Quick assembly of 1-alkylidenyl-tetrahydroisoquinolines *via* a Catellani reaction/NBS-mediated cyclization sequence and synthetic applications

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We herein disclose a modular synthesis of 1-bromomethylene-THIQs involving a Catellani reaction of aryl iodides, aziridines, and terminal alkynes followed by an *N*-bromosuccinimide (NBS)-mediated cyclization. This approach features mild reaction conditions, wide substrate scope, good step-economy and good scalability. Based on this new method, we have accomplished the concise total synthesis of (±)-cularine, formal synthesis of 8-oxopseudopalmatine as well as the first total synthesis of dactyllactone A, demonstrating the wide synthetic potential of this method.

1-bromomethylene-THIQ, Catellani reaction, (±)-cularine, 8-oxopseudopalmatine, dactyllactone A

1-Alklidenyl-tetrahydroisoquinolines (1-alklidenyl THIQs) are prevalent scaffolds found in many bioactive alkaloids such as dactyllactone A [1], dehydroglaucine [2], berberine [3], 8-oxopseudopalmatine [4]. They also serve as versatile synthetic intermediates to access more diverse THIQ alkaloids, including cularine [5], thalicarpine [6] and thalicultratine C [7], and others [8] (Scheme 1a). Therefore, considerable efforts have been devoted to the development of efficient methods to assemble these privileged scaffolds. Traditionally, they have been synthesized through sequential acylations and cyclizations between phenylethylamine and carboxylic acids and their derivatives [9] or isomerization of 1-methyl-3,4-dihydroisoquinolines [10]. Alternative methods include Sr-mediated cascade intermolecular alkene and intramolecular alkyne hydroamination [11], or Pd-catalyzed intramolecular aza-Heck cyclization [12] (Scheme 1b, top). Despite being effective, these approaches usually require specially functionalized and complex substrates or harsh reaction conditions, resulting in a relatively narrow substrate scope. As such, there is a continuing demand for a general and efficient strategy to assemble these scaffolds, particularly from simple readily accessible starting materials. Recently, our group developed a three-component Catellani reaction [13] followed by an Au-catalyzed 6-*exo-dig* cyclization [14] sequence for the rapid assembly of 1-methylene-THIQs (Scheme 1b, bottom, left) [15]. This method offered a new and convergent platform for the modular synthesis of

diverse 1-methylene-THIQs. Its synthetic value has been well demonstrated in the concise total syntheses of four naphthylisoquinoline alkaloids (korupensamines A and B and michellamines B and C) [15] and two proaporphine alkaloids (stepharine and pronuciferine) [16,17]. However, the scope of this method was limited with regards to the alkyne unit, allowing for incorporation of only the simplest acetylene unit, introduced from (triisopropylsilyl)acetylene. When aryl-substituted internal alkynes were used as the substrates, the Catellani reaction proceeded, but the subsequent cyclization step did not occur, making this a non-viable route to 1-alklidenyl THIQs. To overcome this limitation, we report herein, a modular and efficient method for the assembly of 1-bromomethylene-THIQs *via* the three-component Catellani reaction followed by an NBS-mediated cyclization [18], using readily available aryl iodides, aziridines and (trialkylsilyl)acetylene as the starting materials (Scheme 1b, bottom, right). Notably, the 1-bromomethylene-THIQs are versatile building blocks in synthetic organic chemistry for synthesizing highly value-added compounds. More importantly, by using this newly developed methodology as a key operation, we have accomplished the concise

total synthesis of (±)-cularine, formal synthesis of 8-oxopseudopalmatine as well as the first total synthesis of dactyllactone A.

