A strategy for the synthesis of 2,3-disubstituted indoles starting from *N*-(*o*-halophenyl)allenamides†

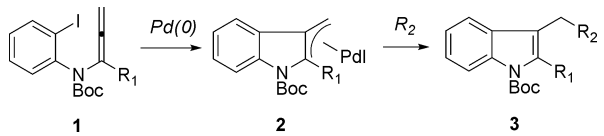
Haruhiko Fuwa* and Makoto Sasaki*

Received 15th May 2007, Accepted 30th May 2007
First published as an Advance Article on the web 19th June 2007
DOI: 10.1039/b707338k

A strategy for the synthesis of 2,3-disubstituted indole derivatives based on an intramolecular carbopalladation–anion capture cascade has been developed, wherein construction of the pyrrole ring and functionalisation of the indole C2 and C3 positions were achieved by extensive use of palladium(0)-catalysed coupling reactions.

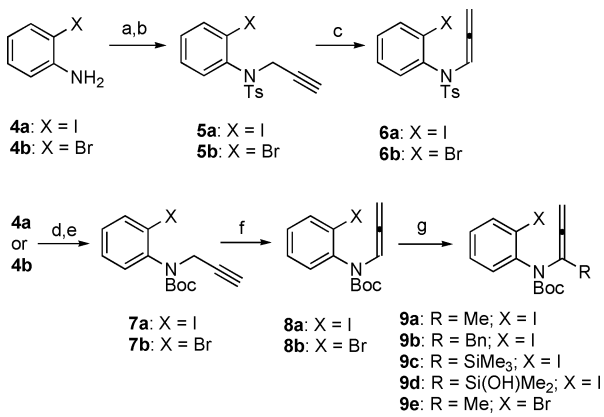
The indole nucleus is a prominent and privileged structure that is widely found in naturally occurring substances and bioactive molecules of pharmaceutical importance.[1] Since the discovery of the Fischer indolisation,[2] the synthesis of indole derivatives has been an active area of research, and numerous reports dealing with their synthesis have been recorded to date.[3] Among these, Fukuyama radical cyclisation,[4] Larock heteroannulation,[5] and Cacchi aminopalladation[6] are the principal general strategies that enable a facile and efficient preparation of 2,3-disubstituted indoles under mild conditions.

Over the past two decades, palladium-catalysed cascade reactions have attracted a great deal of attention from organic chemists because of their ability to generate multiple carbon–carbon bonds to build up complex polycyclic frameworks in a single operation with high atom economy.[7] Grigg and co-workers have reported that the allenyl group can serve as a relay unit in palladium-catalysed cascade reactions; they reported the synthesis of nitrogen heterocycles based on palladium-catalysed cyclisation–anion capture processes involving allenyl species.[8] This strategy has only been applied to the synthesis of an indole-3-acetamido derivative.[9] We envisaged that utilisation of *N*-(*o*-halophenyl)allenamide (**1**), which bears a substituent (R_1) at the α position of the allenamide, would allow for facile generation of the π-allylpalladium intermediate (**2**) *via* carbopalladation, which in turn could be trapped with an appropriate nucleophile, such as an aryl or alkenyl boronic acid or alkylborane,[10] generating a 2,3-disubstituted indole (**3**) (Scheme 1). Importantly, the use of a silicon group as a substituent at the α position of the allenamide moiety would allow for further functionalisation at the C2 position by means of palladium-catalysed cross-coupling reactions. In this sense, construction of the pyrrole ring as well as functionalisation of the C2 and C3 positions can be achieved by extensive use of palladium(0)-catalysed reactions. We describe herein the development of a strategy for the synthesis of 2,3-disubstituted indole derivatives based on a carbopalladation–anion capture cascade starting from *N*-(*o*-halophenyl)allenamides.



Scheme 1 Concept of the present work.

