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Concise Route to 3-Arylisoquinoline Skeleton by Lewis Acid Catalyzed C(sp^3)−H Bond Functionalization and Its Application to Formal Synthesis of (±)-Tetrahydropalmatine

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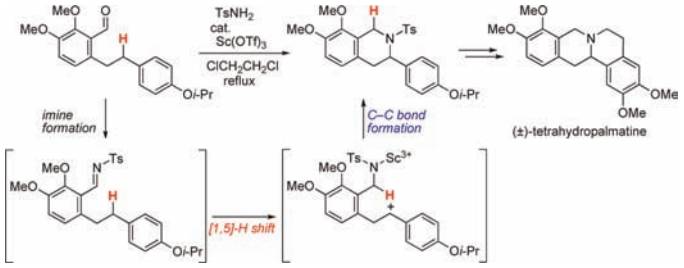
ABSTRACT



An expeditious route to furnish an isoquinoline skeleton via hydride shift mediated C−H bond functionalization was developed. In this process, an unusual [1,5]-H shift without the assistance of the adjacent heteroatom took place to produce tetrahydroisoquinoline derivatives in good to excellent chemical yields. The formal synthesis of (±)-tetrahydropalmatine was achieved by exploiting this new transformation.

The development of methodology for the direct functionalization of relatively unreactive C−H bonds has become a major topic of research.[1] Recently, the C(sp^3)−H bond functionalization via the hydride shift/cyclization process, namely, the "internal redox process", has attracted much attention for its unique features (Scheme 1).[2] The key feature of this transformation is the [1,5]-hydride shift of the C(sp^3)−H bond α to the heteroatom. Subsequent 6-endo cyclization to cation species affords heterocycle **2**. Although C−H bond functionalization is promoted by a transition metal catalyst in most cases, this type of C−H bond functionalization typically proceeds under thermal conditions or Brønsted or Lewis acid catalysis.[3−6]

Whereas a range of related reactions of heteroatom-containing substrates (X = NR^2 or O) have been reported,

(1) For recent reviews on C−H activation, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Bergman, R. G. *Nature* **2007**, *446*, 391. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (f) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev* **2011**, *40*, 1855. (i) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* 2011, DOI: 10.1021/ar200194b.

(2) For selected recent references, see: (a) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (b) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429. (c) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (d) Barluenga, J.; Fananás-Mastral, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594. (e) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (f) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. (g) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. (h) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543. (i) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593. (j) Haibach, M. C.; Deb, I.; Kanta De, C.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100. (k) Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133*, 7696. (l) Alajarin, M.; Martin-Luna, M.; Vidal, A. *Adv. Synth. Catal.* **2011**, *353*, 557.

(3) These types of reactions are classified under the term "*tert*-amino effect". For reviews, see: (a) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211. (b) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311. (c) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1. (d) Quintela, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 259. (e) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625.

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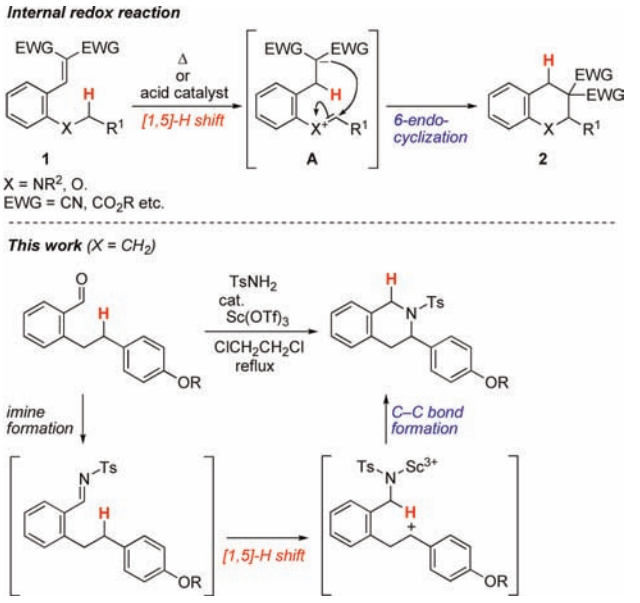
the corresponding carbon analogue (X = CH_2) had been overlooked until quite recently.[7,8] This is due to the difficulties posed by the desired [1,5]-hydride shift of the C−H bond without the assistance of the adjacent heteroatom. As part of our recent program to develop new catalytic C−H bond functionalization methodologies,[6] we have disclosed that the benzylic C−H bond without an adjacent heteroatom could also participate in this type of transformation, giving 3-aryltetraline derivatives.[7] Quite recently, several other groups also reported the platinum-catalyzed benzylic C−H bond functionalization that led to indene derivatives.[8] Stimulated by these achievements, we turned our attention to the construction of another important substructure by exploiting this type of transformation.