We started our investigations with a model reaction using 1-(benzyloxy)-2-iodobenzene (**1a**), 1-tosylaziridine (**2a**), and (triisopropylsilyl)acetylene (**3a**) as the substrates for the synthesis of 2′-alkynylaryl-2-ethylamine **4a**. With our previous conditions [15], which were optimized for substituted aziridines, we observed 63% yield. However, as shown in Table 1, after minor modifications of previously established reaction conditions, including the employment of 0.5 equivalents of K_2CO_3 and decreasing the temperature to 60 °C, the desired product **4a** was obtained in 85% yield (entry 1). A set of control experiments was also conducted: changing the NBE derivative N^2 to simple norbornene N^1 led to a lower yield and no reaction took place in the absence of a Pd catalyst (entries 2 and 3). The base, K_2CO_3 was critical for this process, as the yield of **4a** decreased dramatically without it (entry 4). Poor yields were obtained when either toluene was used as the solvent or the less bulky ligand PPh_3 was used as ligand (entries 5 and 6). Notably, a scale-up operation (3.0 mmol) of this protocol was successfully performed to obtain 1.4 g of product **4a** (82% yield, entry 7), alongside 80% recovery of the N^2 mediator.

With the optimized reaction conditions in hand, we then investigated the substrate scope with respect to aryl iodides (Table 2A). A wide range of aryl iodides with electron-donating, withdrawing and neutral groups were competent substrates, providing the corresponding Catellani products in 40%–93% yields. A number of functional groups were
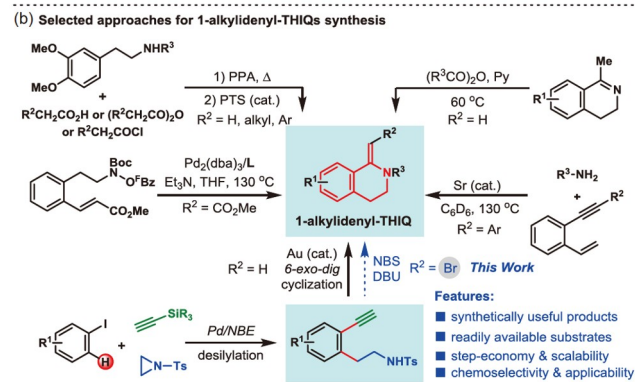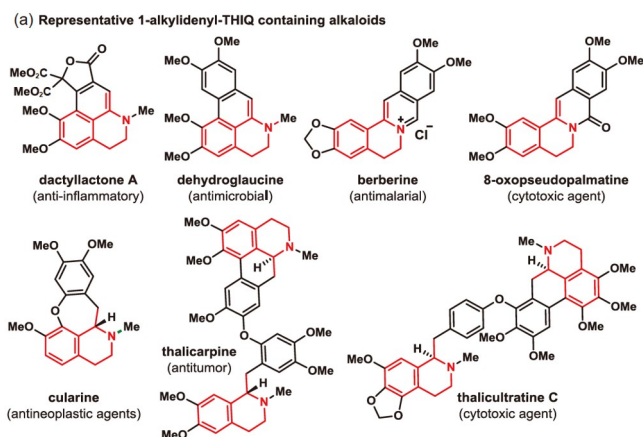
Scheme 1 (a) Representative natural products containing 1-alklidenyl-THIQ scaffold. (b) Selected approaches to access 1-alklidenyll-THIQs. THIQ: tetrahydroisoquinoline; PPA: polyphosphoric acid; PTS: *p*-toluene sulfonic acid monohydrate; [F]Bz: pentafluorobenzoyl; DBU: 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine; NBS: *N*-bromosuccinimide (color online).