We first prepared starting allenamides **6**, **8**, and **9**, as summarised in Scheme 2. Treatment of *o*-haloanilines **4a,b** with *p*-TsCl followed by propargylation gave alkynes **5a,b**, which were exposed to catalytic KO*t*-Bu in THF at room temperature to afford *p*-Ts-protected allenamides **6a,b**. In a similar manner, *N*-Boc allenamides **8a**,**b** were synthesised. Selective functionalisation of the α-position of **8a**,**b** was performed according to the Hsung protocol.[11,12] Thus, exposure of **8a**,**b** to 2.0 equiv of LDA, followed by the addition of an appropriate electrophile, furnished the desired allenamides **9a–e** in good yields without touching the aryl iodide functionality.



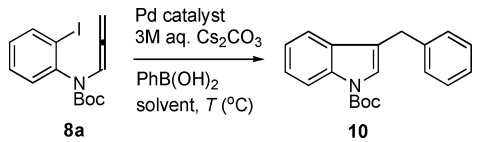
Scheme 2 Synthesis of *N*-(*o*-halophenyl)allenamides. *Reagents and conditions:* (a) *p*-TsCl, pyridine, 80 °C; (b) propargyl bromide, K_2CO_3, DMF, 60 °C, 88% (**5a**), 90% (**5b**); (c) KO*t*-Bu, THF, room temperature, 98% (**6a**), 83% (**6b**); (d) Boc_2O, THF, reflux; (e) propargyl bromide, K_2CO_3, DMF, 60 °C, 89% (**7a**), 100% (**7b**); (f) KO*t*-Bu, THF, room temperature, 83% (**8a**), 91% (**8b**); (g) LDA, THF, −78 °C, then MeI, BnBr, Me_3SiCl or Me_2SiCl_2, −78 °C, 76% (**9a**), 72% (**9b**), ~100% (**9c**), 70% (**9d**), 97% (**9e**).

We then surveyed a series of reaction conditions using allenamide **8a** (1 equiv.), phenylboronic acid (1.1 equiv.), and 3 M aqueous Cs_2CO_3 (3.0 equiv.) as a model case (Table 1). Initial attempts employing $Pd(PPh_3)_4$ or $Pd(OAc)_2$–$2PPh_3$ catalysts were unsuccessful (entries 1 and 2); in each case, only a trace amount of the desired 3-substituted indole **10** was detected in a complex mixture, and no trace amounts of the corresponding "shunt"

Laboratory of Biostructural Chemistry, Graduate School of Life Sciences, Tohoku University, 1-1 Tsutsumidori-amamiya, Aoba-ku, Sendai, 981-8555, Japan. E-mail: hfuwa@bios.tohoku.ac.jp, masasaki@bios.tohoku.ac.jp; Fax: +81-22-717-8896; Tel: +81-22-717-8895

† Electronic supplementary information (ESI) available: Representative experimental procedures and spectroscopic data for compounds **9a**, **10**, **12**–**26**, **28**–**34**. See DOI: 10.1039/b707338k

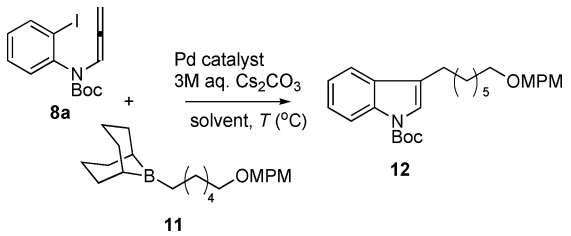
Table 1 Screening of a variety of conditions[a]



Entry	Pd catalyst	Solvent	T/°C	Yield (%)
1	$Pd(PPh_3)_4$	THF	60	Trace
2	$Pd(OAc)_2$–$2PPh_3$	DMF	80	Trace
3	$Pd(OAc)_2$	DMF	80	41
4	$Pd_2(dba)_3$	DMF	80	55
5	$Pd_2(dba)_3$–$8AsPh_3$	DMF	60	36
6	$Pd_2(dba)_3$–$4P(o\text{-tol})_3$	DMF	80	49
7	$Pd_2(dba)_3$	DMF	rt	35
8	$Pd_2(dba)_3$	THF	60	Trace
9	$Pd_2(dba)_3$	Toluene	105	Trace
10	$Pd_2(dba)_3$	CH_3CN	70	31
11	$Pd_2(dba)_3$	EtOH	80	98

[a] All reactions were performed using Pd catalyst (0.1 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), and $PhB(OH)_2$ (1.1 equiv.).

