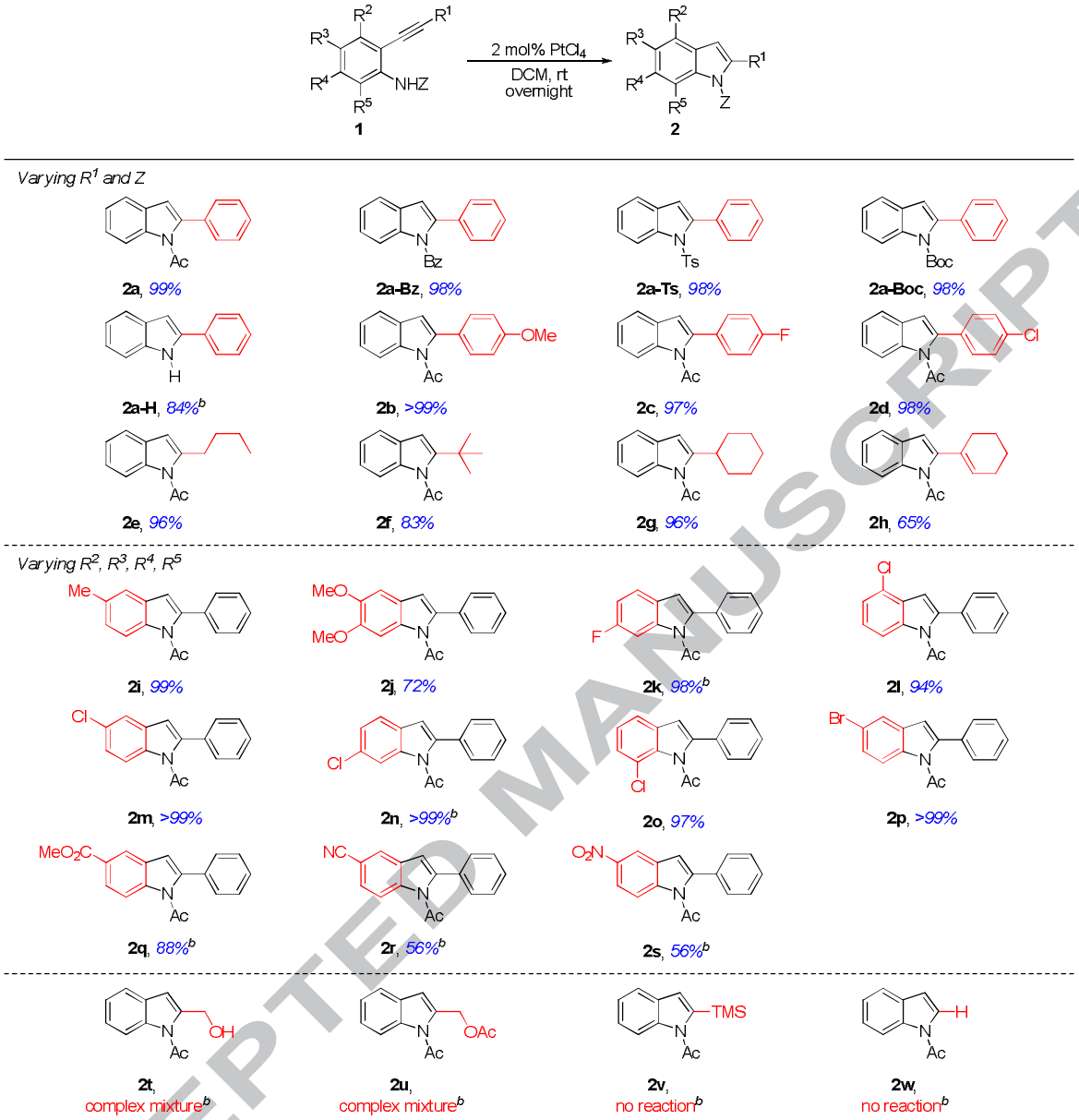
Table 1. Optimization of cyclization of compound **1a** to indole **2a**.

