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COMMUNICATION

Palladium-catalyzed tandem reaction to construct benzo[*c*]phenanthridine: application to the total synthesis of benzo[*c*]phenanthridine alkaloids†

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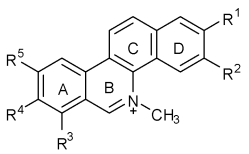
A concise and efficient synthesis of benzo[*c*]phenanthridines was accomplished by the palladium-catalyzed ring-opening coupling of azabicyclic alkene with *o*-iodobenzoates, followed by tandem cyclization. The strategy was successfully applied in the total synthesis of benzo[*c*]phenanthridine alkaloids such as sanguinarine, chelerythrine, nitidine and avicine.

The benzo[*c*]phenanthridine alkaloids are an important group of naturally occurring products possessing various biological activities.[1] Recently, aromatic benzo[*c*]phenanthridine alkaloids have received extensive attention for their interesting biological potential. For example, sanguinarine(**1**) inhibits lipoxygenase and mediates chemical defense against microorganisms, virus and herbivores in plants;[2] while chelerythrine(**2**), fagaronine(**3**) and nitidine(**4**) inhibit protein kinase C and DNA topoisomerase 1 (Fig. 1).[3] Effective syntheses of benzo[*c*]phenanthridine alkaloids and their derivatives have therefore been research subjects of recent interest. In the early reports, much effort was focused upon the construction of the A and D rings of the alkaloids.[4] In addition, synthesis of aminodihydro benzo[*c*]phenanthridine was realized by Clement[5] starting from 2-methylbenzonitrile and 4-(*N*,*N*-dimethylamino)benzaldehyde. However, some drawbacks still remain such as the requirements for a multistep pathway and challenging transformation in some cases. Herein, we wish to report a facile and general approach toward the syntheses of such alkaloids and their derivatives *via* a palladium-catalyzed ring-opening coupling-cyclization sequence.



sanguinarine **1**: $R^1+R^2=OCH_2O$, $R^3=R^4=OCH_2O$, $R^5=H$
chelerythrine **2**: $R^1+R^2=OCH_2O$, $R^3=R^4=OCH_3$, $R^5=H$
fagaronine **3**: $R^1=OH$, $R^2=R^4=R^5=OMe$, $R^3=H$
nitidine **4**: $R^1+R^2=OCH_2O$, $R^3=H$, $R^4=R^5=OMe$
avicine **5**: $R^1+R^2=OCH_2OH$, $R^3=H$, $R^4+R^5=OCH_2O$

Fig. 1 Some benzo[*c*]phenanthridine alkaloids.

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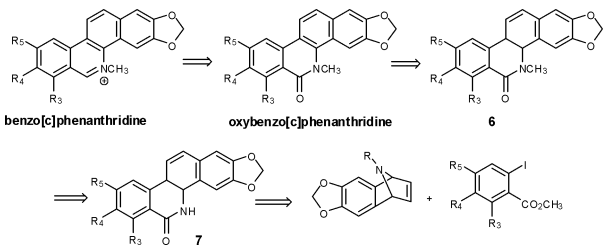
Since the alkaloids shown in Fig. 1 only structurally vary by the substituents and oxidation states in the A and D rings, it is possible to develop a general route toward all the target molecules. To construct the core structure of the benzo[*c*]phenanthridine alkaloids in a one step operation, starting from appropriately chosen components, we envisioned that a tandem strategy consisting of a metal-catalyzed ring-opening coupling of an azabicyclic alkene with *o*-iodobenzoates as the key step,[6] followed by an intramolecular cyclization could be feasible (Scheme 1). Although the first efficient route to unsubstituted benzo[*c*]phenanthridinone by a nickel-catalyzed strategy has been realized by Cheng,[7] the method is limited to unnatural benzo[*c*]phenanthridine and the required substrates such as electron-rich 1,3-benzodioxole azabicycles to synthesize natural benzo[*c*]phenanthridine alkaloids are not effective.[8] Our research interest in the total synthesis of natural benzo[*c*]phenanthridine alkaloids and functionalized derivatives prompted us to re-investigate the metal-catalyzed tandem cyclization of azabicyclic alkene with *o*-iodobenzoates to construct benzo[*c*]phenanthridines with more variable substituents.

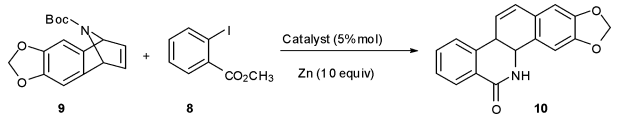


Scheme 1 Retrosynthetic analysis of benzo[*c*]phenanthridines.

