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DEVELOPMENT OF TRIALKYL(2-INDOLYL)BORATES AS POTENTIAL SYNTHETIC INTERMEDIATES

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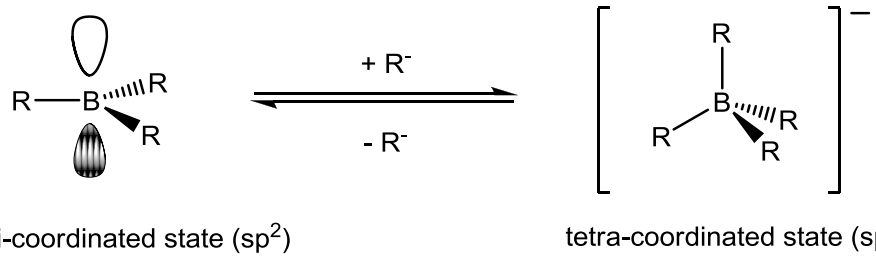
Abstract – This account deals with our investigation of the reaction and synthetic use of indolylborates as versatile synthetic tools; 1) palladium-catalyzed cross-coupling reaction and its use for the synthesis of indole alkaloids and 2) intramolecular alkylmigration in indolylbotrates for the construction of highly elaborate indole derivatives.

INTRODUCTION

The unique electronic structure of boron ($1s^2 2s^2 2p^1$) accounts for its peculiar chemical features. The tri-coordinate state (BR_3; sp^2 hybridization) is in the same plane, with the vacant orbital being perpendicular to the plane. Coordination of R^- to the vacant orbital transforms the tri-coordinate state to a tetra-coordinate state ($^-BR_4$; sp^3 hybridization). This ability of boron to exist in two states (tri-coordinate and tetra-coordinate) is inherently responsible for the unique nature of boron chemistry (Scheme 1).[1]



Scheme 1. Interconversion between two coordinate states

Remarkable advances in organoboron chemistry have produced numerous edifying synthetic applications of organoboron compounds, which have been reviewed several times.[2] The palladium-catalyzed cross-coupling using organoboron compounds in the presence of a base (Suzuki-Miyaura coupling) was developed in 1979, continuing to be an indispensable synthetic methodology.[3]

In spite of the pronounced progress in organoboron chemistry, exploration of organoboron chemistry to heterocyclic chemistry has attracted relatively little attention.[4] We have been intrigued by the direct interaction between boron and the heteroaryl moiety, as well as by the uses of boron-substituted heteroaromatic compounds as powerful reagents in organic syntheses. Accordingly, we have initiated research to elucidate the unique chemical features and the synthetic validity of boryl-substituted heterocyclic compounds as a potential synthetic tool, enabling the development of new synthetic strategies for the construction of elaborate heterocyclic compounds.

First, we prepared a series of dialkylpyridylboranes from the corresponding bromopyridines and trialkylboranes (Figure 1).[5] The dialkylpyridylboranes are exceptionally stable crystals and have chemical features that differ from those of common pyridine derivatives.

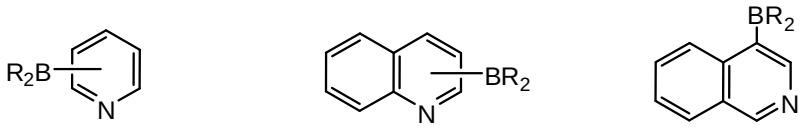
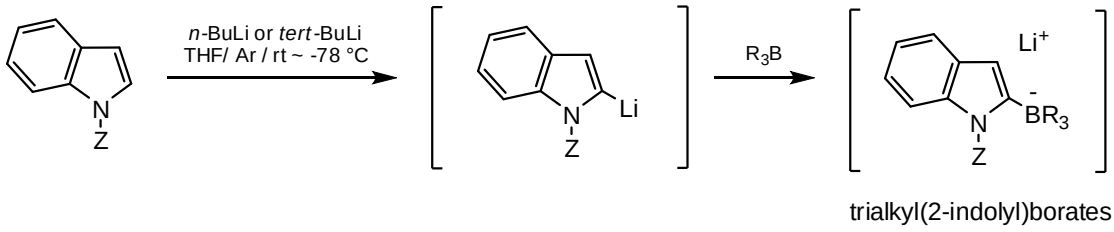


Figure 1. Dialkylpyridylboranes

Next, our attention was turned to investigate boryl-substituted π–excessive heteroaryl compounds. A few examples of π–excessive five-membered heteroaryl boron compounds have been previously reported, but their chemical properties have not been well characterized.[4]

Indole alkaloids and their analogues constitute a structurally diverse class of compounds that exhibit various biological activities, and many of these compounds are widely used as drugs. To date, numerous synthetic strategies have been developed for the preparation of indole derivatives.[6] In the past 10 years or so, we have studied both the reactivity and the synthetic uses of trialkyl(2-indolyl)borates, which are readily generated *in situ* from 2-litioindoles and trialkylboranes. Based on these studies, we have developed new strategies for preparing indole derivatives (Scheme 2).



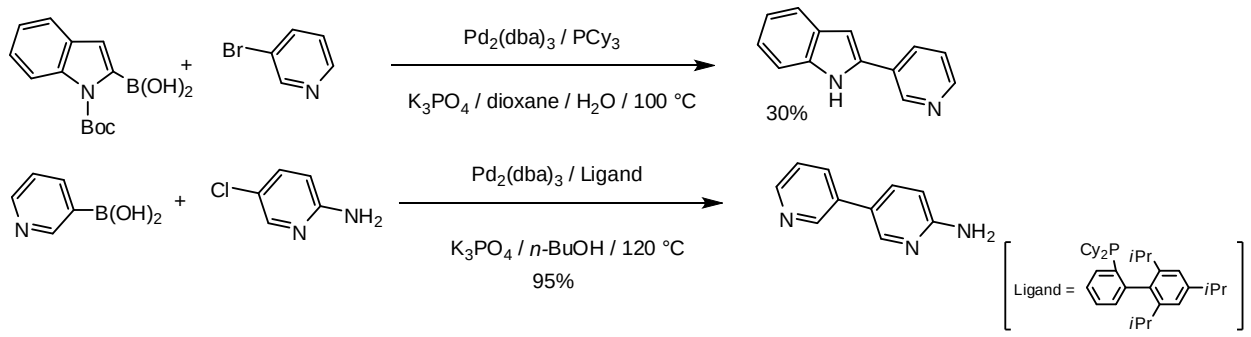
trialkyl(2-indolyl)borates

Scheme 2. Trialkyl(2-indolyl)borates

Characteristically, trialkyl(2-indolyl)borates have an activated enamine moiety because of α-anionic boryl group on the indole ring, which confers trialkyl(2-indolyl)borates with increased reactivity. Here, we disclose a brief overview of trialkyl(2-indolyl)borates as valuable synthetic tools for preparing indole derivatives.

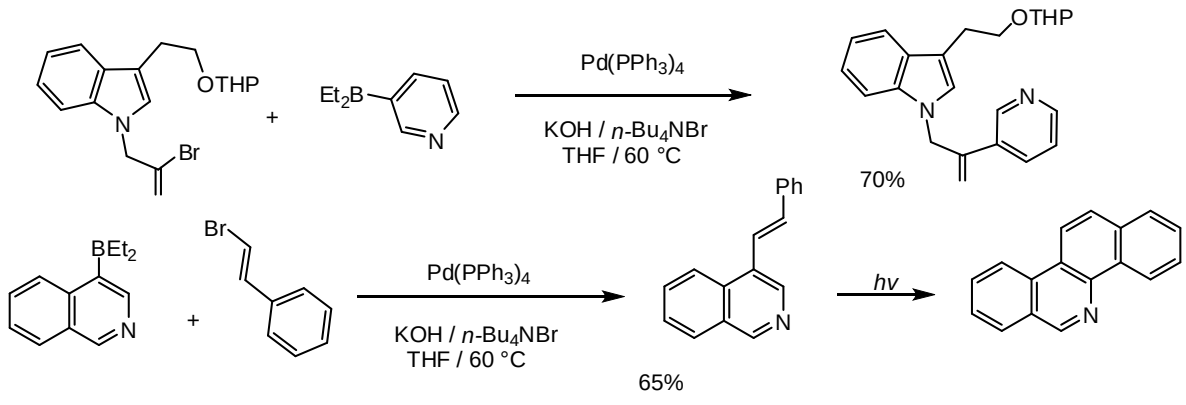
1. PALLADIUM-CATALYZED CROSS-COUPLING REACTION

The use of tri-coordinated organoboron compounds for the palladium-catalyzed reaction in the presence of a base (such as NaOH, K_2CO_3, NaOEt) is a valuable synthetic tool for carbon-carbon bond formation, in which organoboronic acid derivatives are most widely employed as highly effective cross-coupling substrates.[7] Recent progress in this field demonstrated that nitrogen-containing heteroarylboronic acids (such as pyridine, isoquinoline, indole) are adaptable to palladium-catalyzed cross-coupling reactions (Scheme 3).[8]



Scheme 3. Cross-coupling reaction of heteroarylboronic acids

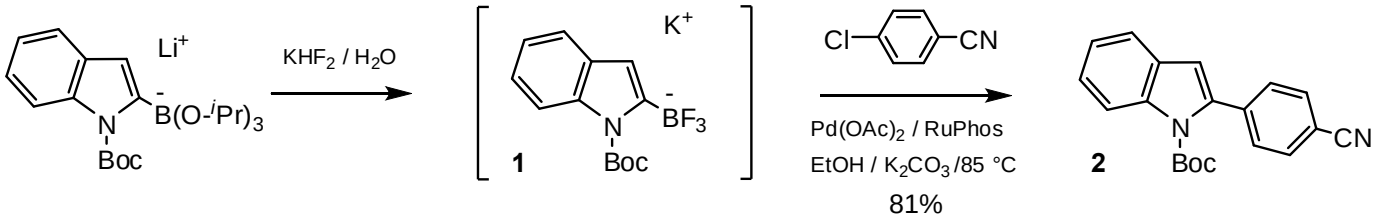
In our previous examination, we established that dialkylpyridylborane derivatives (dialkylpyridyl-, dialkylquinolyl- and dialkylisoquinolyl-boranes) could serve as versatile substrates in the cross-coupling reaction with aryl and alkenyl halides (Scheme 4).[9]



Scheme 4. Cross-coupling reaction of dialkylpyridylboranes

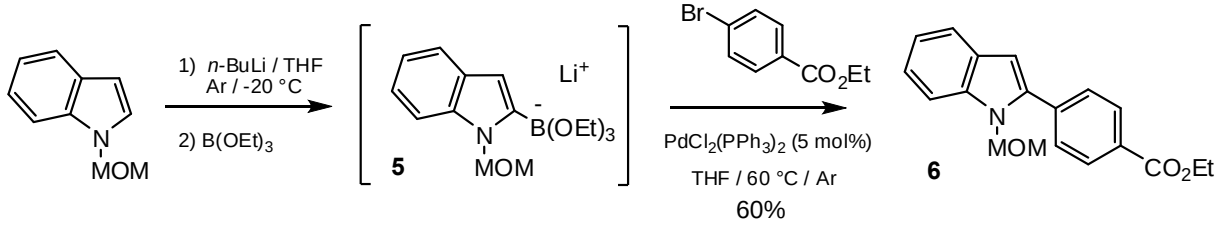
In contrast to numerous examples of cross-coupling reactions using tri-coordinated organoboron compounds, successful applications of tetra-coordinated organoboron compounds are far less common. The reaction of trialkylalkenylborates is sluggish even under forcing conditions.[10] When we attempted the palladium-catalyzed cross-coupling reaction of triethyl(3-pyridyl)borate with iodobenzene, none of the desired cross-coupling products was obtained.[11]

Recently, an efficient cross-coupling protocol was developed that uses heteroaryltrifluoroborates: treatment of (2-indolyl)trifluoroborate **1** with 4-chlorobenzonitrile in the presence of $Pd(OAc)_2$ (1 mol%), RuPhos (2 mol%) and Na_2CO_3 (2 equiv.) in EtOH at 85 °C provided coupling product **2** (Scheme 5).[12]



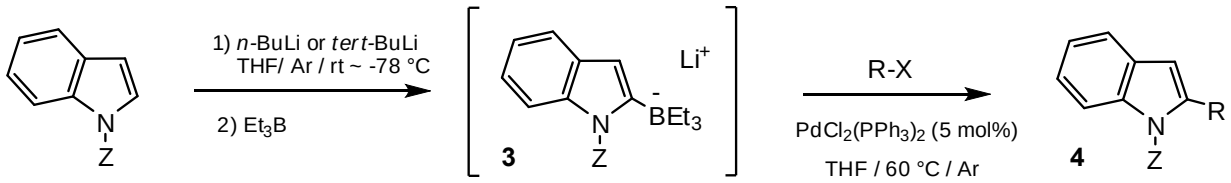
Scheme 5. Cross-coupling reaction of (2-indolyl)trifluoroborate **1**

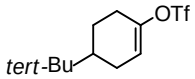
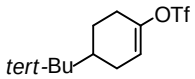
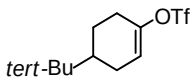
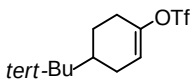
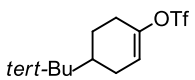
On the other hand, from screening cross-coupling reaction conditions for various heteroaryltrialkylborates, we found that triethyl(2-indolyl)borates **3** showed notable reactivity in the absence of an additional base (Table 1).[13] Typically, the reaction was carried out by simply heating **3**, generated *in situ* from the corresponding 2-lithioindoles and triethylborane, with halides or triflates in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (5 mol%) in THF under an argon atmosphere at 60 °C. The reaction of indolylborates **3a**, **3b** and **3c** having *N*-Me, *N*-OMe and *N*-Boc groups produced 2-substituted indoles **4** in good yields (Runs 1-3, 7-9 and 13-15), while **3d** and **3e** with strongly electron withdrawing *N*-SO_2Ph and *N*-SEM groups, respectively, were far less effective (Runs 4, 5, 10, 11, 15 and 16). Although the reaction of **3f** with *N*-MOM group gave no cross-coupling products (Runs 6, 12 and 17), triethoxyindolylborate **5** reacted with ethyl 4-bromobenzoate to give **6** in 60% yield (Scheme 6).