1a **2a**

Entry	Catalyst	Equiv	Solvent	Temp	Time	Yield[a]
1	K_2PtCl_6	10 mol%	DCM	rt	overnight	86%
2	$PtCl_2$	10 mol%	DCM	rt	overnight	98%
3	$PtCl_2$	2 mol%	DCM	rt	overnight	37%
4	$PtCl_4$	10 mol%	DCM	rt	3 h	96%
5	$PtCl_4$	5 mol%	DCM	rt	5 h	99%
6	$PtCl_4$	5 mol%	CH_3CN	rt	4 h	NR
7	$PtCl_4$	5 mol%	DMF	rt	3 h	NR
8	**$PtCl_4$**	**2 mol%**	**DCM**	**rt**	**overnight**	**99%**
9	$PtCl_4$	1 mol%	DCM	rt	overnight	97%
10	$PtCl_4$	0.5 mol%	DCM	rt	overnight	8%

[a]Isolated yields.

Table 2. Scope of the $PtCl_4$-catalyzed cyclization of 2-alkynylanilines **1** to indoles **2**.[a]



[a]Isolated yields. [b]Reactions were conducted in refluxing DCE and monitored by TLC.

and **2d** in almost quantitative yields (97% and 98%, respectively). Substrates with R^1 = alkyl groups were next investigated. As shown in Table 2, substrates **1e** (R^1 = *n*-Bu), **1f** (R^1 = *t*-Bu), and **1g** (R^1 = cyclohexyl) smoothly underwent the cyclization to produce the desired indoles **2e**-**2g** in excellent yields (96%, 83%, and 96%, respectively), although the yield of **2f** (R^1 = *t*-Bu) was slightly lower possibly due to the bulkiness of the *t*-Bu group. However, this result was still a vast improvement over the previously reported procedure of a similar substrate.[4e] Substrate **1h** (R^1 = 1-cyclohexenyl) was also attempted. However, the reaction of this substrate was less efficient, giving the desired product in only 65% yield. It was speculated that the double bond in the cyclohexenyl group may have interfered with the coordination of $PtCl_4$ on the alkyne as alkene could also coordinate to $PtCl_4$.[7]

Next, the effects of R^2-R^5 substituents were examined while keeping R^1 as phenyl group. 2-Alkynylaniline **1i**, substituted with electronically neutral methyl group at R^3, was subjected to the standard conditions. In this case, the reaction provided the desired indole **2i** in excellent yield (99%). However, when the substrate containing electron-donating OMe groups at R^3 and R^4 (**1j**) was attempted, the reaction was less efficient; product **2j** was yielded in 72%. We also examined substrates substituted with halogen atoms. For substrate **1k** with fluorine atom at R^4, the reaction was more sluggish in DCM at room temperature and required heating at reflux in DCE. Under these conditions, product **2k** was cleanly produced in close to quantitative yield (98%). Next, the substrates containing chlorine atoms at various positions were examined. For **1l** with R^2 = Cl, the reaction could proceed smoothly in DCM at room temperature to produce product **2l** in 94% yield. The similar result was also obtained with substrate **1m** with R^3 = Cl; the reaction also easily occurred at room temperature to give the desired indole **2m** in quantitative yield. For substrate **1n** with chlorine atom at R^4 position, the reaction required heating at reflux in DCE to proceed to completion to give indole **2n** in quantitative yield. It should be noted that the conditions required for substrate **1n** to proceed in this case was identical to substrate **1k** with fluorine atom also at R^4 position. For substrate **1o** with R^5 = Cl, the reaction readily proceeded in DCM at room temperature to afford indole **2o** in 97% yield. We next examined substrate containing bromine atom at R^3 position (**1p**) to find that it could also be converted readily to the corresponding indole **2p** in quantitative yield at room temperature. The result of compound **1p** (R^3 = Br) corroborated

well with that of compound **1m** (R^3 = Cl). Among the substrates containing halogen atoms, the position of these halogen atoms seemed to dictate the reactivity of the substrates. They were more reactive with halogen atoms occupying positions R^2, R^3, and R^5 in the substrates (**1l**, **1m**, **1o**, and **1p**), the reactions of which readily proceeded in DCM at room temperature. However, when the halogen atoms occupied position R^4 in the substrates, which is *para* to the alkynyl bond (**1k** and **1n**), the reactivity of these compounds seemed to drop; heating the reactions in refluxing DCE became necessary to reach complete conversions. Nevertheless, all reactions of compounds containing halogen atoms occurred with excellent efficiencies.