Retrosynthetic analysis of the targeted alkaloids reveals that *cis*-dihydro benzo[*c*]phenanthridinones **7** would be key intermediates. *N*-Methylation of the intermediate **7** could give dihydro benzo[*c*]phenanthridinones **6**. Appropriate oxidation of dihydro benzo[*c*]phenanthridinones **6** would provide the oxybenzo[*c*]phenanthridine, which could be readily converted to aromatic benzo[*c*]phenanthidine by reduction with $LiAlH_4$.[9]

Because most of the natural benzo[*c*]phenanthridines have the 1,3-benzodioxole moiety and multiple methoxy groups, we selected the 1,3-benzodioxole-azabicycle **9** (prepared in 3 steps from catechol)[10] and *o*-iodobenzoate **8** as the model substrates to optimize the conditions effective for formation of the product **10** *via* a cyclization sequence (Table 1). Although the ring-openings of

Table 1 Survey on the model reaction of azabicycle 9 with *o*-iodobenzoate **8**[a]

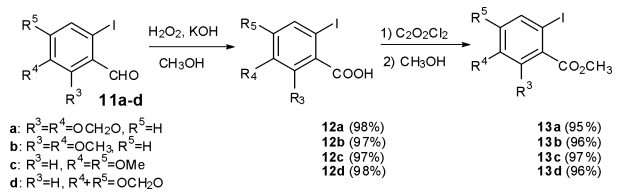


entry	catalyst, ligand (ratio)	solvent	time (h)	yield (%)[b]
1[c]	$NiBr_2$(dppe)	CH_3CN	20	0
2	$Pd(OAc)_2$, PPh_3, (1 : 2.2)	DMF	20	57
3[c]	$NiCl_2$, dppe, (1 : 1)	CH_3CN	12	0
4	$Pd(PPh_3)_4$	DMF	20	55
5	$Pd_2(dba)_3$, dppe (1 : 2)	DMF	12	0
6[c]	$Ni(PPh_3)_2Cl_2$,	CH_3CN	12	0
7	$Pd(CH_3CN)_2Cl_2$, PPh_3(1 : 2)	CH_3CN	12	0
8[d]	$Pd(PPh_3)_2Cl_2$	DMF	20	58
9[d]	$Pd(PPh_3)_2Cl_2$	CH_3CN	20	75
10[d]	$Pd(PPh_3)_2Cl_2$	THF	12	90
11[d]	$Pd(PPh_3)_2Cl_2$	Tol	20	15
12	$Pd(OAc)_2$, PPh_3, (1 : 2.2)	THF	20	0

[a] Conditions: iodo ester (1 mmol), azabicycle (1.5 equiv), Et_3N (8 equiv; used as an additive), solvent (25 mL) were employed. [b] Isolated yield of product after chromatography. [c] Run at 80 °C. [d] $ZnCl_2$ (0.5 equiv) was added.

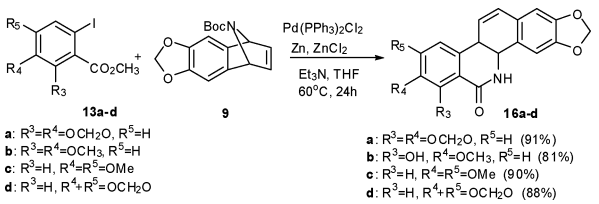
7-oxa- and azanorbornenes could be readily effected by nickel and palladium catalysts,[11] most of them are incapable of converting the azabicycle **9** to amide **10**. As shown in Table 1, when the catalyst was $Pd(OAc)_2/PPh_3$ or $Pd(PPh_3)_4$, moderate yields of the desired annulation product were obtained (entry 2, 4). Only $Pd(PPh_3)_2Cl_2$ in THF gave the amide **10** in excellent yield (entry 10). Nickel complexes such as $NiBr_2$(dppe), $Ni(PPh_3)_2Cl_2$, Ni(dppe)Cl_2, were ineffective to catalyze the coupling reaction. Furthermore, the polarity of the solvent proved to be important, increasing the polarity of solvent tended to lower the yields of **10** because the deamination as the side reaction got worse.

Accordingly, a couple of methyl *o*-iodobenzoates **13a–d** were prepared from the corresponding substituted benzoic acids **12a–d** respectively (Scheme 2). The acids **12a–d** were prepared by oxidation of *o*-iodobenzaldehydes **11a**,[12] **11b**,[13] **11c**[14] and **11d**[14] using the reported procedure.[15]



Scheme 2 Preparation of *o*-iodobenzoates.

