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Palladium (II)-catalysed intramolecular C—H functionalizations: Efficient synthesis of kealiinine C and analogues

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ABSTRACT

An efficient palladium-catalysed C—H functionalization sequence has been developed for the synthesis of 2-aminoimidazole alkaloids (Kealiinine C) and its analogues. This protocol proceeds *via* iodocyclisation of propargylguanidines followed by intramolecular Pd-catalysed cyclisation.

1. Introduction

The potential benefits of maneuvering an inert C—H bond have been repeatedly discussed over the years and is a challenging and intensive topic of research [1]. The significance of such direct transformation of C—H bonds is exemplified by their incorporation into the synthesis of complex molecules from their desired C—H precursors [2–4]. As a result, such strategies have made revolutionary accomplishments towards the total synthesis of natural products [5].

2-Amino imidazole alkaloids isolated from the sponges of *Leucetta* and *Clathrina* families exhibit a range of biological activities namely human *β*-secretase (BACE-1) inhibitors and tubulin-binding agents [6,7]. A subgroup of these alkaloids containing a naphthimidazole moiety *viz.* kealiiquinone **I** and its 2-amino congener (2-amino-2-deoxykealiiquinone **II**) were reported to possess cytotoxic and anticancer activities (Fig. 1) [8,9]. Moreover, naturally occurring analogues of kealiiquinone and the kealiinines were isolated and suggested to serve as biosynthetic precursors of **I** and **II**.

Over the past years, the total synthesis of kealiinine alkaloids [10] have been reported by Lovely and co-workers [11]. They organized the synthesis of kealiinine A-C, through a series of position-specific Grignard reactions followed by an intramolecular Friedel-Crafts-dehydration sequence of the formed bis benzylic diol. Further, C2-azidation and its hydrogenation provided the final kealiinine framework [12]. Simultaneously, Looper et al. reported the synthesis of kealiinines B and C *via* an electrophilic activation/cyclization sequence of the ene-guanidine intermediate with NBS [13].

In 2010, our group has synthesized polysubstituted 2-aminoimidazoles by a Ag-mediated guanylation–cyclization protocol [14] followed by a metal free, phenyliodonium diacetate (PIDA) mediated oxidative cascade cyclization of propargylguanidines to obtain the kealiinine framework [15]. Broadening our existing methodologies, we herein report a transition metal catalyzed C—H activation sequence for the synthesis of kealiinine C and analogues. It was envisioned that iodocyclisation of guanylated propargylamines followed by an intramolecular Pd-catalyzed cyclisation might be a suitable alternative (Scheme 1).

2. Experimental

2.1. Materials

All the starting materials, reagents and catalysts were purchased from Sigma-Aldrich or Acros or TCI Europe and used as such. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV254 and 70–230 mesh silica gel (E. M. Merck) were used). Column

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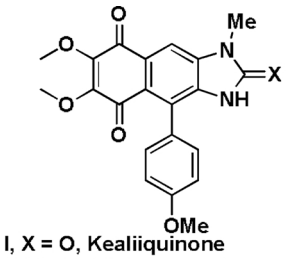


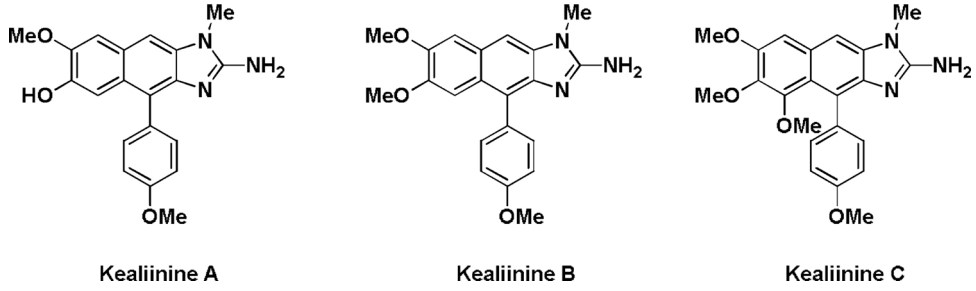
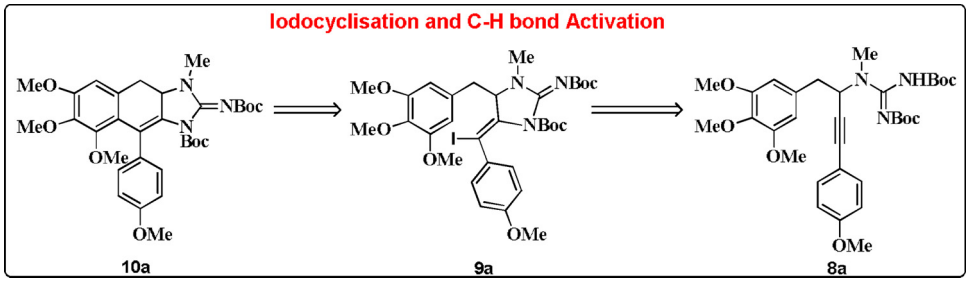