For the substrates containing strongly electron-withdrawing substituents on the aniline ring at R^3, as in substrates **1q** (R^3 = CO_2Me), **1r** (R^3 = CN), and **1s** (R^3 = NO_2), all three reactions required refluxing in DCE to achieve the desired conversions. The efficiencies of these reactions became lower when compared to those substrates containing halogen atoms (*vide supra*). For substrate **1q**, the reaction provided the corresponding product (**2q**) in 88% yield while substrates **1r** and **1s** were less efficiently converted to the products, both giving the corresponding indoles **2r** and **2s** in 56% yields. In comparing the reactivity of substrates **1q**-**1s** to substrates **1m** (R^3 = Cl) and **1p** (R^3 = Br) where these substituents were all located at the *para*-position to the amine group, it was clear that the inductive effect of the halogen atoms did not affect the nucleophilicity of the amine group to participate in the hydroamination reaction as much as that of the more strongly electron-withdrawing groups. The inductive effect of halogen atoms was more noticeable when they were at the R^4 position (*para* to the alkynyl group) as evidenced in the reactions of substrates **1k** (R^4 = F) and **1n** (R^4 = Cl), both of which required heating at reflux in DCE to achieve full conversions.

We also attempted the reactions with substrates **1t** with R^1 = CH_2OH and found that the reaction was not successful even with heating in refluxing DCE. The reaction only yielded decomposition with a small amount of the substrate was recovered. A similar result was also observed in the substrate with R^1 = CH_2OAc (**1u**) where it also decomposed under heating in refluxing DCE. These results were not unexpected as allylic and propargylic systems substituted with hydroxyl and acetate groups are known to participate in a variety of transition metal-catalyzed reactions.[8] When we attempted the reactions with substrates **1v** (R^1 = TMS) and **1w** (R^1 = H), we found that there was no reaction in both cases and starting materials were recovered.

In addition to applicability of the procedure to wide scope of substrates, the current conditions could be amenable to gram-scale preparation of indoles. As illustrated in Scheme 2, when substrate **1a** (1.084 g, 4.61 mmol) was subjected to the optimal conditions using 2 mol% of $PtCl_4$, after stirring at room temperature for 70 h, the reaction cleanly afforded indole **2a** in 99% yield (1.074 g, 4.56 mmol). Although requiring longer reaction time for a gram-scale synthesis, the reaction still proceeded with excellent efficiency.

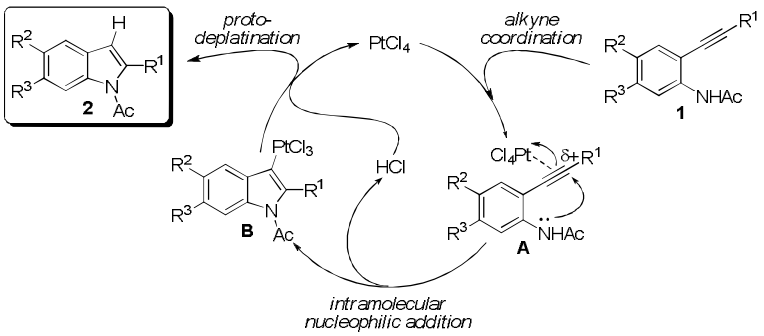
1a (1.084 g, 4.61 mmol) **2a**, 99% (1.074 g, 4.56 mmol)

Scheme 2. Gram-scale preparation of indole **2a**.

The catalytic cycle of the current $PtCl_4$-catalyzed hydroamination of *N*-acetyl-2-alkynylanilines (**1**) was proposed as shown in Scheme 3. The reaction started when $PtCl_4$ coordinated with and activated the triple bond of substrate **1** which would lead to intermediate **A** with nascent partial positive character of the carbon atom next to R^1 group which may be stabilized by R^1. The lone pair electrons on the *ortho*-nitrogen atom then added to the electrophilically activated triple bond. Upon a loss of HCl, intermediate **B** was generated. Proto-deplatination of intermediate **B** ensued to give the corresponding indole product **2** along with the re-generation of $PtCl_4$ to participate in the next catalytic cycle.[9] In hindsight, for the cyclization reactions of substrates **1v** (R^1 = TMS) and **1w** (R^1 = H) (Table 2), we speculated that upon activation by $PtCl_4$ the partial positive character of the alkynyl carbon (intermediate **A**) could not be sufficiently stabilized, and therefore the reactions could not proceed further and only starting materials were recovered (*vide supra*).