Table 2 Screening of a variety of conditions[a]



Entry	Pd catalyst	Solvent	T/°C	Yield (%)
1	$Pd_2(dba)_3$	EtOH	80	Trace
2	$Pd_2(dba)_3$	DMF	rt	38
3	$PdCl_2(dppf)$	DMF	50	53
4	$PdCl_2(dppf)$–$4AsPh_3$	DMF	50	42

[a] All reactions were performed using Pd catalyst (0.1 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), and alkylborane (1.2 equiv.).

product was observed. In contrast, the use of "ligandless" catalysts such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ turned out to be effective for the present process, giving **10** in moderate yields (entries 3 and 4). Combined use of $Pd_2(dba)_3$ with a weakly donating ligand ($AsPh_3$) or an electron-rich bulky ligand ($P(o\text{-tol})_3$) was found to be detrimental (entries 5 and 6).[13] It is known that oxidative addition of aryl iodides to ligandless palladium(0) catalysts readily occurs because of their high reactivity, although the use of a supporting ligand is generally preferred for Suzuki–Miyaura reaction.[10] An attempt to bring about the present cascade at room temperature lowered the product yield, suggesting a necessity for heating (entry 7). Finally, we examined the effects of solvent. Although changing the solvent to THF, toluene, or CH_3CN led to discouraging results (entries 8–10), the present reaction proceeded smoothly in EtOH at 80 °C, affording the desired **10** in a remarkable 98% yield (entry 11).

We then attempted to apply the established conditions for the synthesis of a variety of 3-substituted indole derivatives. Unfortunately, however, we soon recognised that the conditions developed above did not work well for the case wherein an alkylborane was employed as a nucleophile. This drawback may be attributed to the different nucleophilic properties between arylboronic acid and alkylborane in palladium(0)-catalyzed cross-coupling reactions.[9] Alkylboranes have rarely been used in palladium(0)-catalysed cascade processes[14] and have not been utilized in cyclopalladation–anion capture cascades. Therefore, we also screened the reaction conditions suitable for an alkylborane nucleophile (Table 2). As noted above, only a trace amount of the desired product **12** was obtained using alkylborane **11** (1.2 equiv.), $Pd_2(dba)_3$, and 3 M aqueous Cs_2CO_3 in EtOH at 80 °C. Changing the solvent back to DMF gave a better result, affording a moderate yield of **12** (entry 2). We eventually found that the product yield could be improved to practical levels when $PdCl_2(dppf)$ was employed as a catalyst (entries 3, 4).

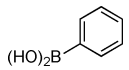
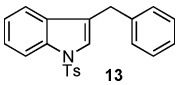
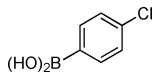
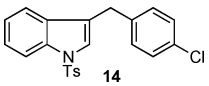
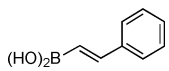
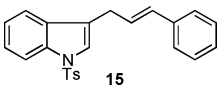
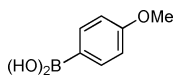
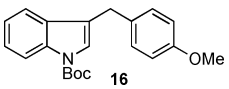
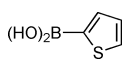
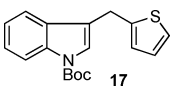
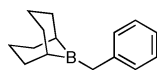
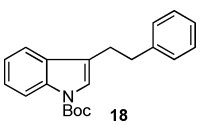
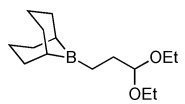
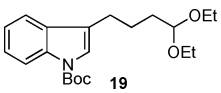
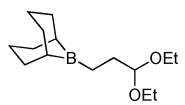
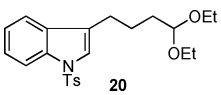
Having established two reliable conditions, we next synthesised a series of 3-substituted indole derivatives to address the versatility of our cascade process. The results are summarised in Table 3. *N*-Tosyl allenamide **6a** also served as a good starting material in the present process (entries 1–3). A wide range of nucleophiles, including arylboronic acids (entries 1, 2 and 4), alkenylboronic acid (entry 3), 2-thiopheneboronic acid (entry 5), and alkylboranes (entries 6–8) were successfully employed, giving a variety of 3-substituted indoles in good to excellent yields. Notably, the aryl bromide **6b** also smoothly entered the carbopalladation–cross-coupling cascade to give **20** in 82% yield.