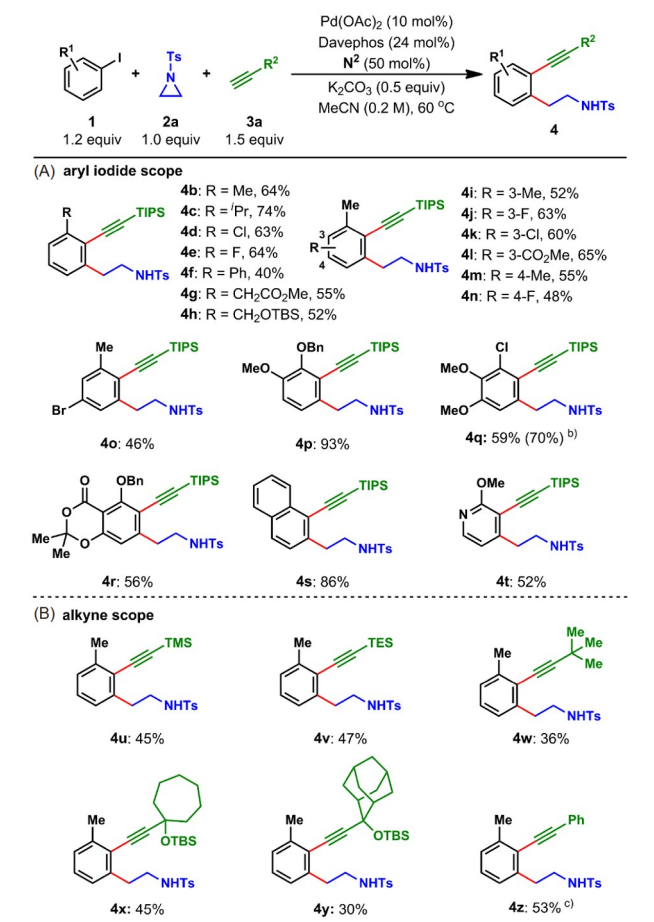**Table 1** Optimization of reaction conditions [a] (color online)
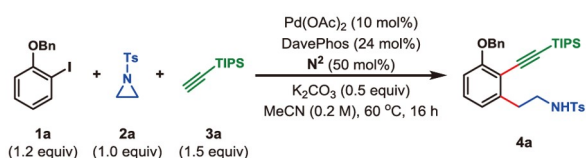
Entry	Change from the standard condition	Yield (%) [b]
1	none	85 (85) [c]
2	N^1 instead of N^2	27
3	no Pd(OAc)$_2$	0
4	no K_2CO_3	19
5	toluene instead MeCN	33
6	PPh_3 instead of DavePhos	10
7	3.0 mmol scale	(1.4 g, 82) [c]

a) All reactions were performed on a 0.1 mmol scale; b) ^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard; c) isolated yield in parentheses. Tol: *p*-tolyl; Cy: cyclohexyl; Ts: *p*-toluenesulfonyl.

compatible, including alkoxy (**4a**, **4p–4r**, and **4t**), fluoro (**4e**, **4j**, and **4n**), chloro (**4d**, **4k**, and **4q**), bromo (**4o**), methyl ester (**4g** and **4l**), and TBS-protected hydroxymethyl (**4h**). Moreover, densely functionalized aryl iodides (**4q** and **4r**), bicyclic aryl iodides (**4r** and **4s**), and heteroaryl iodide (**4t**) were also suitable substrates. Products **4p** and **4q** deserve special note, as they are important synthetic intermediates for the total synthesis of (±)-cularine, 8-oxopseudopalmatine and dactyllactone A. The yield of product **4q** could be improved to 70% when 2.0 equivalents of 5-norbornene-2-carbonitrile were used as the mediator and 2.0 equivalents of K_2CO_3 as the base.

We subsequently proceeded to examine the substrate scope with respect to the alkyne **3**. As shown in Table 2B, in addition to TIPS, TMS- and TES-substituted alkynes were also suitable substrates, wherein their reactions with **1b** and **2a** afforded products **4u–4v** in 45%–47% yields. Moreover, alkynes with bulky substituents were amenable for this reaction, affording the desired products **4w–4y** in 30%–45% yields. Notably, when trimethoxy(phenylethynyl)silane was

used as the terminating reagent, the phenyl-substituted product **4z** was obtained in 53% yield.

We then examined the Au-catalyzed cyclization of the internal alkynes for the assembly of 1-alklidenyl-THIQs. However, to our disappointment, the cyclizations did not occur and only trace amounts of desired 1-alklidenyl-THIQs were observed alongside large amounts of remaining starting materials (Scheme 2A) [19]. As such, we moved to investigate alternative methods to synthesize diverse 1-alkllidenyl-THIQs.