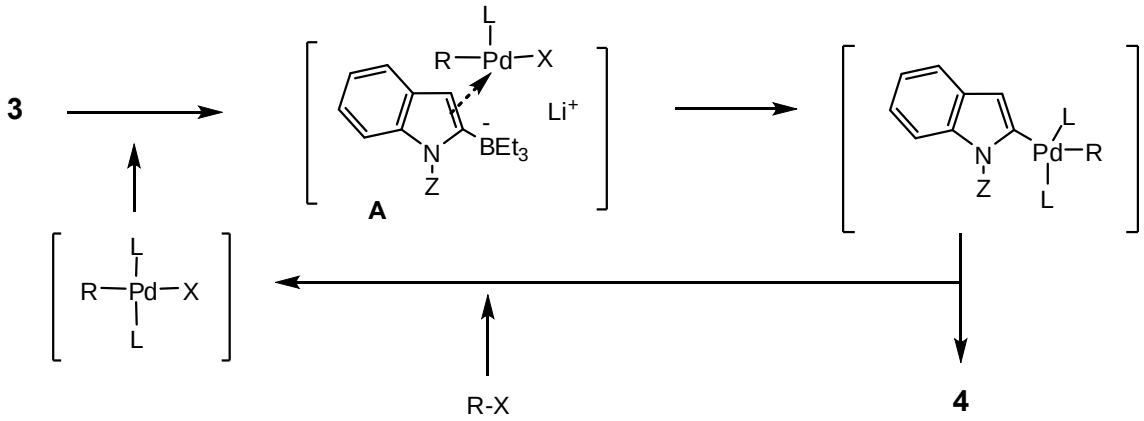
Scheme 6. Cross-coupling reaction of triethoxyindolylborate **5**

Table 1. Palladium-catalyzed cross-coupling reaction of triethyl(2-indolyl)borates **3**



Run	**3**	R-X	Time	**4**[a]	Run	**3**	R-X	Time	**4**[a]
1	**3a** (Z=Me)	Ph-I	0.5 h	80%	13	**3a**		0.5 h	80%
2	**3b** (Z=OMe)	Ph-I	0.5 h	70%					
3	**3c** (Z=Boc)	Ph-I	1 h	80%	14	**3b**		0.5 h	73%
4	**3d** (Z=SO_2Ph)	Ph-I	3 h	35%					
5	**3e** (Z=SEM)	Ph-I	3 h	35%	15	**3c**		1 h	77%
6	**3f** (Z=MOM)	Ph-I	3 h	----					
7	**3a**	Ph-CH=CH-Br	0.5 h	80%	16	**3e**		3 h	21%
8	**3b**	Ph-CH=CH-Br	0.5 h	60%					
9	**3c**	Ph-CH=CH-Br	1 h	78%	17	**3f**		3 h	----
10	**3d**	Ph-CH=CH-Br	3 h	15%					
11	**3e**	Ph-CH=CH-Br	3 h	30%					
12	**3f**	Ph-CH=CH-Br	3 h	----					

A plausible reaction course for the cross-coupling reaction is shown in Scheme 7. The successful reaction of **3** could be explained by the coordination of electron-rich enamine system to Pd (complex A), which in turn drives the catalytic cycle in the desired direction (Scheme 7).



Scheme 7. Plausible reaction mechanism

The need for an additional base in the reaction medium severely limits the scope of the Suzuki reaction.

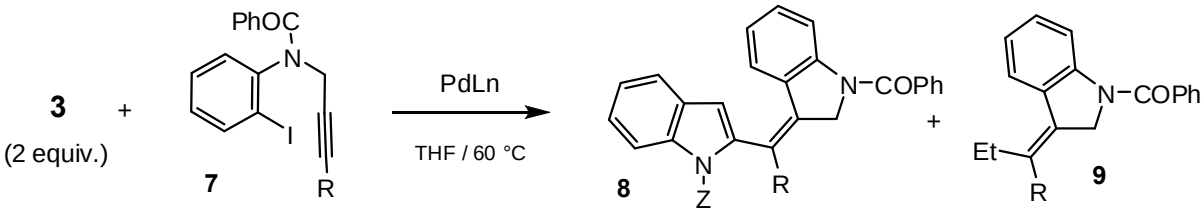
However, our findings suggest that an additional base is not required in the reaction using **3**; this prompted us to investigate the further scope of the cross-coupling reaction.

2. PALLADIUM CATALYZED TANDEM CYCLIZATION-CROSS-COUPLING REACTION

There are several examples of tandem cross-coupling processes, in which organozinc, organomagnesium and organotin reagents are used as transfer agents owing to their high reactivity.[14] However, organoboron compounds are less effective as transfer agents because of their low reactivity and low selectivity.[15] To increase the synthetic applicability of the cross-coupling reaction using indolylborates **3**, the feasibility of a tandem cyclization cross-coupling reaction was examined. In contrast to the majority of tetra-coordinated organoboron compounds, indolylborates **3** have been found to be highly effective to the tandem processes.[16]

Acetylenic substrates **7** participated in a tandem reaction when simply heated in the presence of **3** and a catalytic amount of palladium complex in THF under an argon atmosphere (Table 2). An excess of **3** (2 equiv.) was essential to obtain the coupling products **8** in good yields, while the reaction was imperfectly completed by using equimolar quantities of **3** and **7**.

Table 2. Tandem reaction of **3** with **7**

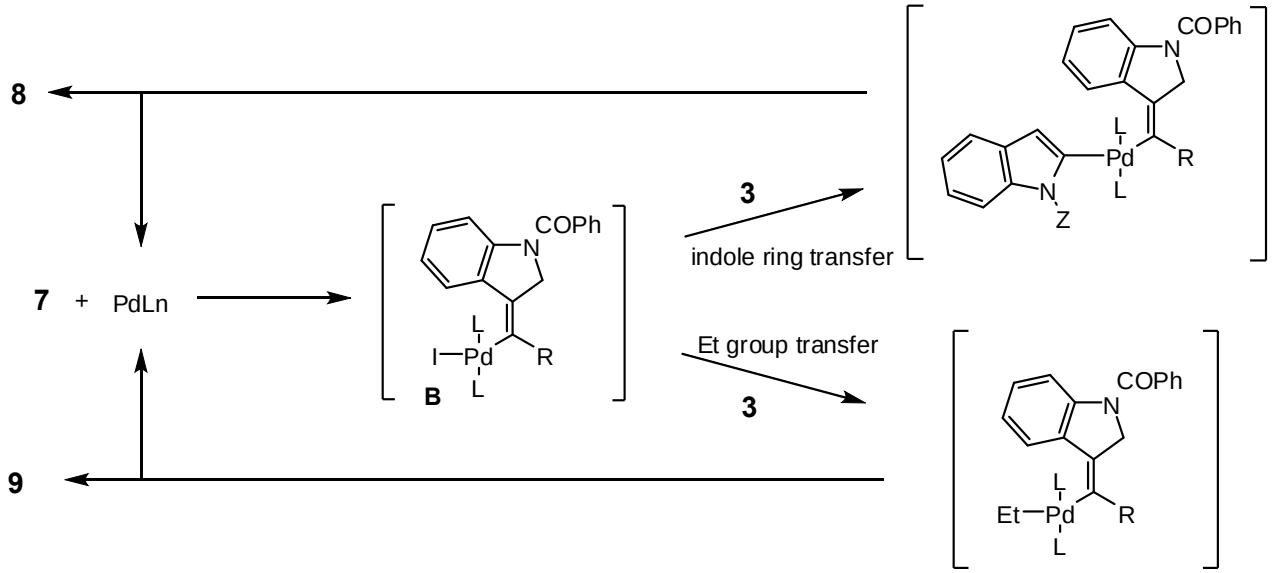


Run	**3**	**7**	Conditions	**8**	**9**
1	**3a**	**7a** (R=Me)	$Pd(OAc)_2$ / 0.5 h	78%	----
2	**3a**	**7a**	$Pd(OAc)_2 + 2PPh_3$ / 1 h	37%	30%
3	**3a**	**7b** (R=TMS)	$Pd(OAc)_2$ / 0.5 h	71%	----
4	**3b**	**7a**	$Pd(OAc)_2$ / 1 h	70%	----
5	**3b**	**7b**	$Pd(OAc)_2$ / 1 h	65%	10%
6	**3c**	**7a**	$Pd(OAc)_2$ / 3 h	23%	20%
7	**3c**	**7b**	$Pd(OAc)_2$ / 3 h	----	----

Treatment of **3a**,**b** with **7** in the presence of $Pd(OAc)_2$ gave **8** in good yields (Runs 1, 3-5). On the other hand, the production of **8** was markedly decreased in the reaction of **3a** with **7a** when $Pd(OAc)_2$+$2PPh_3$

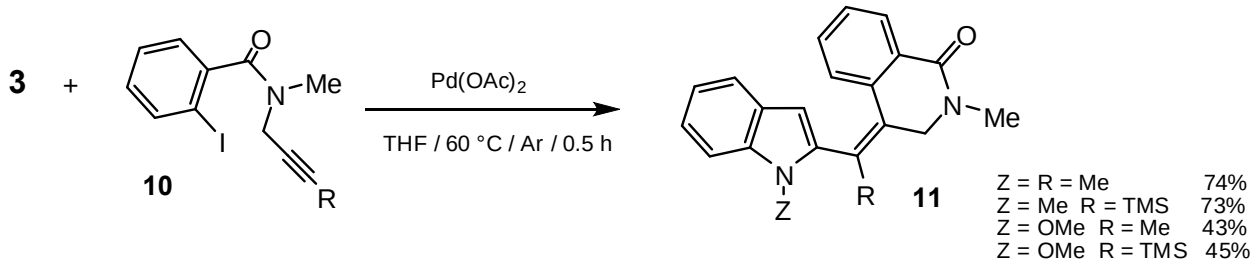
was used (Run 2). The reaction of **3c** with **7a** was sluggish, affording **8** and **9** in yields of 23% and 20%, respectively (Run 6). The reaction of **7b** having a bulky TMS group with **3c** did not give coupling products and a substantial amount of **7b** was recovered (Run 7).

The results may be interpreted by the following mechanistic scheme; 1) Pd-catalyzed cyclization of **7** leading to complex **B**, 2) the transmetallation between complex **B** and **3** possibly involving transfer of the indole ring and/or the Et group, and 3) reductive elimination leading to **8** and/or **9** (Scheme 8).