Conclusions

In conclusion, we have developed a mild and very efficient $PtCl_4$-catalyzed hydroamination of 2-alkynylaniline derivatives for the convenient preparation of 2-substituted indoles. The procedure was applicable to a wide range of substrates and required very low catalyst loading of 1-2 mol%. Most substrates were cleanly converted to the desired 2-substituted indole products in DCM at room temperature in good to excellent yields, while in some substrates, especially those containing halogen atoms at certain positions and strongly electron-withdrawing substituents, required refluxing DCE conditions to still afford the desired indole products in moderate to excellent yields. The current procedure is very convenient and scalable for gram-scale preparation of indoles, as well as applicable to a wide variety of substrates, thus it would serve as a valuable synthetic tool to organic chemists for the construction of this important *N*-heterocyclic scaffold.



Scheme 3. Proposed mechanism of $PtCl_4$-catalyzed hydroamination of *N*-acetyl-2-alkynylanilines.

Experimental section

General procedure for $PtCl_4$-catalyzed intramolecular hydroamination of N-acetyl-2-alkynylaniline substrates for the synthesis of N-acetyl-2-substituted indole derivatives (Procedure A): A solution of *N*-acetyl-2-phenylethynyllaniline (**1a**) (60.1 mg, 0.2554 mmol, 1.00 equiv) in DCM (5.0 mL) was added with $PtCl_4$ (1.6 mg, 0.0060 mmol, 0.02 equiv) in one portion. The resulting reaction mixture was allowed to stir at room temperature until the reaction was complete as monitored by TLC. Upon completion, the reaction mixture was filtered through a short plug of silica gel while rinsing with DCM to remove the catalyst. The filtrate solution was concentrated under reduced pressure to give 59.4 mg (99 %) of analytically pure indole **2a**.

General procedure for $PtCl_4$-catalyzed intramolecular hydroamination of N-acetyl-2-alkynylaniline substrates for the synthesis of N-acetyl-2-substituted indole derivatives (Procedure B): A solution of *N*-(5-fluoro-2-(phenylethynyl)phenyl)acetamide (**1k**) (52.8 mg, 0.2085 mmol, 1.00 equiv) in DCE (5.0 mL) was added with $PtCl_4$ (1.2 mg, 0.0045 mmol, 0.02 equiv) in one portion. The resulting reaction mixture was equipped with a condenser and heated at reflux until the reaction was complete as monitored by TLC. Upon completion, the reaction mixture was filtered through a short plug of silica gel while rinsing with DCM to remove the catalyst. The filtrate solution was concentrated under reduced pressure to give 51.7 mg (98 %) of analytically pure indole **2k**.

Acknowledgments

This research work was supported in part by grants from Chulabhorn Research Institute (CRI), Chulabhorn Graduate Institute (CGI), Mahidol University, the Center of Excellence on Environmental Health and Toxicology, Science & Technology Postgraduate Education and Research Development Office (PERDO), Ministry of Education. We would also like to gratefully acknowledge the assistance in this work by Mr. Auttaphon Chachavalvuttikul (2016 undergraduate summer intern from Chiang-Mai University, Chiang-Mai, Thailand) and Mr. Itthinan Duangngam (2017 undergraduate summer intern from Chulalongkorn University, Bangkok, Thailand).