Table 2 Scope with respect to aryl iodides and alkynes [a] (color online)

Scheme 2 Reaction conditions: a) TBAF (2.0 equiv.), THF, r.t.; b) NBS (1.1 equiv.), DBU (2.4 equiv.), MeCN, r.t. to 80 °C; c) Pd(PPh₃)₄ (10 mol%), Cs₂CO₃ (2.0 equiv.), THF, 70 °C; d) Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), Et₃N (1.1 equiv.), DMF, 110 °C; e) Pd(OAc)₂ (15 mol%), PCy₃ (30 mol%), K₂CO₃ (2.0 equiv.), DMA, 110 °C; f) Ni(acac)₂ (30 mol%), CuI (30 mol%), Cs₂CO₃ (3.0 equiv.), dioxane, 110 °C; g) Pd(dppf)Cl₂ (5 mol%), KOAc (2.0 equiv.), dimethyl sulfoxide (DMSO), 80 °C, 12 h (color online).
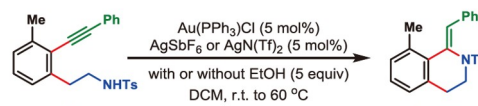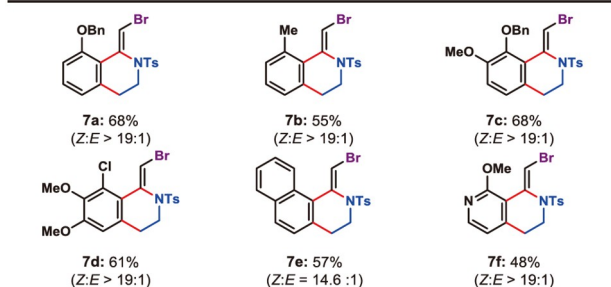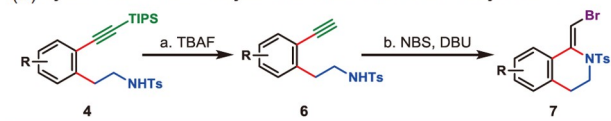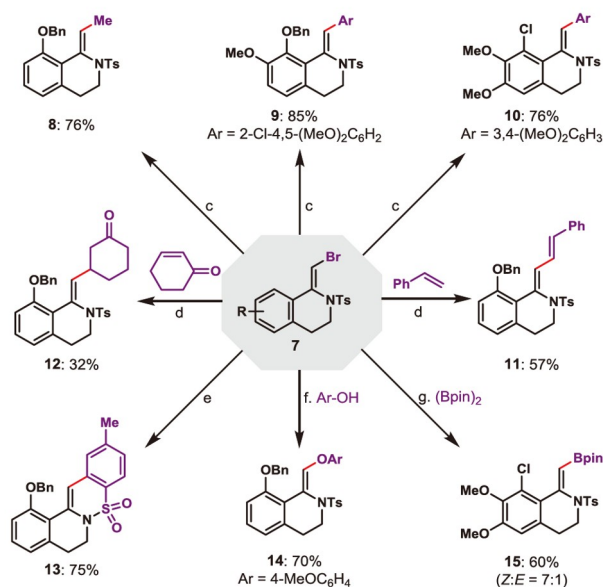
a) All reactions were performed on a 0.2 mmol scale. Isolated yields are reported. b) The reaction was carried out with 2.0 equivalents of 5-norbornene-2-carbonitrile and K₂CO₃. c) The reaction was performed on a 0.1 mmol scale. 12 mol% of TFP was applied instead of DavePhos and trimethoxy(phenylethynyl)silane was used as the terminating reagent.

As exhibited in Scheme 2B, we subsequently examined the cyclization for the assembly of 1-bromomethylene-THIQs. To our delight, starting from the silyl substituted Catellani product **4a**, desilylation with TBAF followed by an NBS-mediated cyclization took place smoothly, and the desired 1-bromomethylene-THIQ **7a** was generated in 68% yield over two steps. Notably, this cyclization proceeded with excellent regioselectivity and stereoselectivity, since only the cyclization product with the (*Z*)-configuration was obtained. This two-step protocol was also applicable to other Catellani products, such as **4b**, **4p**–**4q**, **4s**–**4t**, and the corresponding 1-bromomethylene-THIQs **7a**–**7f** were obtained in 48%–68% overall yields with excellent (*Z*)-selectivity. Hence, a modular method for the assembly of 1-bromomethylene-THIQ scaffolds was developed with commercially available feedstock chemicals as the starting materials.