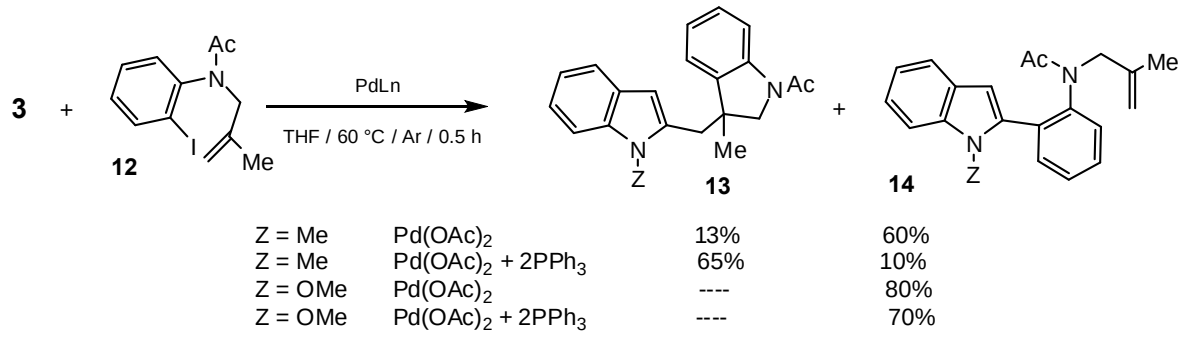
Scheme 8. Possible reaction course of the tandem reaction of **3**

Similarly, the reaction of **3** with **10** in the presence of $Pd(OAc)_2$, which involved the formation of 6-membered ring, afforded **11** in good yields (Scheme 9).



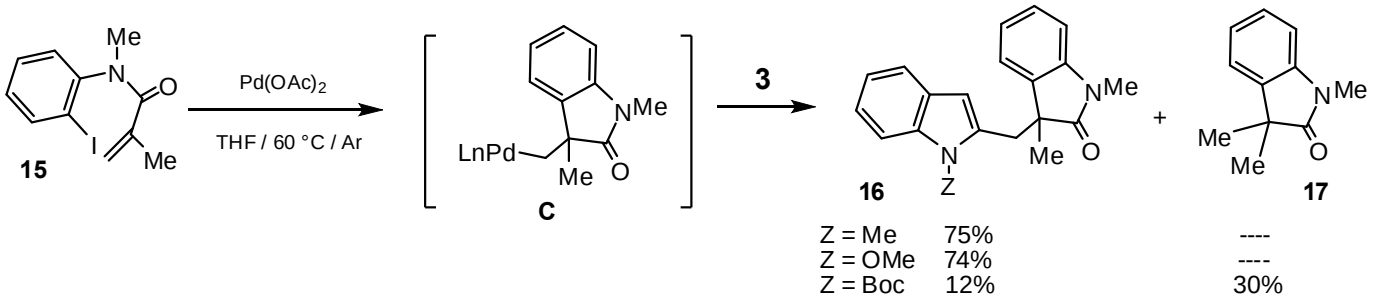
Scheme 9. Tandem reaction of **3** with **10**

In exploring the advantages of the tandem reaction, this procedure was examined with olefinic substrate **12**. Treatment of **3a** with **12** in the presence of $Pd(OAc)_2$+$2PPh_3$ provided **13** in 65% yield, as well as direct cross-coupling product **14** in 10% yield. To our surprise, treatment of **3b** with **12** in the presence of $Pd(OAc)_2$ with or without $2PPh_3$ provided exclusively direct cross-coupling product **14** (Scheme 10).



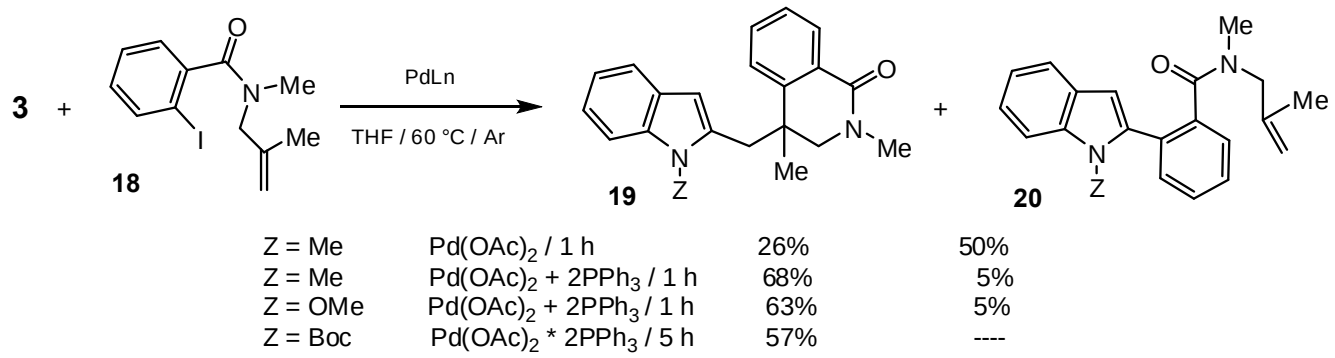
Scheme 10. Tandem reaction of **3** with **12**

Subjection of olefin **15** to the reaction with **3a**,**b** in the presence of $Pd(OAc)_2$ provided **16** as the sole product in high yields, while the reaction of **15** with **3c** was sluggish, giving **16** and **17**. The product **17** might be formed through homolytic cleavage of the C-Pd bond of the σ–alkyl Pd complex **C** (Scheme 11).



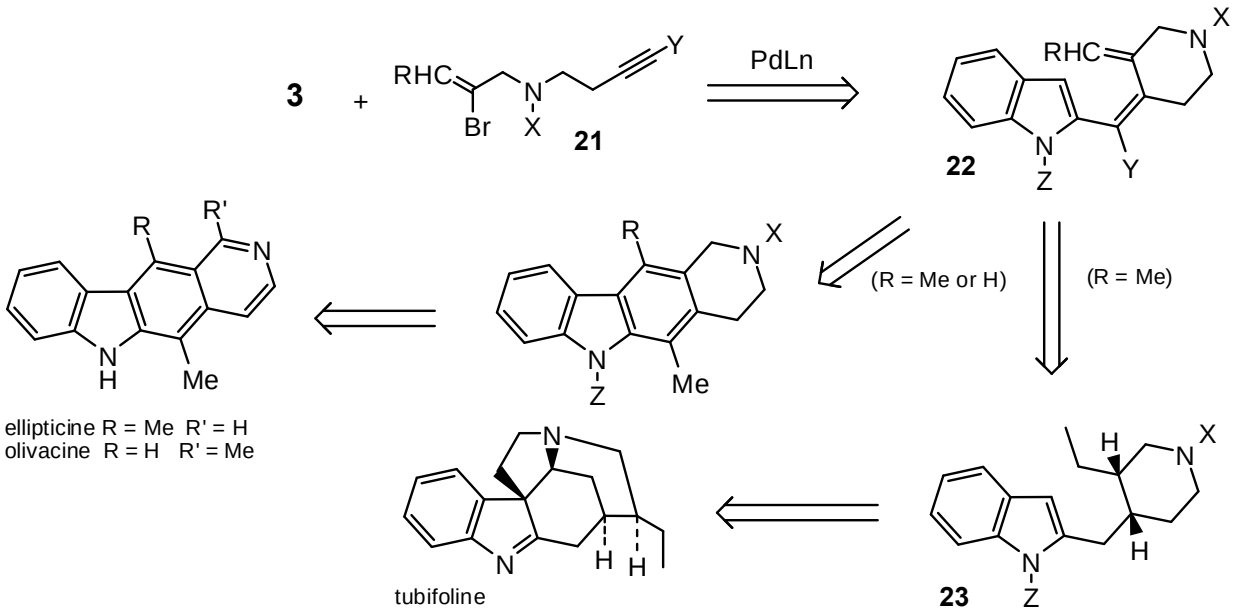
Scheme 11. Tandem reaction of **3** with **15**

Treatment of **3a** with **18** provided cross-coupling products **19** and **20**, which exhibited marked propensity that the yield of **19** exceeded that of **20** in the presence of $Pd(OAc)_2$+$2PPh_3$ (Scheme 12).



Scheme 12. Tandem reaction of **3** with **18**

Next, we envisioned further exploration of the tandem protocol for the synthesis of indole alkaloids by taking advantage of the one-pot construction of vinylpyridines **22** through the reaction of **3** with vinylbromides **21** as a common strategy (Scheme 13). Pyridocarbazole alkaloids (olivacine, ellipticine) can concisely be accessed through the cyclization of **22**, followed by an oxidation step. On the other hand, catalytic hydrogenation of **22** to piperidine **23** allows potential access to tubifoline.

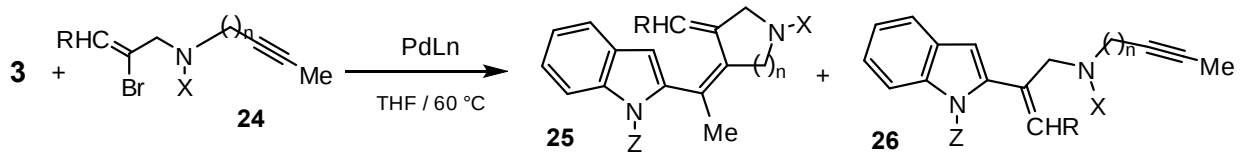


Scheme 13. Synthetic path

On first examination, the reaction of **3** with vinylbromides **24** in the presence of palladium complex (5 mol%) in THF produced both tandem cross-coupling product **25** and simple cross-coupling product **26** (Table 3).[17] The ratio of the two products varied with changes in the palladium complex or the structure of vinylbromides **24**. The use of Pd complex without Ph_3P drove the reaction of **3a**,**b** with **24** (R=H, n=2) in the direction of **25**, while **26** was obtained predominately in the presence of Pd complex with Ph_3P (Runs 1, 2, 3 and 7). Notably, **25** was exclusively isolated in the reaction of **3a** with **24** (R=Me) in the presence of Pd complex with Ph_3P (Runs 4, 5 and 6). The observed results on the reaction with **24** (R=H, n=1, 3) are associated with the relative ease of ring-closure as a function of ring size (Runs 8 and 9).

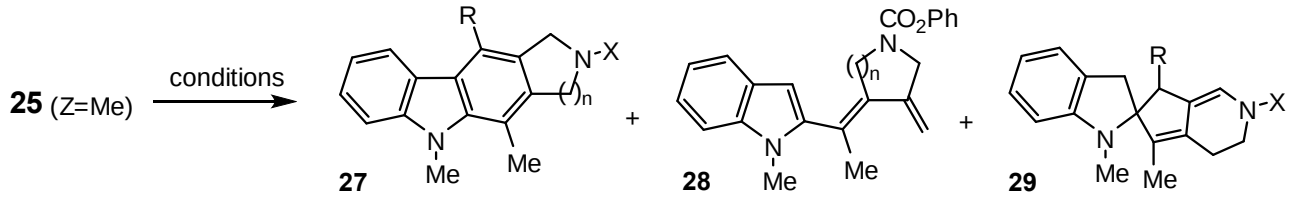
With vinylindoles **25** in hand, we then turned our attention to the cyclization of **25** (Z=Me) to pyridocarbazole derivatives **27** (Table 4). Since the 6π-electrocyclization of a hexatriene system has been carried out under various conditions, we first examined a photochemical cyclization of **25**; irradiation of **25** (R=H, n=2) in benzene with a high-pressure mercury lamp afforded **27** and isomer **28** (Run 1). On the other hand, photochemical ring-closure of **25** (R=H, n=1,3; R=Me) produced exclusively **27** (Runs 2,3 and 7).