Next, under the optimized conditions, the palladium-catalyzed tandem coupling–cyclization of functionalized *o*-iodobenzoates **13a–d** with azabicycle **9** were investigated to achieve the total syntheses of natural benzo[*c*]phenanthridine alkaloids (Scheme 3). In contrast with that of the *o*-iodobenzoate, the reaction of functionalized **13a–d** required a longer reaction time, presumably due to the highly electron-rich character of the ring-opening coupling intermediate **14**. Removal of the Boc group from unannulated **14** by following literature precedent[16] failed to give the expected product, but the corresponding naphthalene derivatives



Scheme 3 Pd-catalyzed tandem coupling cyclization of azabicycle **9** with functionalized *o*-iodobenzoates.

15 (Fig. 2) were obtained instead through a deamination process. In the case of methyl 6-iodo-2,3-dimethoxy benzoate **13b**, a demethylated product 7-hydroxy-8-methoxy-2,3-methylenedioxy dihydrobenzo[*c*]phenanthridinone **16b** was obtained instead of the normal product. Product **16b** was fully identified by ^1H and ^{13}C NMR and MS (M + Na^+: 360.0847). Demethylation could be attributed to the effect of Lewis acid (ZnX_2) and formation of a hydrogen bond.[17]

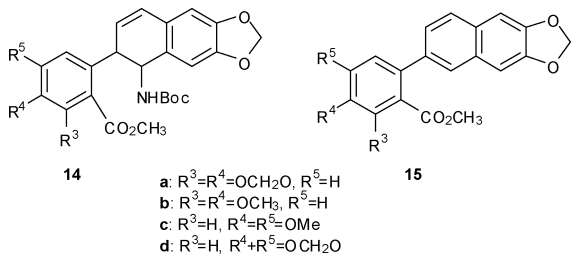
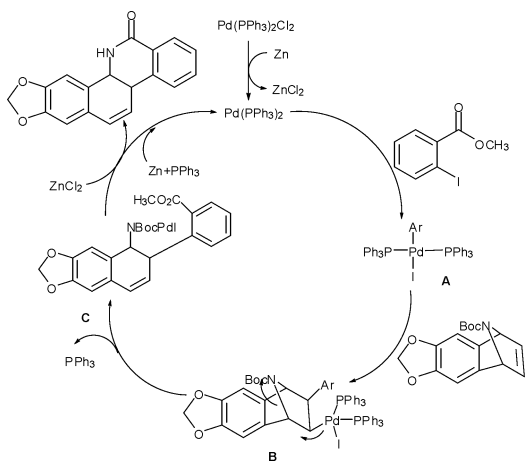


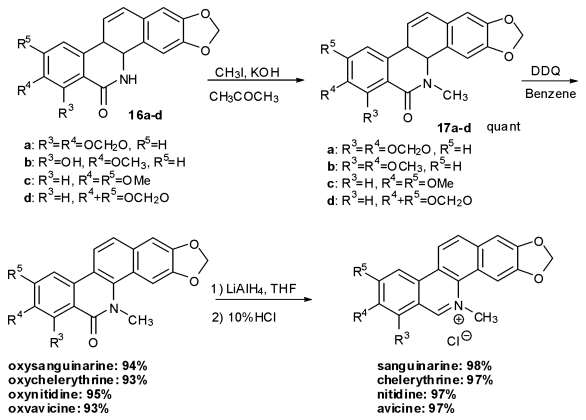
Fig. 2 Structures of **14** and **15**.

A proposed catalytic cycle is depicted in Scheme 4, which initiates with the reduction of Pd(II) by zinc to Pd(0). Oxidative addition of RI to the Pd(0) species forms $Pd(PPh_3)_2RI$ **A**. Exo addition of R–Pd to the azabicyclic alkene affords an intermediate **B**, which undergoes β-heteroatom elimination to bring about the ring-opening intermediate **C**. Transmetalation of **C** with $ZnCl_2$, followed by an amidation and deprotection of the Boc group produces the tandem ring-opening coupling product benzo[*c*]phenanthridinones and regenerates the Pd(II) species (Scheme 4).



Scheme 4 A proposed catalytic cycle for Pd-catalyzed tandem ring-opening coupling–cyclization.

Utilization of the benzo[*c*]phenanthridinones **16** in the total syntheses of natural alkaloids has been demonstrated as shown in Scheme 5. Oxidation of amides **16** with DDQ in either benzene or 1,4-dioxane failed in giving the desired dehydrogenated products. However, the *N*-methylated products **17** could be readily aromatized by oxidation of DDQ. Thus, treatment of dihydro benzo[*c*]phenanthridinones **16** with iodomethane and potassium hydroxide in acetone afforded the corresponding *N*-methylated products **17** in quantitative yields. Oxidation of **17** with DDQ was successfully carried out, giving oxybenzo[*c*]phenanthridine alkaloids in good yields. Reduction[9] of oxybenzo[*c*]phenanthridines with $LiAlH_4$ followed by treatment with HCl gave the desired quaternary benzo[*c*]phenanthridine chlorides in high yields (Scheme 5).