Application of the present strategy for the synthesis of 2,3-disubstituted indoles starting from α-functionalised allenamides **9a–e** was also successful (Table 4). The indole derivatives with methyl, benzyl, trimethylsilyl, and dimethylsilanolyl functionalities at the C2 position were prepared in good to excellent yields. However, when **9e** was employed as a substrate and an alkylborane generated from acrolein diethylacetal was used as a nucleophile, the desired product **26** was isolated in 42% yield. The major product of this reaction was the shunt product **27**,[15] which was isolated in 56% yield. An attempt to utilise Ph_3As as a co-ligand was not effective for improving the yield of **26**.

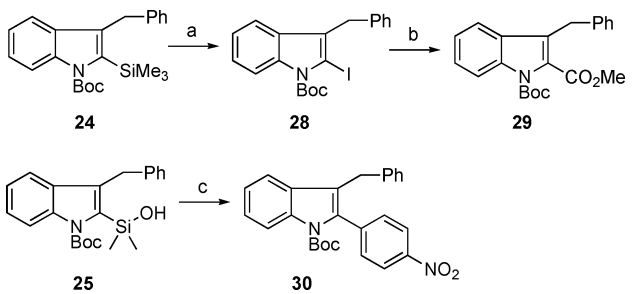
The indole derivatives with a silicon functional group at the C2 position (*e.g.*, **24** and **25**) serve as potential precursors for further palladium(0)-catalysed transformation (Scheme 3).[4] Thus, exposure of **24** to ICl in the presence of $AgBF_4$ (2 : 1 MeOH–THF)[16] smoothly afforded 2-iodo derivative **28**, which in turn underwent clean methoxycarbonylation using a $PdCl_2(dppf)$ catalyst, providing methyl indole-2-carboxylate **29** in a quantitative yield. On the other hand, the Denmark variant[17] of Hiyama cross-coupling[18] of **25** with 4-iodonitrobenzene in the presence of a $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst, CuI, and NaO*t*-Bu in toluene at room temperature furnished the desired cross-coupled product **30** in 89% yield. To the best of our knowledge, this is the first example of a successful application of the Denmark–Hiyama coupling to synthesis of a 2,3-disubstituted indole.

Extension of our strategy could be accomplished simply by trapping the π-allylpalladium intermediate with nucleophiles other than organoboron species.[9] For instance, utilization of *p*-$TolSO_2Na$, NaN_3, and vinyl tri-*n*-butyltin afforded the corresponding sulfone, azide, and vinyl derivatives in excellent yields, respectively (Scheme 4). Upon treatment of **8** with $PdCl_2(dppf)$ in

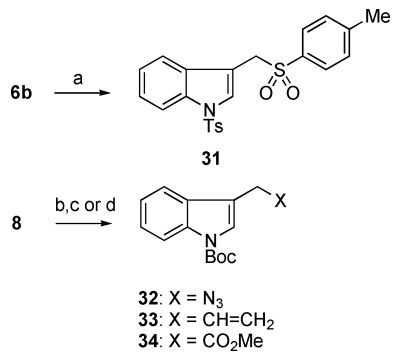
Table 3 Synthesis of 3-substituted indole derivatives

Entry	Allenamide	Boron nucleophile	Product	Yield (%)
1[a]	**6a**		 **13**	88
2[a]	**6a**		 **14**	71
3[a]	**6a**		 **15**	73
4[a]	**8**		 **16**	90
5[a]	**8**		 **17**	58
6[a]	**8**		 **18**	64
7[b]	**8**		 **19**	66
8[c]	**6b**		 **20**	82

[a] $Pd_2(dba)_3$ (0.05 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), EtOH, 80 °C. [b] $PdCl_2(dppf)$ (0.1 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), DMF, 50 °C. [c] $PdCl_2(dppf)$ (0.1 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), DMF, 70 °C.