Fig. 1. Structures of kealiinine family analogues.



Scheme 1. Plausible retrosynthetic strategy.

chromatography was performed using silica gel (Merck, 60–120 mesh size). Anhydrous solvents were purchased from Acros Organics and stored over molecular sieves. The chromatographic solvents used for isolation/purification of compounds were distilled prior to use. The chromatographic solvents are mentioned as volume: volume ratios. Microwave reactions were typically run in microwave CEM-Discover or oven dried screw-cap vials.

2.2. Apparatus

^{1}H and ^{13}C NMR spectra were recorded on a 300 and 400 MHz instrument using $CDCl_3$/DMSO as a solvent. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) using the residual solvent signal as the internal reference. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, q = quartet, t = triplet, m = multiplet. The ^{13}C NMR spectra are proton decoupled. The melting points were determined on a digital Barnsted Electrothermal 9200 apparatus and are uncorrected. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150–250 °C, as required. High resolution EI-mass spectra were performed with a resolution of 10,000. The low-resolution spectra were obtained with a HP5989 A MS instrument. The low resolution ESI-MS were obtained with a Thermo Scientific instrument.

2.3. Synthesis of intermediates and deprotection

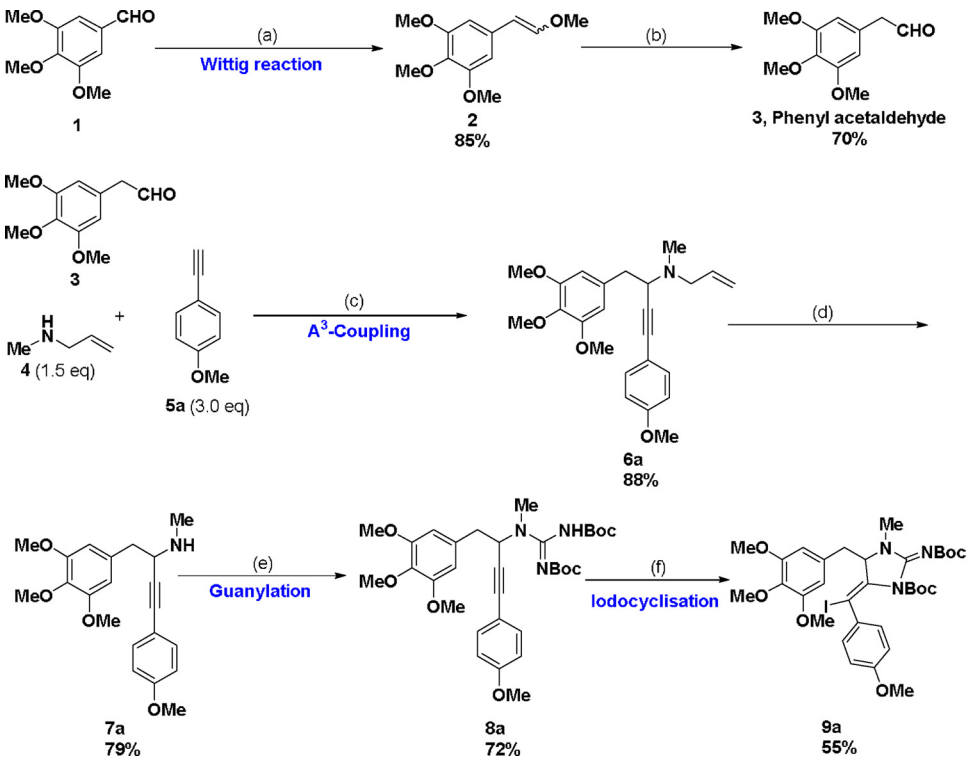
Synthesis of iodocyclised propargylguanidines (**9**) as well as the synthesis of kealiinine C and analogues (Boc-deprotection) is described in supporting information in details *via* the reported procedures and has been mentioned in the Scheme 2.