Table 3. Tandem reaction of **3** with **24**



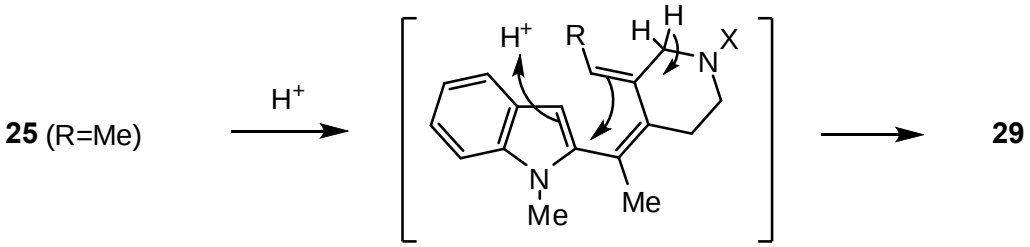
Run	**3**	R	X	n	PdLn	**25**	**26**
1	**3a**	H	Ac	2	$Pd(OAc)_2$	43%	29%
2	**3a**	H	Ac	2	$Pd(OAc)_2 + 2PPh_3$	10%	60%
3	**3a**	H	Boc	2	$Pd_2(dba)_3 \cdot CHCl_3$	43%	22%
4	**3a**	Me	Ac	2	$PdCl_2(MeCN)_2$	23%	----
5	**3a**	Me	Ac	2	$PdCl_2(PPh_3)_2$	67%	----
6	**3a**	Me	Boc	2	$PdCl_2(PPh_3)_2$	69%	----
7	**3b**	H	Cbz	2	$PdCl_2(MeCN)_2$	43%	15%
8	**3a**	H	Cbz	1	$Pd(OAc)_2$	61%	10%
9	**3a**	H	COPh	3	$Pd(OAc)_2$	21%	40%

Table 4. 6-π-Electrocyclization of **25** (Z=Me)



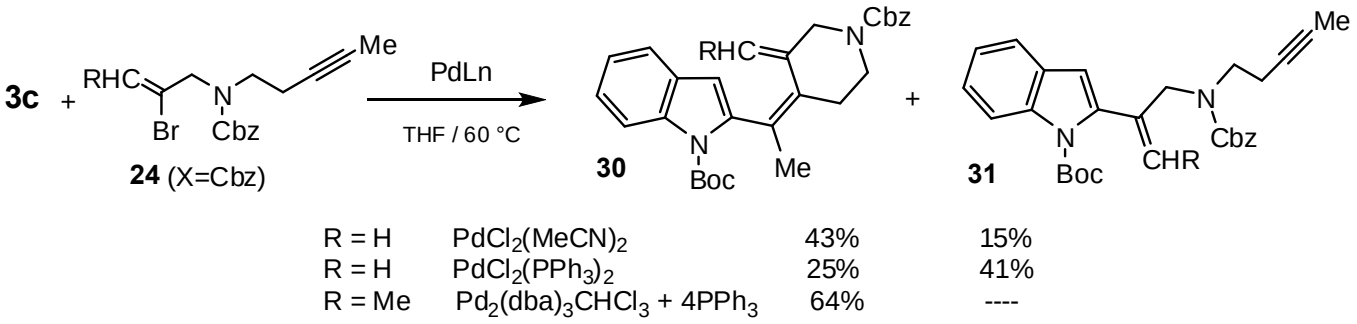
Run	R	n	X	conditions	**27**	**28**	**29**
1	H	2	CO_2Ph	*hv* / benzene / 0 °C	35%	30%	----
2	H	1	Cbz	*hv* / benzene / 0 °C	40%	----	----
3	H	3	COPh	*hv* / benzene / 0 °C	41%	----	----
4	H	2	Ac	TFA / CH_2Cl_2 / rt	----	----	68%
5	H	2	Ac	$BF_3 \cdot OEt_2$ / CH_2Cl_2 / rt	----	----	67%
6	H	2	CO_2Ph	$TiCl_4$ / CH_2Cl_2 / -78 °C	68%	----	----
7	Me	2	CO_2Ph	*hv* / benzene / 0 °C	48%	----	----
8	Me	2	CO_2Ph	$BF_3 \cdot OEt_2$ / CH_2Cl_2 / rt	----	----	40%
9	Me	2	CO_2Ph	$TiCl_4$ / CH_2Cl_2 / -78 °C	70%	----	----

Alternatively, an acid-promoted ring-closing reaction of **25** (Z=Me) was examined. Treatment **25** (Z=Me) of with TFA or $BF_3 \cdot OEt_2$ in CH_2Cl_2 led to the formation of spiroindole **29** (Runs 4, 5 and 8), which can be accounted for by the reaction path shown in Scheme 14. In contrast, cyclization of **25** to give pyridocarbazoles **27** with high selectivity was performed using $TiCl_4$ (runs 6 and 9).



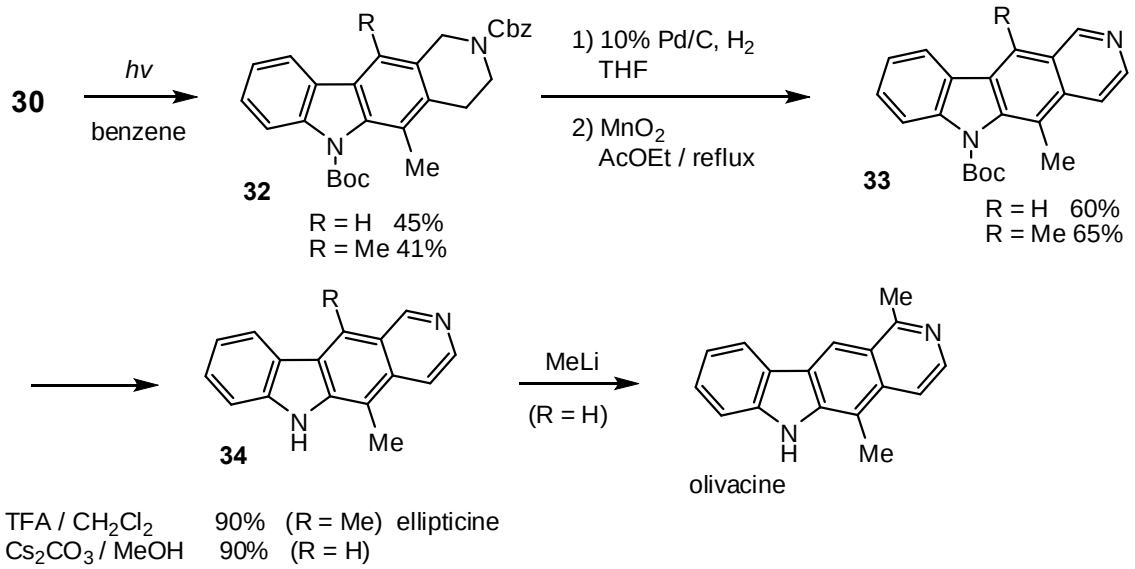
Scheme 14. Formation of spiroindoles **29**

The present tandem cyclization cross-coupling protocol was extended to the reaction of indolylbotate **3c** with vinylbromides **26** in the presence of a catalytic amount of Pd complex, leading to vinylindoles **27** and/or simple cross-coupling products **28** (Scheme 15).



Scheme 15. Tandem reaction of **3c** with **24** (X=Cbz)

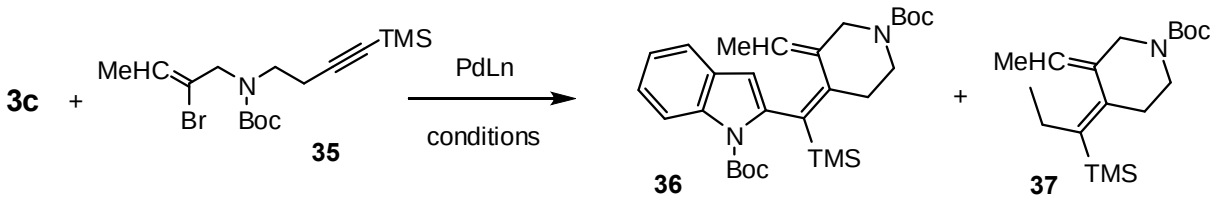
Cyclization of **30** by irradiation in benzene produced carbazoles **32**. Reductive cleavage of the *N*-Cbz group of **32** and subsequent oxidation with MnO_2 yielded **33**. Finally, the removal of the *N*-Boc group of **33** provided pyridocabazoles **34** (R=H and R=Me; ellipticine), and the conversion of **34** (R=H) to olivacine has already been reported (Scheme 16).[18]



Scheme 16. Total synthesis of ellipticine and olivacine

Next, we set about the synthesis of (±)-tubifoline, in which piperidylmethylindole **23** is a profitable intermediate for the further transformation to tubifoline (Scheme 13).[19] The successful route to **23** involves the reduction of **22** (R=Me, Y=H) having no substituent on the olefinic carbon. First, it was assumed that the reaction of **3c** with bromide **21** (R=Me, Y=H) would provide a direct route to **22**, though this resulted in the formation of complex mixtures.

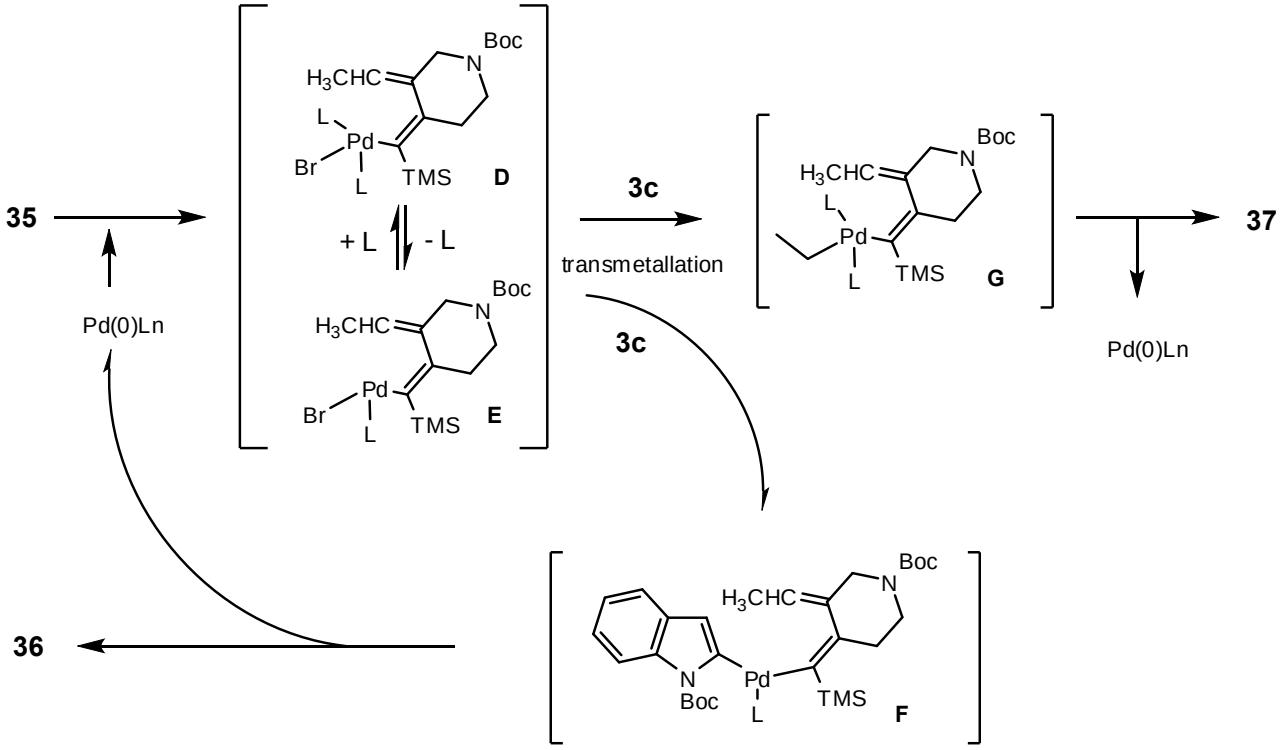
Table 5. Tandem reaction of **3c** with **35**



Run	PdLn	conditions	**36**	**37**
1	$Pd(OAc)_2$	THF / 60 °C / 3 h	7%	56%
2	$PdCl_2(PPh_3)_2$	THF / 60 °C / 3 h	8%	50%
3	$Pd(OAc)_2$	DME / 85 °C / 3 h	14%	35%
4	$PdCl_2(Ph_3P)_2$	DME / 85 °C / 3 h	11%	50%
5	$PdCl_2[(o\text{-tol})_3P]_2$	DME / 85 °C / 3 h	55%	18%