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

References and note

1. (a) *The Chemistry of Heterocyclic Compounds;* Taylor, E. C., Saxton, J. E., Eds.; Wiley-Interscience: New York, 1983; Vol. 25. (b) Sundberg, R. J. In *Indoles;* Academic Press: New York, 1996. (c) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761–793. (d) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361. (e) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662. (f) Sonsona, I. G. *Synlett* **2015**, *26*, 2325–2326. (g) El Sayed, M. T.; Hamdy, N. A.; Osman, D. A.; Ahmed, K. M. *Adv. Mod. Oncol. Res.* **2015**, *1*, 20–35. (h) Sravanthi, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, *91*, 1–10.
2. (a) Gribble, G. W. In *Indole Ring Synthesis: From Natural Products to Drug Discovery;* John Wiley & Sons: West Sussex, UK, 2016. (b) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195–7210. (c) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469–6480.
3. (a) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534. (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59* 1571–1587. (c) Arcadi, A.; Bianchi, G.; Inesi, A.; Marinelli, F.; Rossi, L. *Eur. J. Org. Chem.* **2008**, 783–787.
4. (a) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277–4278. (b) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866. (c) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527–1530. (d) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett.* **2007**, 1775–1779. (e) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160–4165. (f) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B. *Tetrahedron Lett.* **2008**, *49*, 7213–7216. (g) Kumaran, E.; Leong, W. K. *Tetrahedron Lett.* **2014**, *55*, 5495–5498. (h) Liang, S.; Hammond, L.; Xu, B.; Hammond, G. B. *Adv. Synth. Catal.* **2016**, *358*, 3313–3318.
5. (a) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001–1011. (b) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2406 – 2409. (c) Tang, S.; Xie, Y.-X.; Li, J.-H.; Wang, N.-X. *Synthesis* **2007**, 1841–1847. (d) Praveen, C.; Karthikeyan, K.; Perumal, P. T. *Tetrahedron* **2009**, *65*, 9244–9255. (e) Xu, C.; Murugan, V. K.; Pullarkat, S. A. *Org. Biomol. Chem.* **2012**, *10*, 3875–3881. (f) Janreddy, D.; Kavala, V.; Kuo, C.-W.; Kuo, T.-S.; He, C.-H.; Yao, C.-F. *Tetrahedron* **2013**, *69*, 3323–3330. (g) Liu, J.; Xie, X.; Liu, Y. *Chem. Commun.* **2013**, *49*, 11794–11796. (h) Feng, X.; Wang, H.; Yang, B.; Fan, R. *Org. Lett.* **2014**, *16*, 3600–3603. (i) Li, Y.-L.; Li, J.; Yu, S.-N.; Wang, J.-B.; Yu, Y.-M.; Deng, J. *Tetrahedron* **2015**, *71*, 8271–8277. (j) Li, P.; Weng, Y.; Xu, X.; Cui, X. *J. Org. Chem.* **2016**, *81*, 3994–4001.
6. For preparation of compound **1a**, and other compounds, as well as their characterization data, please see supporting information.
7. (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398. (c) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042–4059.
8. For some recent examples, please see: (a) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006–3019. (b) Lu, L.; Liu, X.-Y.; Shu, X.-Z.; Yang, K.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 474–477. (c) McAdam, C. A.; McLaughlin, M. G.; Johnston, A. J. S.; Chen, J.; Walter, M. W.; Cook, M. J. *Org. Biomol. Chem.* **2013**, *11*, 4488–4502. (d) Kwon, Y.; Kim, I.; Kim, S. *Org. Lett.* **2014**, *16*, 4936–4939.
9. The generation of HCl and the HCl-induced proto-deplatination of reactions involving organoplatinum species within a catalytic cycle have been studied and proposed previously, please see: (a) Kong, W.; Cui, J.; Yu, Y.; Chen, G.; Fu, C.; Ma, S. *Org. Lett.* **2009**, *11*, 1213–1216. (b) Bender, C. F.; Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2016**, *35*, 113–125.

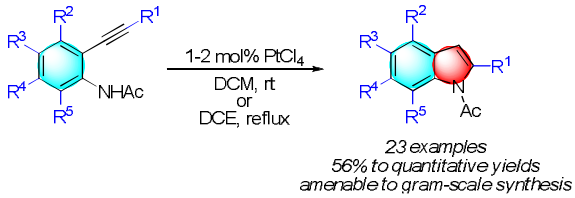
Graphical Abstract

To create your abstract, type over the instructions in the template box below.

$PtCl_4$-Catalyzed cyclization of *N*-acetyl-2-alkynylanilines: a mild and efficient synthesis of *N*-acetyl-2-substituted indoles

Leave this area blank for abstract info.

Nattawadee Chaisan, Wilailak Kaewsri, Charnsak Thongsornkleeb, Jumreang Tummatorn, Somsak Ruchirawat



Fonts or abstract dimensions should not be changed or altered.

$PtCl_4$-Catalyzed cyclization of *N*-acetyl-2-alkynylanilines: a mild and efficient synthesis of *N*-acetyl-2-substituted indoles

Nattawadee Chaisan,[a] Wilailak Kaewsri,[a] Charnsak Thongsornkleeb,[a,b,*] Jumreang Tummatorn,[a,c] and Somsak Ruchirawat[a,c]

[a] *Program on Chemical Biology, Chulabhorn Graduate Institute, Center of Excellence on Environmental Health and Toxicology (EHT), Ministry of Education, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.*
[b] *Laboratory of Organic Synthesis, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.*
[c] *Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.*

Highlights

- $PtCl_4$ is an efficient catalyst for intramolecular cyclization of 2-alkynylanilines.
- A variety of 2-substituted indoles are synthesized in moderate to excellent yields.
- The procedures can be easily applied to a wide scope of easily prepared substrates.
- Only 1-2 mol% loading of $PtCl_4$ is required for efficient and effective conversions.
- The current protocol is applicable to gram-scale preparation of indole derivatives.