Scheme 3 Palladium(0)-catalysed functionalisation of the C2 position. *Reagents and conditions:* (a) ICl, $AgBF_4$, 2 : 1 MeOH–THF, 0 °C, 97%; (b) $PdCl_2(dppf)\cdot CH_2Cl_2$, Et_3N, MeOH–DMF, CO (1 atm), 60 °C, 100%; (c) 4-iodonitrobenzene, $Pd_2(dba)_3\cdot CHCl_3$, CuI, NaO*t*-Bu, toluene, room temperature, 89%.

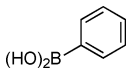
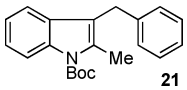
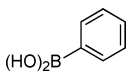
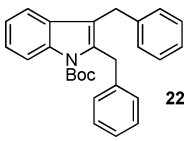
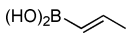
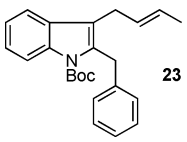
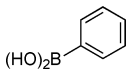
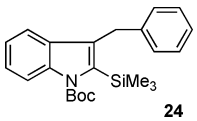
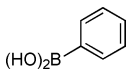
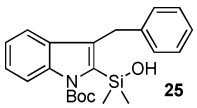
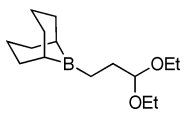
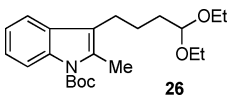
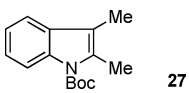


Scheme 4 Synthesis of additional series of 3-substitued indoles. *Reagents and conditions:* (a) *p*-$TolSO_2Na$, $Pd(PPh_3)_4$, DMF, 70 °C, 83%; (b) NaN_3, $Pd(PPh_3)_4$, DMF, room temperature, 97%; (c) vinyl tri-*n*-butyltin, $Pd_2(dba)_3$, DMF, 80 °C, 96%; (d) $PdCl_2(dppf)$, Et_3N, 1 : 2 MeOH–DMF, CO (1 atm), 60 °C, 49%.

the presence of Et_3N in 1 : 2 MeOH–DMF under a CO atmosphere (1 atm), indole-3-acetic acid derivative **34** was synthesised in moderate yield. The above examples further potentiate the generality and versatility of our strategy.

In conclusion, we have developed an efficient strategy for the synthesis of 2,3-disubstituted indole derivatives starting from *N*-(*o*-halophenyl)allenamide based on the carbopalladation–anion capture cascade. Selective introduction of an appropriate silicon group to the α position of the allenamide allows for the synthesis of 2-silyl substituted indole derivatives, which serve as powerful

Table 4 Synthesis of 2,3-disubstituted indole derivatives[a]

Entry	Allenamide	Boron nucleophile	Product	Yield (%)
1	**9a**		 **21**	81
2	**9b**		 **22**	98
3	**9b**		 **23**	84
4	**9c**		 **24**	71 (from 8)
5	**9d**		 **25**	61
6[b]	**9e**		 **26**	42
			 **27**	56

[a] All reactions were performed using $Pd_2(dba)_3$ (0.05 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), boronic acid (1.1 equiv.) in EtOH at 80 °C unless otherwise noted. [b] The reaction was performed using $PdCl_2(dppf)$ (0.1 equiv.), 3 M aq. Cs_2CO_3 (3 equiv.), alkylborane (1.2 equiv.) in DMF at 70 °C.

substrates for further palladium(0)-catalysed transformations at the C2 position. In addition, we have demonstrated that the strategy can be easily extended by utilisation of appropriate nucleophiles in place of organoboron species, providing an additional series of indole derivatives. Application of the present strategy to the search for new bioactive substances is currently underway.

This work was supported in part by a Grant-in-Aid for Scientific Research by the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT).

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