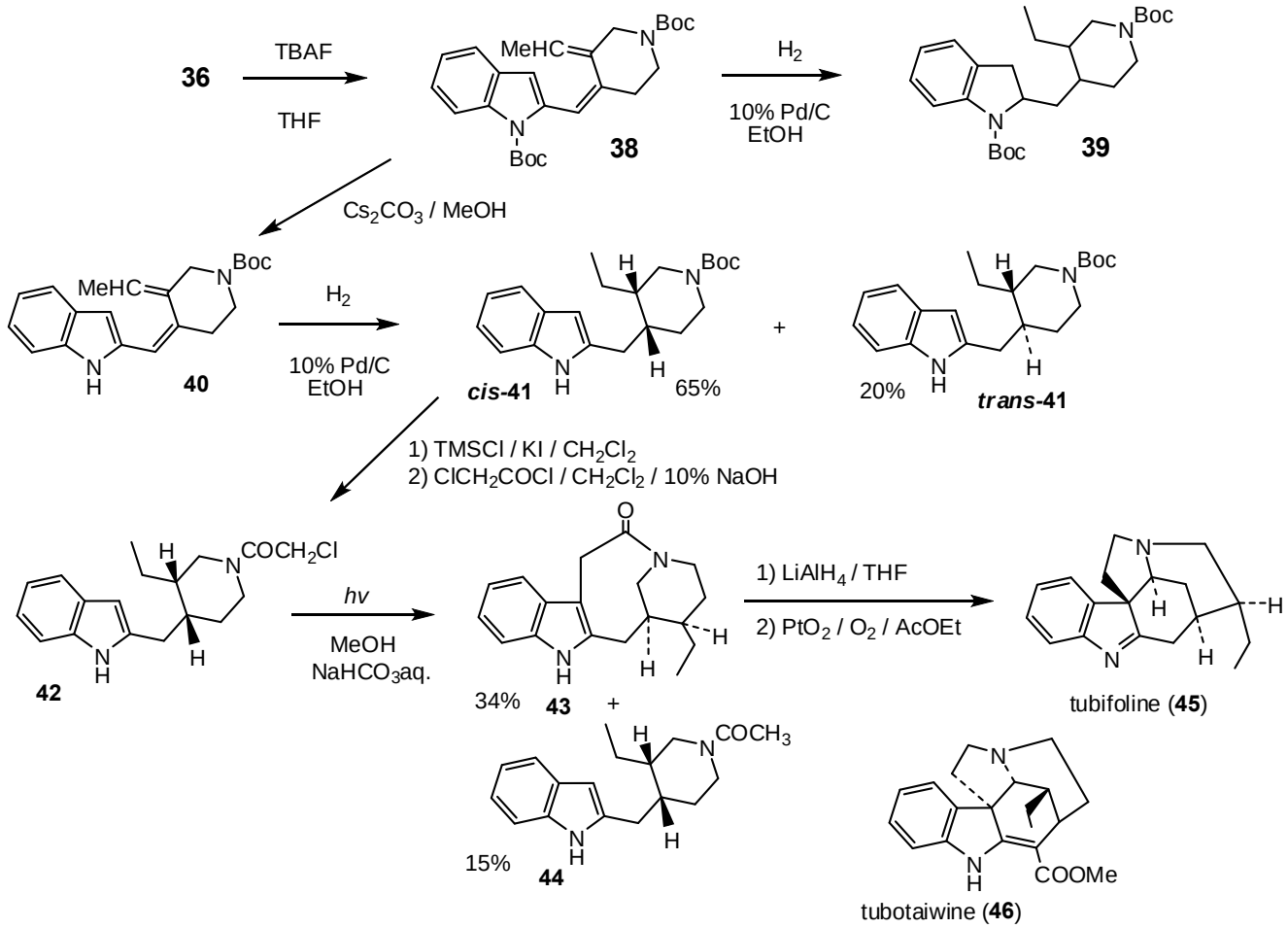
Thus, **35** was subjected to the reaction with **3c** in the presence of Pd complex under the aforementioned conditions (in THF at 60 °C), but resulted in significant suppression of the reaction (Table 5): only trace amounts of **36** along with substantial amounts of **37** resulted (Runs 1-4). We attributed this suppression to the serious steric repulsion between the TMS group and the *N*-Boc group in the transmetallation step. After screening the reaction conditions, a marked improvement in the yield of **36** was obtained through the use of $PdCl_2[(o\text{-tol})_3P]_2$ in DME at 85 °C (Run 5).

The ligation of bulky $(o\text{-Tol})_3P$ to Pd shifts the equilibrium between **D** and **E** in favor of the less crowded **E**, which promptly promotes the transfer of the indole ring of **3c** and in turn leads to **36** through complex **F**. On the other hand, competitive transfer of the Et group allows the formation of **37** through complex **G** (Scheme 17).



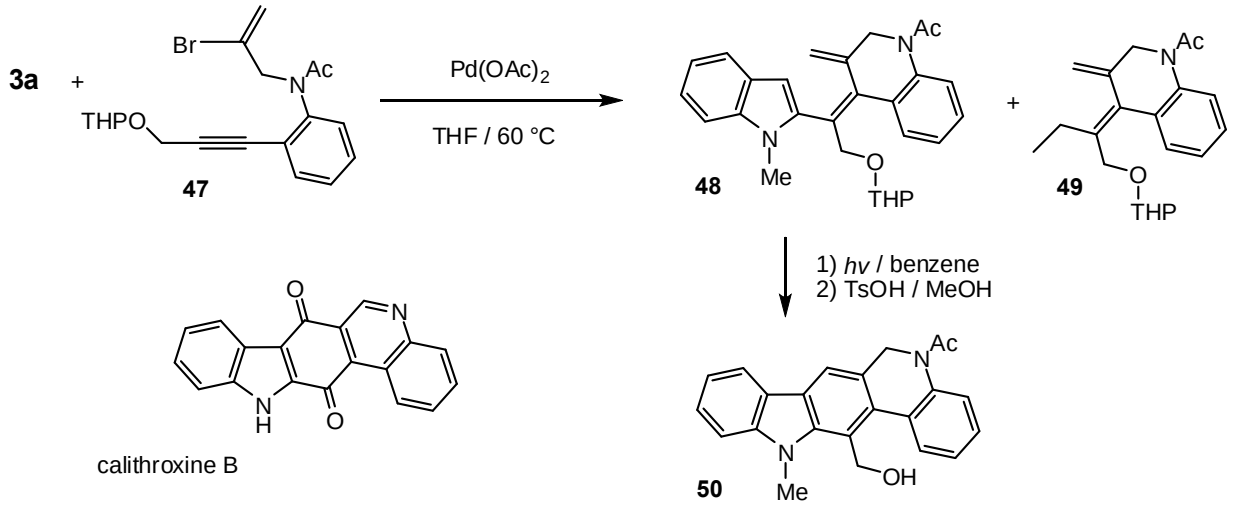
Scheme 17. Possible reaction course

The TMS group of **36** was readily removed by treatment with TBAF in THF to provide **38**. Since catalytic hydrogenation of **38** led to indoline **39** as mixtures of stereoisomers, the N^a-Boc group was removed and catalytic hydrogenation of **40** was performed over 10% Pd/C in EtOH, producing ***cis*-41** along with ***trans*-41**. Removal of the N^b-Boc group of ***cis*-41** followed by treatment with $ClCH_2COCl$ produced **42**. Then, irradiation of **42** with a low-pressure mercury lamp afforded **43** and **44**. Subsequently, **43** was reduced with $LiAlH_4$, followed by oxidation with PtO_2/O_2, affording (±)-tubifoline (**45**). Currently, conversion of ***cis*-41** to (±)-tubotaiwine (**46**) is also in progress (Scheme 18).



Scheme 18. Total synthesis of (±)-tubifoline (**45**)

In addition, the present tandem cross-coupling reaction was applicable to the reaction of **3a** with bromide **47**, which yielded **48** and **49**. Irradiation of **48** in benzene with high-pressure mercury lamp afforded pentacyclic carbazole **50**, a core framework of the antitumor antibiotic calithroxine B.

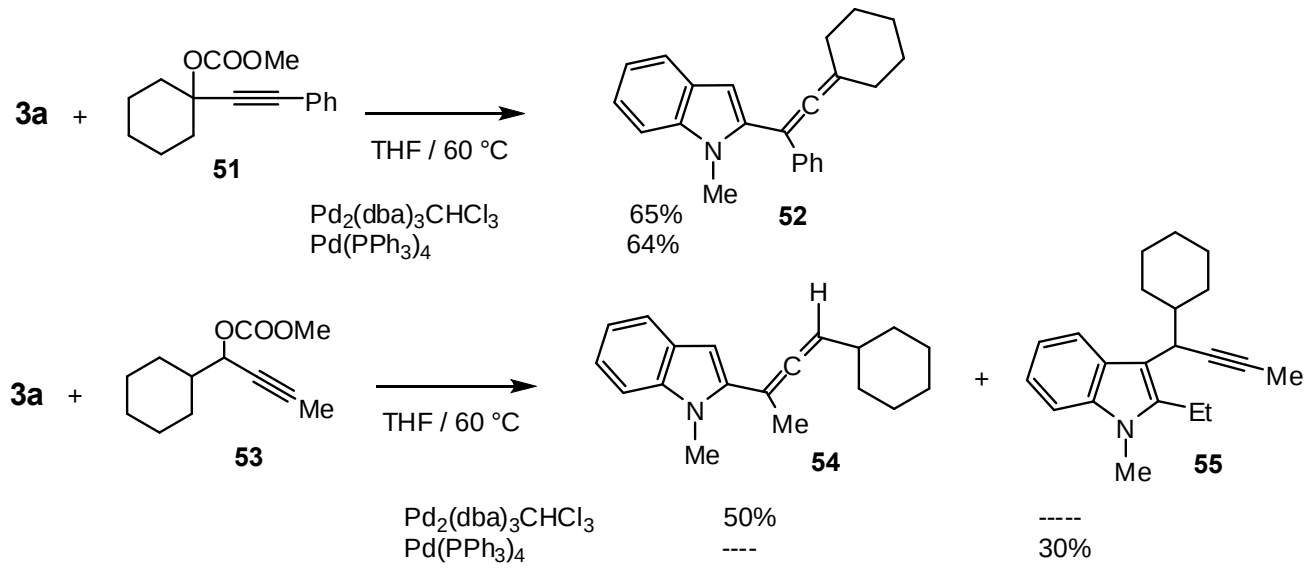


Scheme 19. Synthetic study of calithroxine B

3. CROSS-COUPLING REACTION WITH PROPARGYL CARBONATES

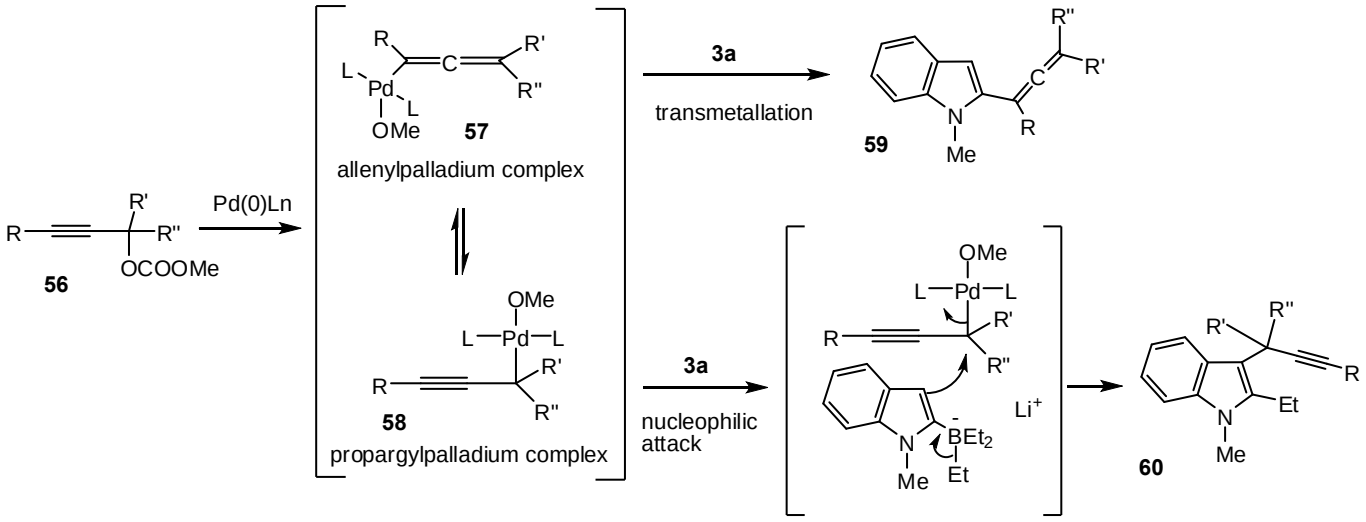
The addition of various metal complexes to propargyl halides and esters is a well-known process for the formation of allenylmetal complexes, whose conversion to allene derivatives has been the subject of much recent work.[20] Thus, we were intrigued by the idea of using the cross-coupling reaction of **3** with an allenylpalladium complex to construct allenylindole derivatives.

Our initial experiment showed that the reaction of **3a** with *tert*-propargyl ester **51** in the presence of a catalytic amount of palladium complex afforded hitherto unknown 2-allenylindole **50**.[21] Otherwise, the reaction of **3a** with *sec*-propargyl ester **53** resulted in the formation of 2-allenylindole **54** or 2-alkyl-3-propargylindole **55**, depending on the palladium complex used. A palladium complex coordinated by Ph_3P favored the formation of 3-propargylindole **55** (Scheme 20).



Scheme 20. Cross-coupling reaction of **3a** with propargyl carbonates **51**, **53**

A plausible reaction course is depicted in Scheme 21. Oxidative addition of propargyl ester **56** to the palladium complex comes to an equilibrium between the allenylpalladium complex **57** and the propargylpalladium complex **58**. The transmetallation between **3a** and complex **57** produces 2-allenylindole **59**, while the nucleophilic attack of **3a** to complex **58** (R'=H, R''=alkyl) accompanied by alkyl migration leads to 3-propargylindole **60**, which is a rare reaction manner. In the reaction of *sec*-propargyl ester using palladium complex coordinated by Ph_3P, large sterical repulsion between the substituent (R group) and PdLX (L being Ph_3P) in **57** shifts the equilibrium toward the propargylpalladium complex **58**, making the nucleophilic attack path a favorable course (Scheme 21).