2.4. General procedure for palladium–catalysed C—H activation step

To a reaction vial were added, iodocyclized compound (0.04 mmol), palladium acetate (10 mol %), Cs_2CO_3 (1.5 equiv.), pivalic acid (30 mol %) and triphenyl phosphine (20 mol %) in anhydrous chlorobenzene (1.0 mL). The mixture was degassed with N_2. The reaction vessel was sealed and heated at 120 °C for 24 h. Then the mixture was diluted with EtOAc (5 ml) and washed with water (2 × 3 mL), dried over Na_2SO_4 and concentrated on rotary evaporator gave the crude product. Elution of the column with 35% ethyl acetate/heptane mixture gave the desired product as solid which was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

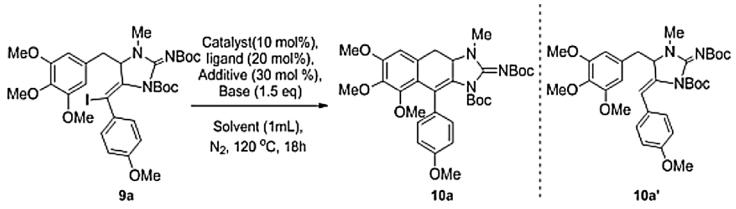
2.5. Characterization of the products

All compounds were fully characterized with 1H and 13C NMR, melting points and HR-MS analysis. The detailed synthetic procedures, spectral characterization of the compounds, as well as the NMR spectra can be found in the supplementary material.



Scheme 2. Synthetic strategy towards **9a**. Reagents and conditions : a) $CH_3OCH_2PPh_3Cl$, (1.5 equiv), ^tBuOK (2.5 equiv), THF, rt, 12 h; b) TFA:H_2O (1:1), DCM, rt, 12 h; c) CuBr (20 mol %), toluene, MW (100 °C, 1 h); d) $Pd(PPh_3)_4$ (5 mol%), DMBA (1.5 equiv), DCM, reflux, 6 h; e) DBTU (1.5 equiv), DIPEA (3 equiv), EDCl (2 equiv), DCM, rt, 8 h; f) I_2 (2 equiv), K_2CO_3, DCM, rt, 5 h.

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Ligand	Additive	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	–	Cs_2CO_3	Toluene	26
2	$Pd(OAc)_2$	PPh_3	–	Cs_2CO_3	CH_3CN	nd
3	$Pd(OAc)_2$	PPh_3	–	Cs_2CO_3	MeOH	nd
4	$Pd(OAc)_2$	PPh_3	–	Cs_2CO_3	DMSO	13
5	$Pd(OAc)_2$	PPh_3	–	Cs_2CO_3	Chlorobenzene	46
6	$Pd(OAc)_2$	PPh_3	–	Cs_2CO_3	DMF	nd
7	$Pd(OAc)_2$	PPh_3	–	NaOAc	Chlorobenzene	nd
8	$Pd(OAc)_2$	PPh_3	–	TEA	Chlorobenzene	nd
9	$Pd(OAc)_2$	PPh_3	–	K_2CO_3	Chlorobenzene	17
10	$Pd(OAc)_2$	PPh_3	–	DABCO	Chlorobenzene	nd
11	$Pd(OAc)_2$	PPh_3	–	K_3PO_4	Chlorobenzene	nd
12	$Pd(OAc)_2$	PPh_3	–	DIPEA	Chlorobenzene	nd
13	**$Pd(OAc)_2$**	**PPh_3**	**PivOH**	**Cs_2CO_3**	**Chlorobenzene**	**62**
14	$PdCl_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	nd
15	$Pd(OAc)_2(PPh_3)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	nd
16	$Pd(dba)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	nd
17	$Pd(PPh_3)_4$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	nd
18	$Pd(OAc)_2$	Davephos	PivOH	Cs_2CO_3	Chlorobenzene	38
19	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	PivOH	Cs_2CO_3	Chlorobenzene	30
20	$Pd(OAc)_2$	CyJohnPhos	PivOH	Cs_2CO_3	Chlorobenzene	31
21	$Pd(OAc)_2$	P(*t*Bu)$_3$	PivOH	Cs_2CO_3	Chlorobenzene	nd

[a] All reactions were run with **1a** (0.04 mmol), catalyst (10 mol%), ligand (20 mol%), additive (30 mol%), base (1.5 equiv) in the indicated solvent (1.0 mL) at 120 °C for 24 h under nitrogen atmosphere in a closed vessel.