We describe herein an expeditious route to an isoquinoline skeleton, which is frequently encountered in numerous biologically active compounds, via the hydride shift/cyclization sequence.[9] In this reaction, three transformations (imine formation, [1,5]-hydride shift, and 6-*endo* cyclization) occurred successively to afford isoquinoline derivatives in good to excellent chemical yields. The application of this methodology to the formal synthesis of (±)-tetrahydropalmatine is also demonstrated.

Scheme 1. C(sp^3)−H Bond Functionalizaiton via Internal Redox Process



We have already reported that the internal redox reaction that employed imine as an electrophilic partner could be achieved in a one-pot process from aldehyde and amine (without isolation of the corresponding imine).[6a] At the outset, a solution of aldehyde **3a** with *p*-methoxyphenethyl moiety and $TsNH_2$ in $ClCH_2CH_2Cl$ was exposed to 10 mol % of acid at reflux temperature (Table 1). Various Lewis acids, such as $SnCl_4$, $TiCl_4$, and $BF_3 \cdot OEt_2$, were ineffective, and only corresponding imine **5a** was obtained after 24 h (entries 1−3). Gratifyingly, $FeCl_3$ promoted the two desired reactions (imine formation and internal redox reaction) to give isoquinoline **4a** in moderate yield (62%, entry 4). Further screening of the catalyst revealed that strong Brønsted acids and lanthanoid triflates promoted this transformation efficiently: on treatment with $TsOH \cdot H_2O$, **4a** was obtained in 39% yield (entry 5). TfOH was more effective, affording **4a** in 78% isolated yield (entry 6). $Sc(OTf)_3$ was the catalyst of choice, and **4a** was obtained in excellent yield (90%, entry 8). Fortunately, the catalyst loading of $Sc(OTf)_3$ could be reduced to 5 mol % without sacrificing the chemical yield (92%, entry 9).

Further examination suggested that the strong electrophilicity of the imine moiety was crucial for this transformation: when aniline was employed in place of $TsNH_2$, the

(4) (a) Reinhoudt, D. N.; Visser, G. W.; Verboom, W.; Benders, P. H.; Pennings, M. L. M. *J. Am. Chem. Soc.* **1983**, *105*, 4775. (b) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (c) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3136. (d) Groenen, L. C.; Verboom, W.; Nijhuis, W. H. N.; Reinhoudt, D. N.; Van Hummel, G. J.; Teil, D. *Tetrahedron* **1988**, *14*, 4627. (e) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199. (f) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Van Hummel, G. J.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 209. (g) De Boeck, B.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1995**, *51*, 13239. (h) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (i) Che, X.; Sheng, L.; Dang, Q.; Bai, X. *Synlett* **2008**, 2373. (j) Polonka-Bálint, A.; Saraceno, C.; Ludányi, K.; Bényei, A.; Mátyus, P. *Synlett* **2008**, 2846. (k) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (l) Ruble, J. C.; Hurd, A. R.; Johnson, T. A.; Sherry, D. A.; Barbachyn, M. R.; Toogood, P. L.; Bundy, G. L.; Graber, D. R.; Kamilar, G. M. *J. Am. Chem. Soc.* **2009**, *131*, 3991. (m) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972. (n) Földi, A. A.; Ludányi, K.; Bényei, A. C.; Mátyus, P. *Synlett* **2010**, 2109. (o) Dunkel, P.; Túrós, D.; Bényei, A.; Ludányi, K.; Mátyus, P. *Tetrahedron* **2010**, 2331.

(5) Examples of enantioselective internal redox reactions: (a) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (b) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (c) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600. (d) Zhou, G.; Liu, F.; Zhang, J. *Chem.—Eur. J.* **2011**, *17*, 3101.

(6) (a) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524. (b) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. *Org. Lett.* **2010**, *12*, 1732. For an asymmetric version of internal redox reaction catalyzed by chiral phosphoric acid, see: (c) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166.

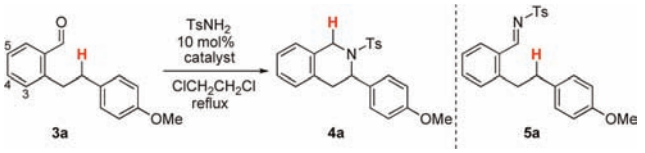
(7) (a) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 2424. (b) Mori, K.; Sueoka, S.; Akiyama, T. *Chem. Lett.* **2011**, *40*, 1386.