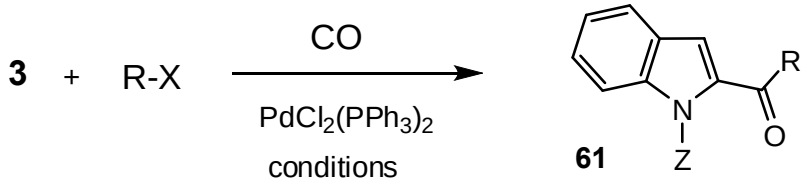
Scheme 21. Possible reaction course

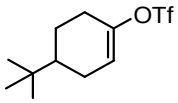
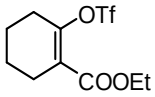
4. CARBONYLATIVE CROSS-COUPLING REACTION

To put the cross-coupling procedure using indolylborates **3** into proper perspective, we examined a methodology for the construction of indolyl ketones *via* the carbonylative cross-coupling reaction. Various kinds of organometallic compounds (organozinc and organotin compounds and tri-coordinated organoboron derivatives) have been used for this carbonylative process.[22] However, it has been reported that tetra-coordinated organoboron compounds are not suitable.[23]

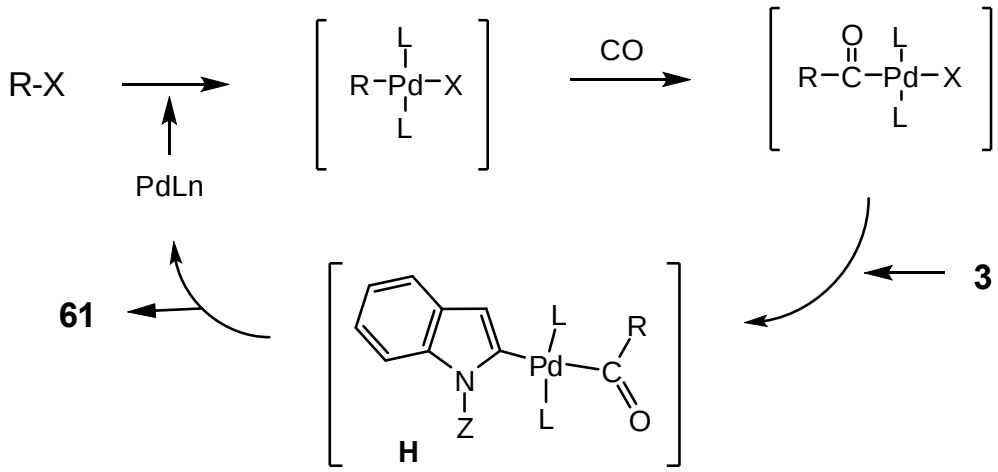
Initially, reaction of **3a** with bromobenzene in the presence of a catalytic amount of palladium complex under a pressurized carbon monoxide atmosphere (10 atm) was examined, but the reaction was sluggish to give ketone **61** (Table 6; Run 1) in low yield. The reaction of **3a** with iodobenzenes in xylene at 90 °C successfully gave ketones **61** (Runs 2-3). The reaction of **3** smoothly proceeded under less forcing conditions (in THF at 60 °C) with the use of triflates and alkenyl bromides to give ketones **61** (Runs 4-10).[24]

Table 6. Carbonylative cross-coupling reaction of **3**



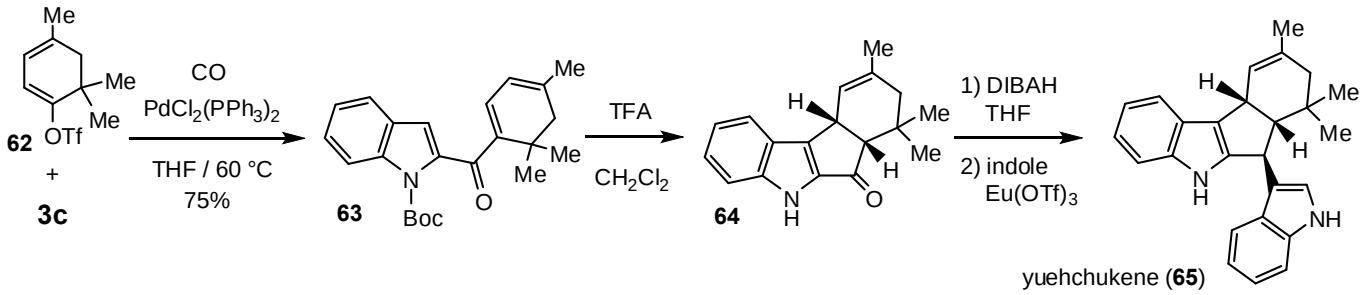
Run	Z	R-X	conditions	**61**
1	Me	Ph-Br	xylene / 90 °C / 60 h	20%
2	Me	Ph-I	xylene / 90 °C / 60 h	80%
3	Me	4-Br-Ph-I	xylene / 90 °C / 60 h	72%
4	Me	Ph-CH=CH-Br	THF / 60 °C / 20 h	78%
5	Me		THF / 60 °C / 40 h	77%
6	OMe		THF / 60 °C / 40 h	60%
7	Boc		THF / 60 °C / 40 h	50%
8	Me		THF / 60 °C / 40 h	64%
9	OMe		THF / 60 °C / 40 h	58%
10	Boc		THF / 60 °C / 40 h	45%

A common carbonylation path could account for the present reaction, in which the transmetallation step implies that increasing the positive charge on the palladium may enhance the coordination-transmetallation step to form acyl palladium complex **H** (Scheme 22)



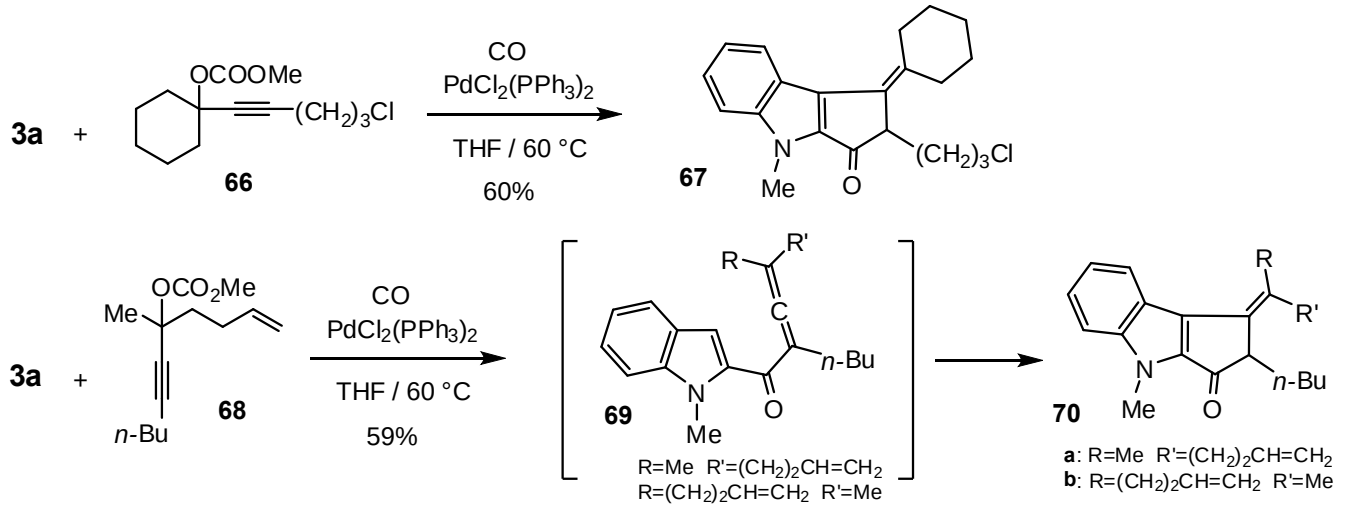
Scheme 22. Reaction mechanism

The total synthesis of the bisindole alkaloid, yuehchukene (**65**), could be achieved based on the present carbonylation protocol.[25] Reaction of **3c** with cyclohexenyl triflate **62**, derived from isophorone, in the presence of a catalytic amount of palladium complex in THF under carbon monoxide (10 atm) at 60 °C for 20 h gave ketone **63** in 75% yield. Cyclzation and removal of the *N*-Boc group was concomitantly performed by the treatment with TFA in CH_2Cl_2 at room temperature, leading to **64**. Reduction of the carbonyl group in **64** was carried out with DIBAH, followed by reaction with indole in the presence of $Eu(OTf)_3$, yielding yuechukene (**65**) in 60% yield.



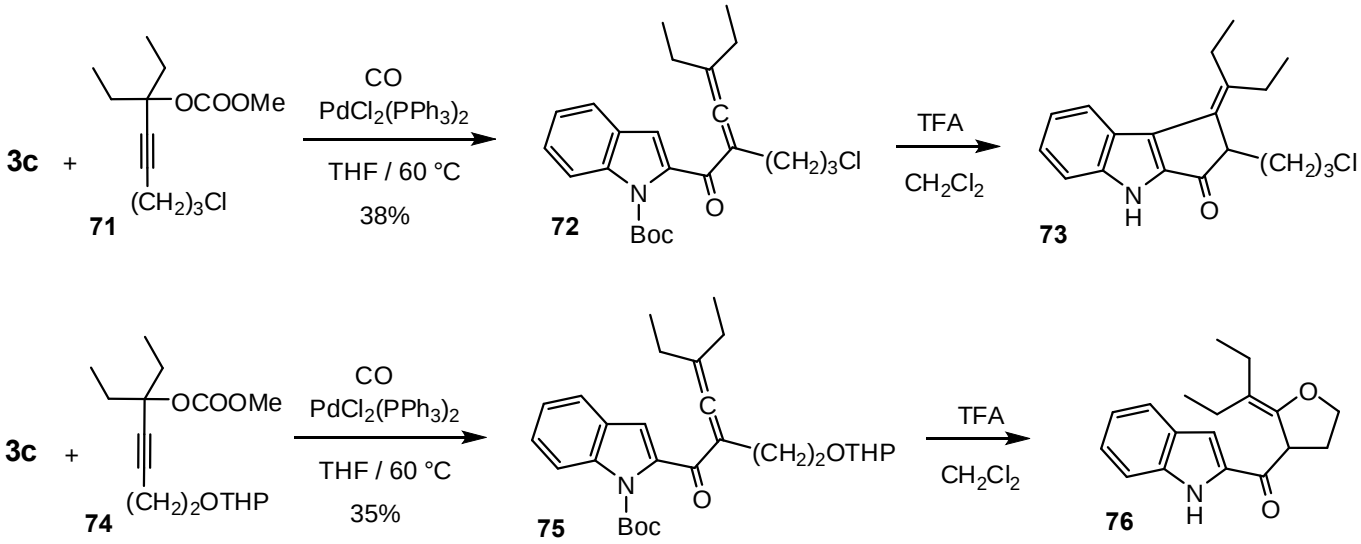
Scheme 23. Total synthesis of yuehchukene (**65**)

Since the transmetalation between **3** and an allenylpalladium complex **57** afforded 2-allenylindole **59**, our interest was turned to explore the possibility of using a carbon monoxide atmosphere to access allenylindolyl ketone. The carbonylation reaction of **3a** with propargyl carbonate **66** under carbon monoxide (10 atm) in the presence of a palladium complex allowed the isolation of cyclopenta[*b*]indole **67** in 60% yield. Notably, the reaction of **68** with borate **3a** produced a 1:1 mixture of geometrical isomers **70a** and **70b**. This can be interpreted by the intermediary formation of allenyl ketone **69** and subsequent cyclization (Scheme 24).[26]



Scheme 24. Carbonylative cross-coupling reaction of **3a** with propargyl carbonates **66**,**68**

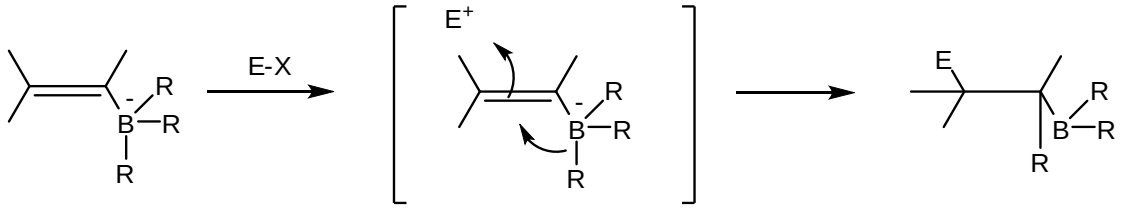
We anticipated that the presence of an electron-withdrawing group might suppress the cyclization step, so that the anticipated allenyl ketone would be isolable. To our delight, the carbonylation reaction of **3c** with propargyl carbonates **71** and **74** gave allenyl ketones **72** and **75**. Treatment of **72** with TFA in CH_2Cl_2 produced cyclopenta[*b*]indole **73**, while furan **76** resulted from **75** (Scheme 25).