[b] isolated yields.

3. Result and discussion

The required substrate, propargylguanidine **8a** was synthesized *via* chemistry earlier described by our group [14]. It was initiated with a Cu (I)-catalyzed three-component iminium acetylide addition (A^3-coupling) of 4-ethynylanisole, *N*-methylallylamine and the aryl

Table 2
Altering the standard conditions.[a]

Entry	Catalyst	Ligand	Additive	Base	Solvent	Yield (%)[b]
Effect of time, temperature and microwave irradiation						
1	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	nd[c]
2	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	21[d]
3	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	61[e]
4	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	nd[f]
Change in molar equivalents						
5	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	40[g]
6	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	21[h]
7	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	24[i]
8	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	30[j]
9	$Pd(OAc)_2$	PPh_3	PivOH	Cs_2CO_3	Chlorobenzene	34[k]

[a] All reactions were run with **1a** (0.04 mmol) under nitrogen atmosphere in a closed vessel.
[b] isolated yields.
[c] at 50 °C.
[d] at 100 °C.
[e] reaction time 48 h.
[f] microwave irradiation at 120 °C for 1 h.
[g] $Pd(OAc)_2$ 5 mol%.
[h] $Pd(OAc)_2$ 20 mol%.
[i] PPh_3 10 mol%.
[j] PivOH 20 mol%.
[k] Cs_2CO_3 (2 equiv).

acetaldehydes (obtained *via* Wittig reaction) (Scheme 2). Further deallylation of these intermediates with $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid (DMBA) provided the secondary propargylamines **7a**. Guanylation of these intermediates with *bis* Boc protected isothiourea and base yielded the propargylguanidines **8a** in good yield.

For investigation of our intramolecular cyclization studies, we selected kealiinine C as our prime target, thereby avoiding regioselectivity issues to assemble the naphthimidazole system. For the rapid and efficient construction of the kealiinine ring structure, we initiated our investigations by exploring the intramolecular cyclization of iodocyclised propargylguanidines **9a** under Pd(II)-catalysis in the presence of PPh_3 as ligand and Cs_2CO_3 as the base in various solvents such as toluene, CH_3CN, MeOH, DMSO, chlorobenzene and DMF and by heating the reaction at 120 °C for 24 h (Table 1, entries 1-6). Among all, chlorobenzene proved to be the best choice, affording the cyclised product **10a** in 46% yield (Table 1, entry 5). The de-halogenated product **10a'** has been the obvious major product in most of the cases. To direct the reaction towards intramolecular cyclization, a toolbox of bases, catalysts, ligands and additives were tested.

Accordingly, varying the base such as NaOAc, Et_3N, K_2CO_3, DABCO, K_3PO_4 and DIPEA (Table 1, entries 7-12), it was found that, none of them succeeded in providing the desired product except K_2CO_3 in 17% yield (Table 1, entry 9). However, the yield of the isolated product was surprisingly increased to 62% by performing the reaction in the presence of pivalic acid as an additive (30 mol%) indicating that the reaction might be going through a concerted metalation deprotonation (CMD) pathway (Table 1, entry 11-13).

Follow-up reactions with Pd catalysts other than $Pd(OAc)_2$ such as $PdCl_2$, $Pd(OAc)_2(PPh_3)_2$, $Pd(dba)_2$ and $Pd(PPh_3)_4$ did not deliver the desired product (Table 1, entries 14-17). Further altering the ligands, for instance, Davephos, P(*o*-totyl)$_3$ and CyJohnphos, yielded 38%, 30% and 31% of the required product respectively, whereas P(*t*Bu)$_3$ did not form any product (Table 1, entries 18-21). This revealed that only triphenylphosphine provided the best yield of the desired product (Table 1, entry 13). Also, performing the reaction at lower temperatures (50 °C, 100 °C) or longer duration did not result in any improvements in the yields (Table 2, entries 1-3). Moreover, reaction was also performed under microwave conditions at 120 °C for 1 h but the alternative de-halogenated product was obtained as the major product (Table 2, entries 4). Further varying the molar ratio of catalyst, ligand, additive and base ascertain that the use of 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, 30 mol% of pivalic acid and 1.5 equiv of Cs_2CO_3 provided the best yields of the desired product **10a** (Table 2, entries 5-9). The structure of **10a** was confirmed by ^1H and ^{13}C NMR analysis as well as mass spectrometry.