Next, the general synthetic utility of this method was explored as shown in Scheme 2C. Firstly, the Suzuki-Miyaura coupling reactions [20] between 1-bromomethylene-THIQ **7** and methylboronic acid or arylboronic acid pinacol ester gave the corresponding 1-ethylidene-THIQ **8**, 1-(2-chloro-3,4-dimethoxybenzylidene)-THIQ **9** and 1-(3,4-dimethoxybenzylidene)-THIQ **10** in 76%–85% yields. Secondly, products **11** and **12** were obtained under typical Heck reaction conditions [21]. In addition, the Pd-catalyzed intramolecular cyclization *via* aromatic C–H bond activation delivered **13** in 75% yield [22]. A Ni-catalyzed C–O coupling reaction [23] between **7a** and 4-methoxyphenol afforded 1-((4-methoxyphenoxy)methylene)-THIQ **14** in 70%

yield. Finally, the 1-bromomethylene-THIQ **7d** was transformed into the corresponding alkenylboron species **15** in 60% yield, which is a very useful synthetic intermediate in organic synthesis [24].

The value of this chemistry was further demonstrated by its application in the efficient synthesis of three THIQ alkaloids: (±)-cularine, 8-oxopseudopalmatine and dactyllactone A, which have been found to display impressive bioactivities, including anti-inflammatory, antimicrobial, anxiolytic effect [1,4,5]. As shown in Scheme 3A, hydrogenation of **9** with PtO$_2$, TFA and Et$_3$SiH removed the benzyl-protecting group and reduced the enamide simultaneously to afford **16** in 82% yield. Then, the Pd-catalyzed intramolecular coupling generated **17** in 90% yield. Tosyl removal promoted by naphthalene/Na followed by reductive amination with formaldehyde solution formed (±)-cularine in 81% yield over 2 steps.

Next, starting from 1-(3,4-dimethoxybenzylidene)-THIQ **7e**, a concise formal synthesis of 8-oxopseudopalmatine was accomplished (Scheme 3B). Catalytic hydrogenation and tosyl removal gave intermediate **18** in 65% yield. Then a Mannich reaction between **18** and formalin in AcOH gave xylopinine **19** [25]. Finally, 8-oxopseudopalmatine was accessed through oxidation of **19** in the presence of Pd(OAc)$_2$ (10 mol%), Cu(OAc)$_2$ (10 mol%) and O$_2$ (1 atm) following the reported procedure [26].