Scheme 25. Carbonylative cross-coupling reaction of **3c** with propargyl carbonates **71**,**74**

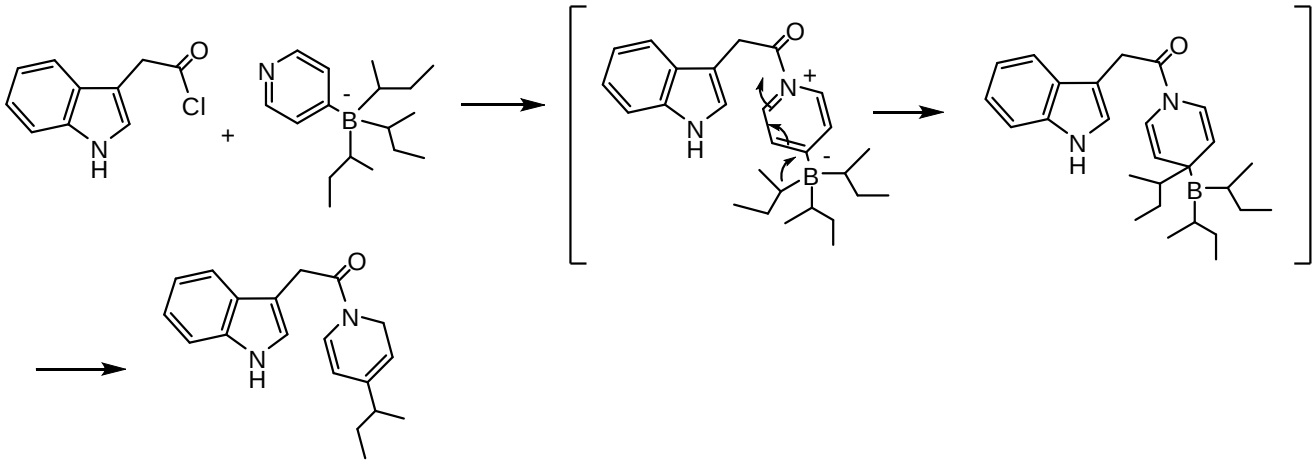
5. INTRAMOLECULAR ANIONIC MIGRATION REACTION

Trialkylalkenylborate complexes are well-studied synthetic intermediates, and their versatility is essentially attributed to an intramolecular alkyl migration reaction from boron to carbon, which is an important class of carbon-carbon bond formation (Scheme 26).[27]



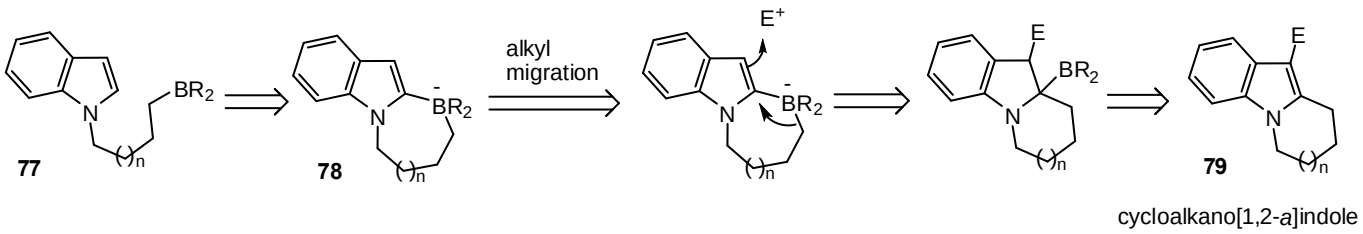
Scheme 26. Intramolecular 1,2-alkyl migration

This anionic 1,2-migration process is also represented by the reaction of borylated heteroaryl (such as thiophene, furan, pyrrole and pyridine) derivatves through the formation of a cationic center on the α–carbon adjacent to the boron on the heteroaromatic ring (Scheme 27).[28]



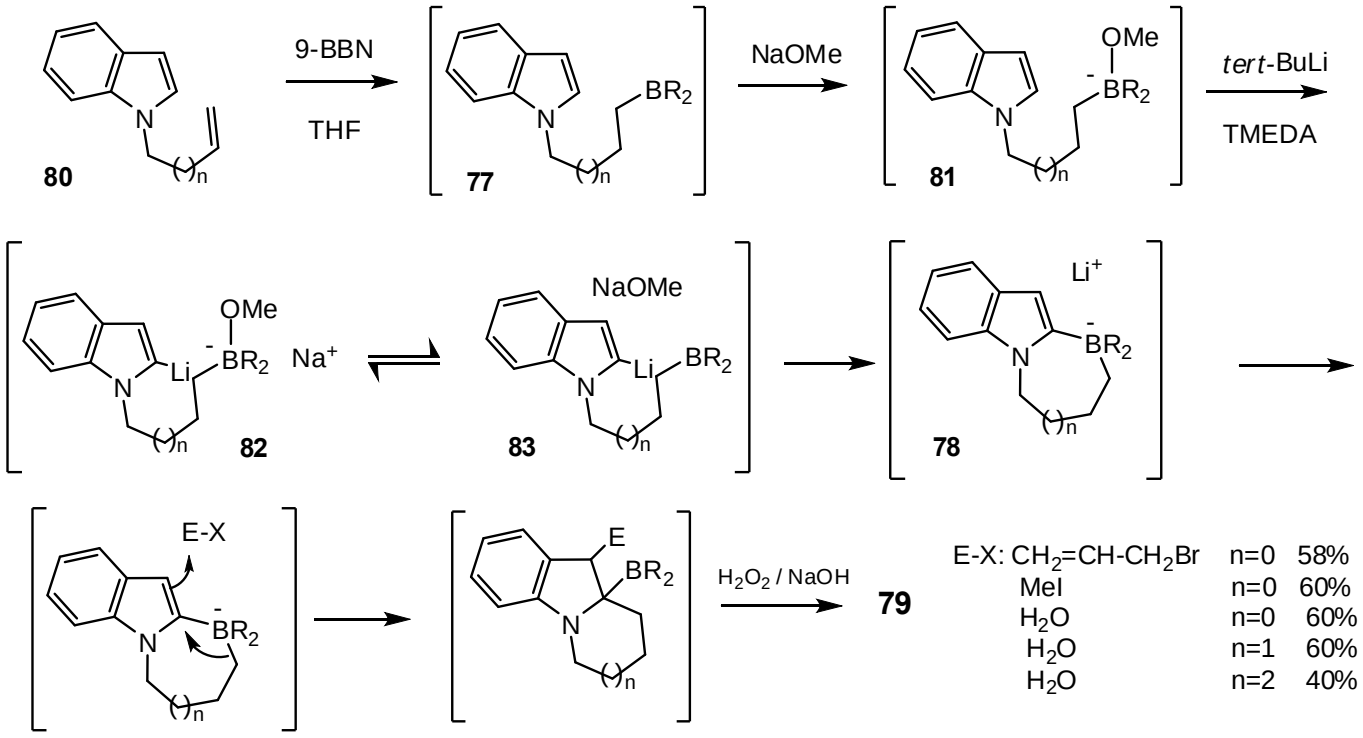
Scheme 27. Anionic 1,2-migration in trialkylpyridylborate

The cycloalkano[1,2-*a*]indole framework represents a structural unit of various naturally occurring substances such as mitomycin, eburnamonine and strychnine. We have developed a new one-pot strategy for the construction of cycloalkano[1,2-*a*]indole core based on an intramolecular alkyl migration in cyclic indolylborate **78**, which was envisioned to be available from trialkylborane **77** through a sequence of lithiation and subsequent cyclization (Scheme 28).[29]



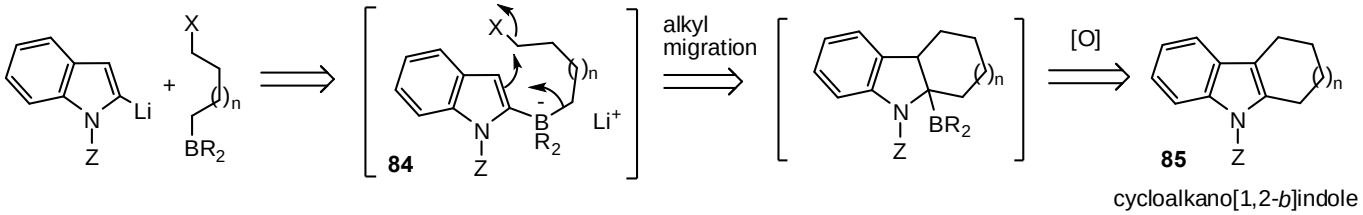
Scheme 28. One-pot strategy to cycloalkano[1,2-*a*]indole **79**

Initially, lithiation of borane **77**, generated *in situ* through hydrboration of olefin **80**, with *tert*-BuLi was attempted (Scheme 29). However, this failed due to a preferential interaction of trialkylborane **77** with the base, which led us to develop a temporarily protected boryl group prior to the lithiation. We eventually developed the desired transformation from **77** to cycloalkano[1,2-*a*]indole **79** through the following steps: 1) the treatment of **77** with NaOMe 2) lithiation with *tert*-BuLi, and 3) the addition of an electrophile (E-X). In the initial step, methoxyborate **81** is likely generated, which allows the selective lithiation at C-2 and leads to 2-lithioindole **82**. This suggests that the intervention of a reversible interconversion between **82** and **83** *in situ* slowly produces cyclic borate **78**. Electrophile could then interact with **78**, promoting the alkyl migration reaction to produce **79** (Scheme 29).



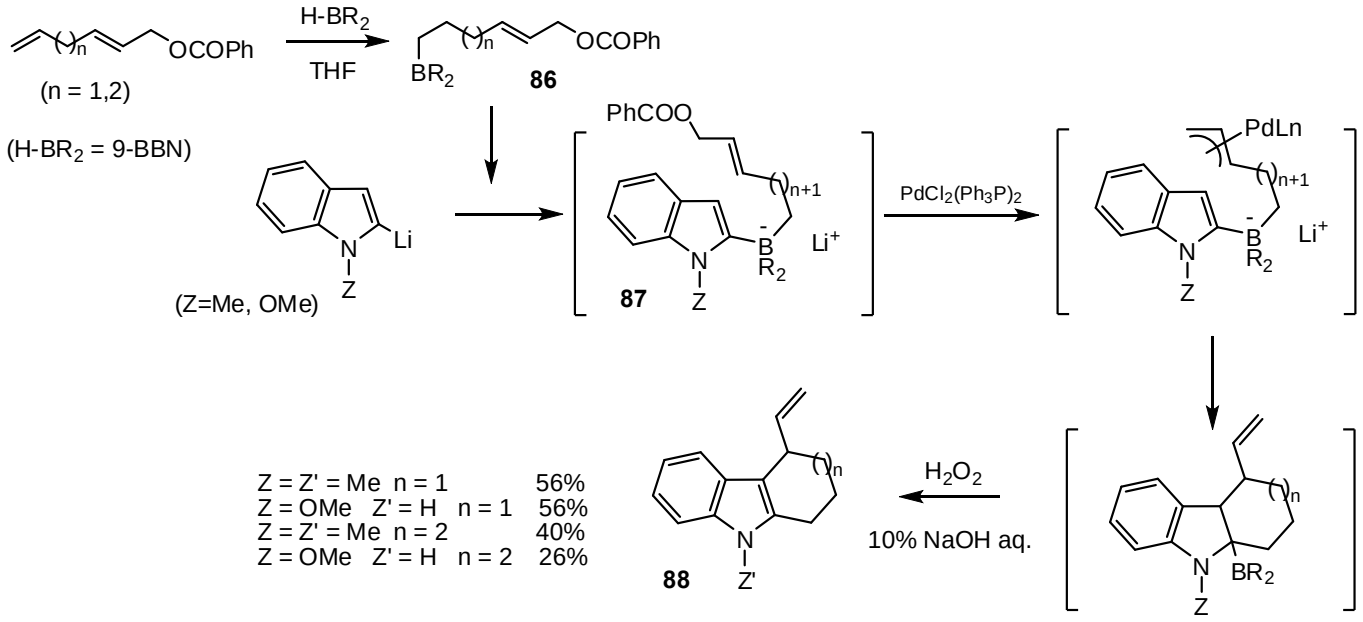
Scheme 29. One-pot formation of cycloalkano[1,2-*a*]indoles **79**

We next examined one-pot construction of cycloalkno[1,2-*b*]indole **85** from borate **84** *via* an intramolecular alkyl migration process, which was expected to occur by intramolecular interaction between the C-3 of the indole and the electrophilic center (Scheme 30).[30]