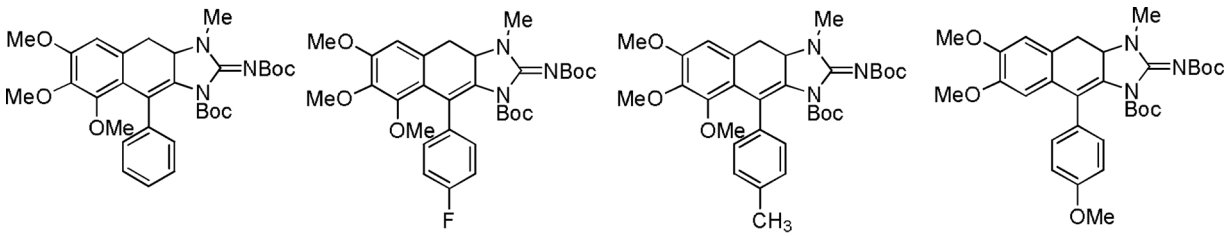
To check the capacity of the C—H activation cyclisation step, we decided to prepare other analogues of the kealiinine family (Scheme 3, **10b-10e**). Their syntheses follow the similar strategy by simply substituting the appropriate benzaldehyde, alkyne or amine in the A^3-coupling step. It was found that the conditions are specific for trimethoxy benzaldehyde only, as in case the di-methoxy benzaldehyde, only the de-halogenated product was obtained as the major one instead of the desired cyclised product. However, when the aryl substituent on the alkyne part was an electron-deficient (—F) or an electron-donating ($-CH_3$), the cyclised product was obtained in good to moderate yields (Scheme 3: **10b**, 62%; **10c**, 58%; **10d**, 64%).

As per the earlier reports, the mechanistic details of the C—H activation step can be explained with initial oxidative addition of the iodocyclised compound **9a** on a ligated Pd(0)-species to generate the Pd (II)-complex **A.** This is followed by a base-assisted formation of pivalate which on coordination to the Pd(II)-center generates intermediate **B**. This acts as a proton shuttle within concerted metalation-deprotonation (CMD) transition state **C** to form intermediate **D**. Finally, a reductive elimination of the intermediate **D** will lead to the desired kealiinine framework and regenerates the Pd(0) species which enters into the next catalytic cycle (Scheme 4).