Encouraged by the concise syntheses of (±)-cularine and 8-oxopseudopalmatine, we set out to synthesize a more challenging target—dactyllactone A, which was isolated from *dactylicapnos scandens* in 2018 [1] but has not yet been
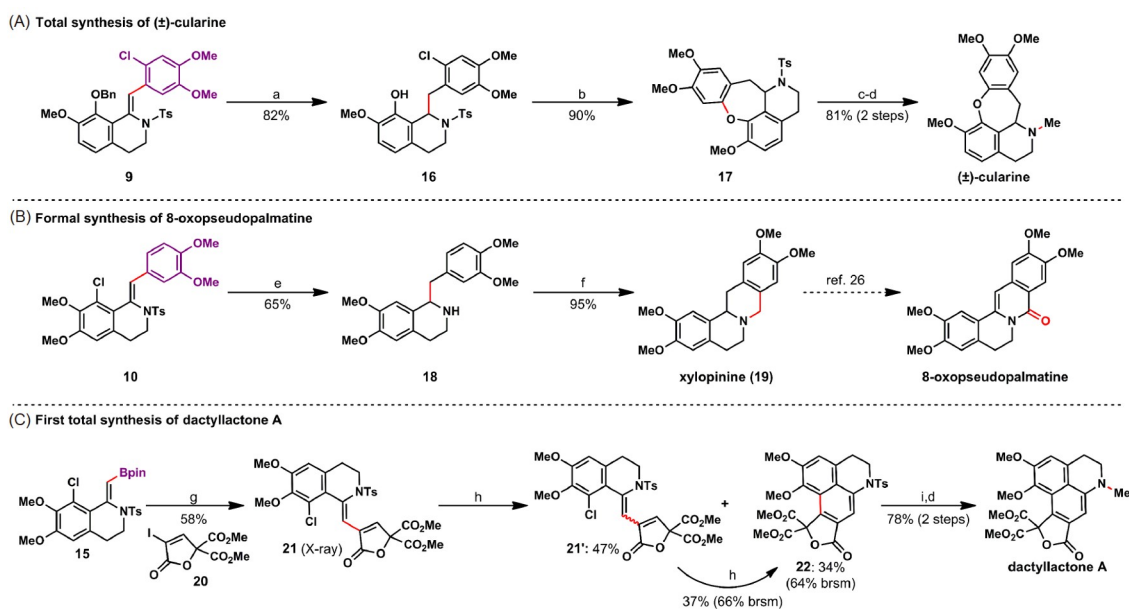
Scheme 3 Reaction conditions: (a) PtO$_2$ (1.0 equiv.), H$_2$ balloon, MeOH: DCM = 1:1, then TFA (5.0 equiv.), Et$_3$SiH (5.0 equiv.), DCM, r.t. 12 h; (b) Pd(OAc)$_2$ (10 mol%), *tert*-butyl-XPhos (15 mol%), NaOH (2.0 equiv.), toluene, 140 °C, 24 h; (c) Na (10 equiv.), naphthalene (10 equiv.), DME, −78 °C, 15 min; (d) formaldehyde solution (37 wt% aq., 4.0 equiv.), NaBH$_3$CN (10.0 equiv.), acetic acid (20.0 equiv.), MeCN, 0 °C, 3 h; (e) Pd/C (10 wt%.), H$_2$ balloon, MeOH/ DCM (1:1), then Mg powder (20.0 equiv.), MeOH, sonication, r.t., 5 h; (f) formaldehyde solution, acetic acid, 100 °C, 2 h; (g) Pd$_2$(dba)$_3$ (10 mol%), AsPh$_3$ (1.0 equiv.), Ag$_2$O (5.0 equiv), **20** (2.0 equiv.), THF, r.t., 3 h; (h) *hv* 365 nm, MeOH, r.t., 3 h; (i) H$_2$SO$_4$ (10.0 equiv.), DCM, r.t., 5 h. brsm: based on recovered starting material (color online).

synthesized. Alkenylboron species **15** underwent Suzuki-Miyaura coupling reaction with alkenyliodide **20** (see Supporting Information online for its synthesis) smoothly to afford the key intermediate **21** in 58% yield, whose structure was further confirmed by X-ray crystallographic analysis [27]. Photocyclization of **21** with 365-nm UV lamps at room temperature gave **22** in 34% yield alongside 47% recovery of starting material with both (*Z*) and (*E*)-configuration. Subjecting the recovered starting material (**21′**) to the same reaction conditions again delivered **22** in 37% isolated yield and 66% brsm. Subsequently, tosyl removal promoted by H$_2$SO$_4$ (aq.) in dichloromethane (DCM) followed by a facile reductive *N*-methylation furnished the desired dactyllactone A in 78% yield over 2 steps (Scheme 3C). It is worth noting that the characterization data of (±)-cularine, 8-oxopseudopalmatine and dactyllactone A are in agreement with those previously reported (see Supporting Information online for the corresponding comparisons) [1,26,28].

In summary, the studies described above have led to the development of a modular synthesis of synthetically useful 1-bromomethylene-THIQ scaffolds involving a Catellani reaction of aryl iodides, aziridines, and terminal alkynes followed by an NBS-mediated cyclization. The resulting 1-bromomethylene-THIQs are versatile intermediates in synthetic organic chemistry, and have been transformed into a series of highly value-added compounds. Based on this new method, a concise synthesis of (±)-cularine, 8-oxopseudopalmatine and the first total synthesis of dactyllactone A have been accomplished. Total syntheses of other more challenging tetrahydroisoquinoline alkaloids invoking this chemistry as a key strategy are currently ongoing in our laboratory.

Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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27 CCDC 2211398 (**21**) contains the supplementary crystallographic data for this paper. These data are provided free of charge from The Cambridge Crystallographic Data Centre
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