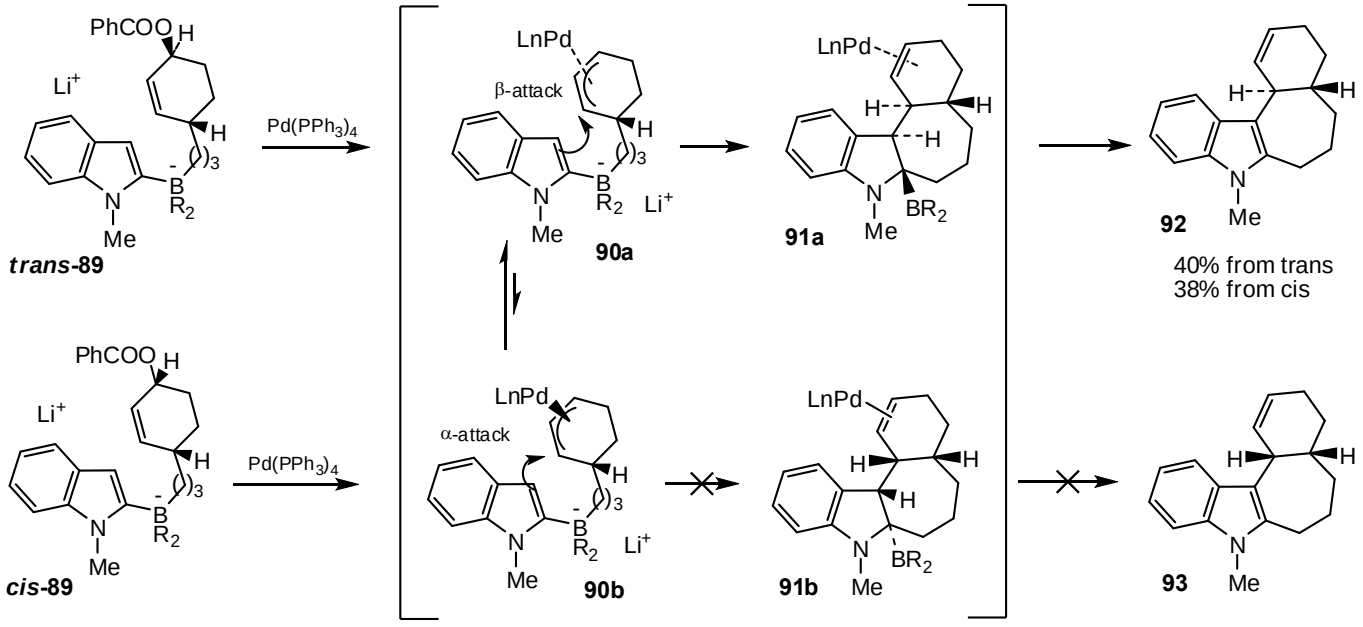
Scheme 30. One-pot construction of cycloalkano[1,2-*b*]indole **85**

From preliminary experiments, it appeared that π–allylpalladium complex was reasonably applicable to the expected intramolecular 1,2-migration process as an intramolecular electrophilic center. Accordingly, borates **87**, generated *in situ* from 2-lithioindole and alkylboranes **86**, were heated in the presence of a catalytic amount of palladium complex at 60 °C in THF. This provided cycloalkano[1,2-*b*]indoles **88** through the expected intramolecular alkyl migration process involving intramolecular nucleophilic attack of the C-3 of the indole on the π–allylpalladium complex (Scheme 31).



Scheme 31. One-pot formation of cycloalkano[1,2-*b*]indoles **88**

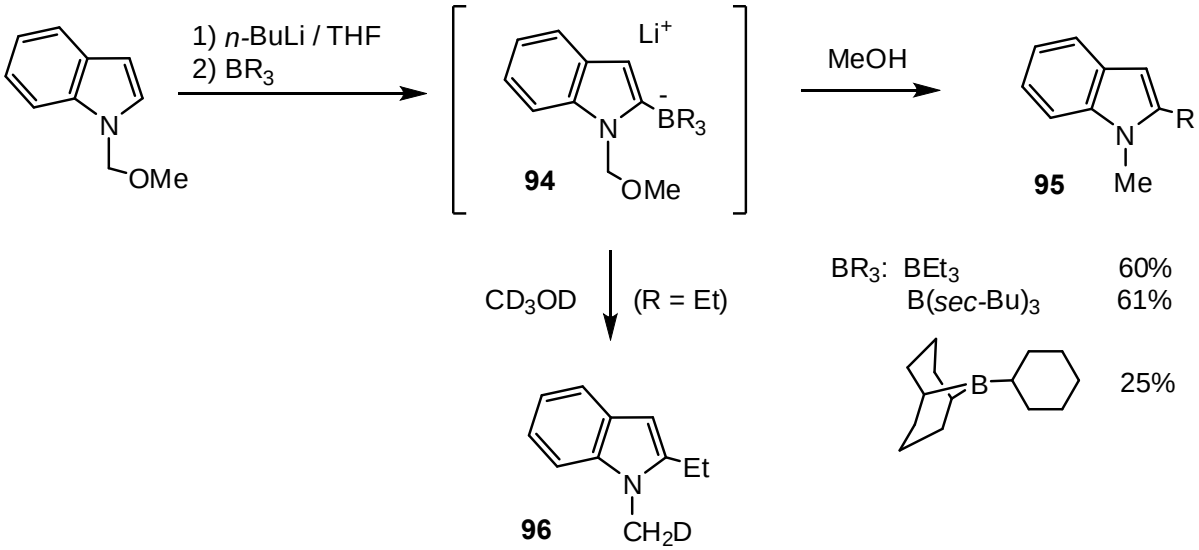
When both isomeric borates ***trans*-89** and ***cis*-89** were separately subjected to the reaction, only *trans*-fused indole **92** was isolated, selectively. The nucleophilic attack of the indole proceeds on the π–allylpalladium complex from the opposite side of the Pd with a simultaneous alkyl migration in *anti* manner. The steric repulsion between the indole and the cyclohexene rings in complex **90b** makes the generation of **93** *via* **91b** unfavorable. Complex **90b** was assumed to isomerize to complex **90a**, leading to **92** *via* **91a** (Scheme 32).



Scheme 32. One-pot formation of cycloalkano[1,2-*b*]indole **92**

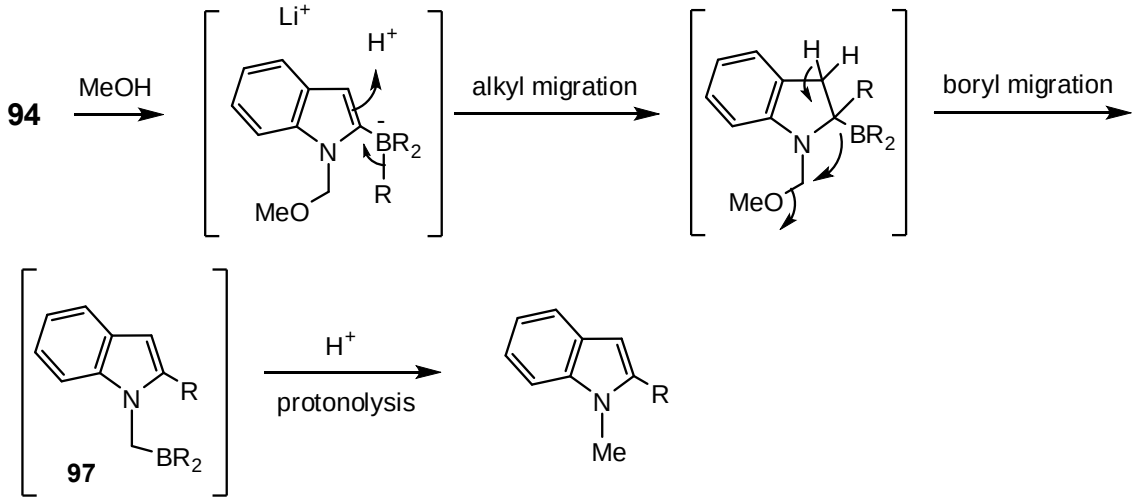
6. ALKYL-BORYL MIGRATION CASCADE

During studies of the intramolecular alkyl migration reaction in indolylborates **3**, we found a novel cascade of alkyl-boryl migration steps in the reaction of trialkyl(*N*-methoxymethylindol-2-yl)borate **94**. When borate **94** was treated with MeOH, 2-alkyl-*N*-methylindoles **95** were isolated. Moreover, addition of CD_3OD to a solution of **94** (R=Et) in THF produced **96**, with the incorporation of a deuterium atom into the *N*-Me group.[31]



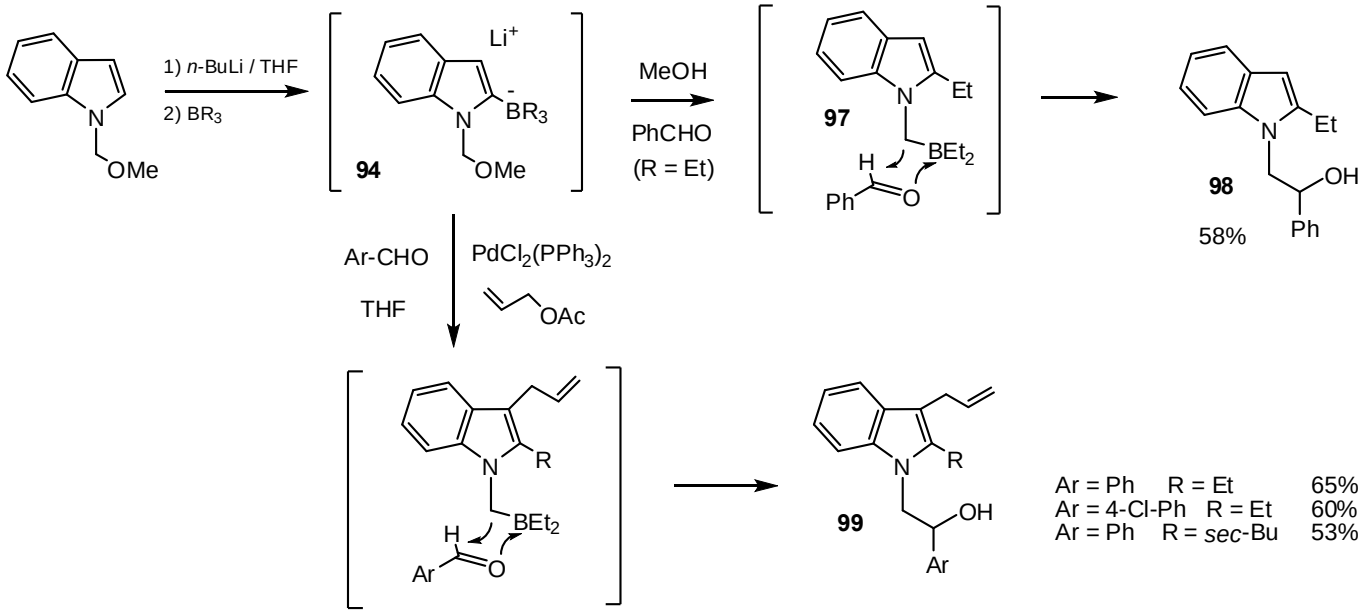
Scheme 33. Alkyl-boryl migration in borate **94**

The results can be explained by a novel class of cascade of alkyl-boryl migration sequences, which involves the intermediary formation of alkylborane **97** through alkyl migration followed by boryl migration, and subsequent protonolysis of the C-B bond of **97** (Scheme 34).



Scheme 34. Plausible reaction mechanism

This unprecedented process was successfully applied to the assembly of more elaborate indoles in a one-pot manner from *N*-methoxymethylindole (Scheme 35). Borate **94** (R=Et), generated *in situ* in THF from *N*-methoxymethylindole, was treated with MeOH in the presence of benzaldehyde. This provided alcohol **98** through the intermediary formation of alkylborane **97** and subsequent C-C bond formation between the C-B bond of **97** and benzaldehyde. Heating a mixture of **94**, allyl acetate, aryl aldehyde and a catalytic amount of palladium complex in THF at 60 °C for 30 min afforded trisubstituted indoles **99**.



Scheme 35. One-pot construction of substituted indoles **98**, **99**

7. CONCLUSION

Here, we have disclosed that trialkyl(2-indolyl)borates are versatile synthetic intermediates for the concise assembly of highly elaborate indole derivatives and natural alkaloids. Investigations are in progress exploring further synthetic applications of trialkyl(2-indolyl)borates based on the effective interaction between the anionic boryl group and the enamine moiety.

ACKNOWLEDGEMENTS

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