Scheme 5 Syntheses of some benzo[*c*]phenanthridine alkaloids.

In conclusion, a concise and versatile strategy for the total synthesis of benzo[*c*]phenanthridine alkaloids using readily available starting materials and inexpensive reagents has been developed. It features a palladium-catalyzed tandem ring-opening coupling–cyclization process as a key synthetic step. This efficient strategy should allow easy access to a variety of benzo[*c*]phenanthridine alkaloids and their analogues.

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Notes and references

1 V. Simanek, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1985, Vol. 26, pp. 185–229.
2 (*a*) C. Vavrečková, I. Gawlik and K. Müller, *Planta Med.*, 1996, **62**, 397; (*b*) T. Schemeller, B. Latz-Bruning and M. Wink, *Phytochemistry*, 1997, **44**, 257; (*c*) F.-C. Huang and T. M. Kutchan, *Phytochemistry*, 2000, **53**, 555.
3 (*a*) Z. Taira, M. Matsumoto, S. Ishida, T. Ichikawa and Y. Sakiya, *Chem. Pharm. Bull.*, 1994, **42**, 1556; (*b*) J. M. Herbert, J. M. Augereau, J. Gleye and J. P. Maffrand, *Biochem. Biophys. Res. Commun.*, 1990, **172**, 993; (*c*) S.-D. Fang, L.-K. Wang and S. M. Hecht, *J. Org. Chem.*, 1993, **58**, 5025; (*d*) T. Nakanishi and M. Suzuki, *J. Nat. Prod.*, 1998, **61**, 1263.
4 (*a*) H. Ishii, Y.-I. Ichikawa, E. Kawanabe, M. Ishikawa, T. Ishikawa, K. Kuretani, M. Inomata and A. Hoshi, *Chem. Pharm. Bull.*, 1985, **33**, 4139; (*b*) T. Harayama, *Heterocycles*, 2005, **65**, 697; (*c*) T. Harayama, T. Sato, Y. Nakano, H. Abe and Y. Takeuchi, *Heterocycles*, 2003, **59**, 293; (*d*) R. P. Korivi and C.-H Cheng, *Chem.–Eur. J.*, 2010, **16**, 282.
5 (*a*) B. Clement, M. Weide, U. Wolschendorf and I. Kock, *Angew. Chem., Int. Ed.*, 2005, **44**, 635; (*b*) I. Kock and B. Clement, *Synthesis*, 2005, 1052.
6 J.-P. Duan and C.-H. Cheng, *Tetrahedron Lett.*, 1993, **34**, 4019.
7 D. K. Rayabarapu, P. Shukla and C.-H. Cheng, *Org. Lett.*, 2003, **5**, 4903.
8 S. Madan and C.-H. Cheng, *J. Org. Chem.*, 2006, **71**, 8312.
9 (*a*) M. Hanaoka, T. Motonishi and C. Mukai, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2253; (*b*) T. Harayama, T. Akiyama, H. Akamastsu, K. Kawano, H. Abe and Y. Takeuchi, *Synthesis*, 2001, 444.
10 H. A. McManus, M. J. Fleming and M. Lautens, *Angew. Chem., Int. Ed.*, 2007, **46**, 433.
11 (*a*) J.-P. Duan and C.-H. Cheng, *Organometallics*, 1995, **14**, 1608; (*b*) C.-C. Feng, M. Nandi, T. Sambaiah and C.-H. Cheng, *J. Org. Chem.*, 1999, **64**, 3538; (*c*) D. K. Rayabarapu and C.-H. Cheng, *Acc. Chem. Res.*, 2007, **40**, 971.
12 R. J. Mattson, C. P. Sloan, C. C. Lockhart, J. D. Catt, Q. Gao and S. Huang, *J. Org. Chem.*, 1999, **64**, 8004.
13 D. E. Bogucki and J. L. Charlton, *J. Org. Chem.*, 1995, **60**, 588.
14 B. A. Hathaway, K. L. White and M. E. McGill, *Synth. Commun.*, 2007, **37**, 3855.
15 Z.-Q. Cong, C.-L. Wang, T. Chen and B.-Z. Yin, *Synth. Commun.*, 2006, **36**, 679.
16 (*a*) F. S. Gibson, S. C. Bergmeier and H. Rapoport, *J. Org. Chem.*, 1994, **59**, 3216; (*b*) D. S. Bose and V. Lakshminarayana, *Synthesis*, 1999, 66; (*c*) T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda and W. Nagata, *Tetrahedron Lett.*, 1979, **20**, 2793; (*d*) R. S. Lott, V. S. Chauhan and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, **11**, 495.
17 H. Nagaoka, G. Schmid, H. Iio and Y. Kishi, *Tetrahedron Lett.*, 1981, **22**, 899.