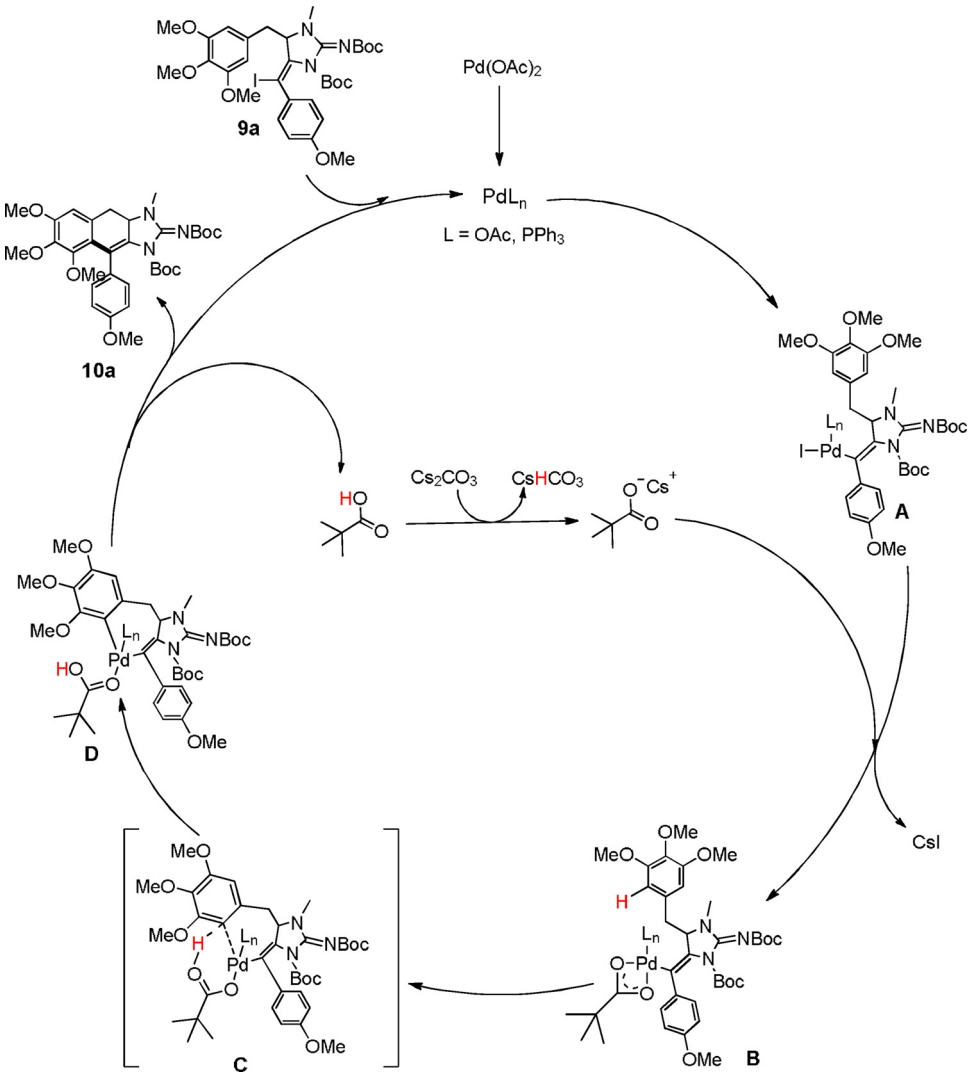
Next, we carried out the deprotection of the cyclized product **10a** upon treatment with a 1:1 mixture of TFA:DCM to afford fully aromatized kealiinine C **11a** upon oxidation in good yields along with other analogues (Scheme 5, **11b-11d**).

4. Conclusions

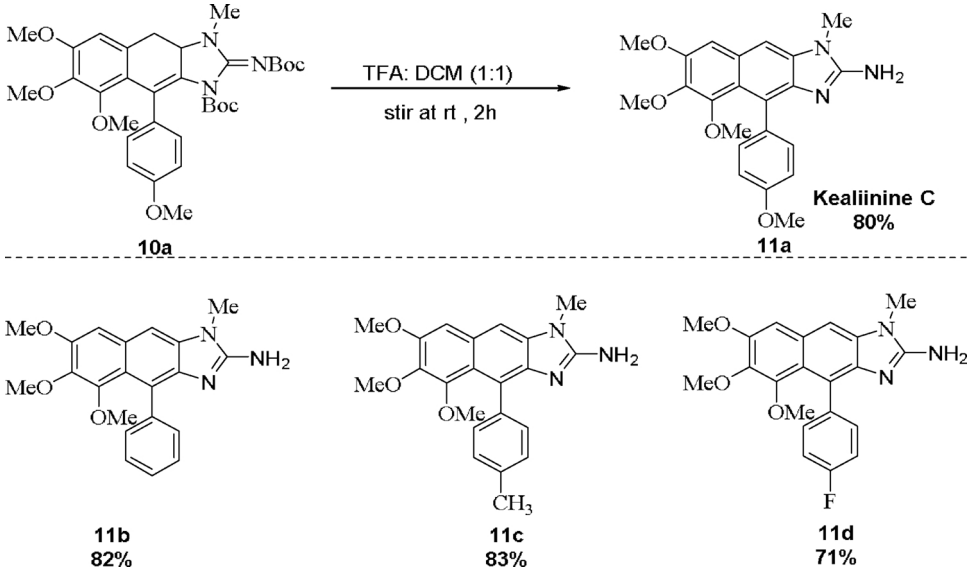
In summary, we have developed a palladium-catalysed C—H functionalization protocol to obtain the tricyclic kealiinine framework in moderate to good yields. The total syntheses of kealiinine C and its analogues was accomplished in a concise way with moderate to good yields.



Scheme 3. Scope of the C–H activation step.



Scheme 4. Proposed mechanistic pathway for the C–H activation step.



Scheme 5. Synthesis of kealiinine analogues.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2018.06.007.

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