(8) (a) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471. (b) Yang, S.; Li, Z.; Jian, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999. Fillion's group found that the *p*-methoxyphenyl group is important for the benzylic hydride shift/ring closure for the formation of tetraline derivatives. See: (c) Mahoney, S. J.; Moon, D. T.; Hollinger, J.; Fillion, E. *Tetrahedron Lett.* **2009**, *50*, 4706. For hydride shifts from di- and/or triarylmethane, see: (d) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204. (e) Alajarin, M.; Bonillo, B.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A.; Orenes, R.-A. *Org. Biomol. Chem.* **2010**, *8*, 4690.

(9) Tietze's group found that this type of cyclic amine formation reaction occurred in steroidal compounds. See: (a) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 200. (b) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **1999**, 3013. (c) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, 90.

(10) Investigation of other solvent systems (toluene, benzene, cyclohexane, and CH_3CN) suggested that nonpolar solvents were suitable for this reaction, and $ClCH_2CH_2Cl$ was found to be the solvent of choice.

Table 1. Examination of Reaction Conditions[a]



entry	catalyst	yield (%) 4a	5a[b]
1	$SnCl_4$	0	98
2	$TiCl_4$	0	98
3	$BF_3 \cdot OEt_2$	0	98
4	$FeCl_3$	62	33
5	$TsOH \cdot H_2O$	39	44
6	TfOH	78	
7	$Yb(OTf)_3$	26	70
8	$Sc(OTf)_3$	90	
9[c]	$Sc(OTf)_3$	92	
10[d,e]	$Sc(OTf)_3$	0	98

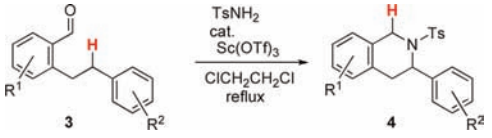
[a] Unless otherwise noted, all reactions were performed with 0.2 mmol of aldehyde **3a** and 0.22 mmol of $TsNH_2$ and 10 mol % of catalyst in $ClCH_2CH_2Cl$ (2.0 mL) at refluxing temperature. [b] The combined yield of corresponding imine **5a** and **3a**. [c] 5 mol % of catalyst loading. [d] Anilline was employed instead of $TsNH_2$. [e] 30 mol % of catalyst loading.

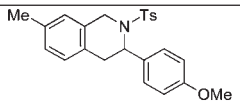
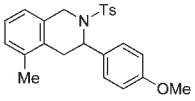
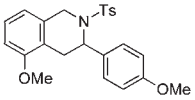
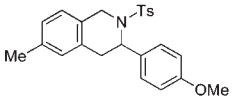
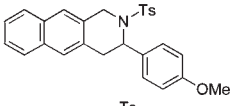
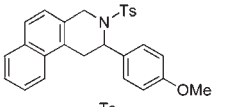
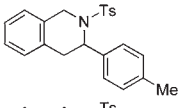
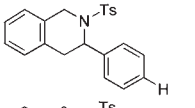
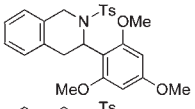
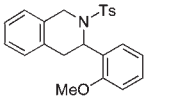
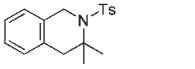
corresponding imine was solely obtained even in 30 mol % catalyst (entry 10).[10–12]

The substrate scope of this transformation is illustrated in Table 2. The position of substituents on the aromatic ring (R^1) significantly affected the reactivity. A substrate with a methyl or methoxy group at the 3- or 5-position (**3b**–**d**) furnished corresponding isoquinolines **4b**–**d** in good to excellent chemical yields with 5 mol % of catalyst (entries 1–3). On the other hand, substrate **3e** having a 4-methyl group dramatically lowered the reactivity, and an increase of the catalyst loading (20 mol %) was required to achieve moderate chemical yield (60%, entry 4). Whereas 30 mol % of catalyst was required for 2,3-naphthyl substrate **3f** (entry 5), 1,2-naphthyl product **4g** was obtained in an excellent chemical yield with low catalyst loading (5 mol %, entry 6).

The electronic and steric factors of the aromatic ring of the phenethyl moiety strongly affected the reactivity of this transformation.[7b] In the case of *p*-tolyl substrate **3h**, which has low electron-donating ability compared with that of the *p*-methoxyphenethyl moiety, desired product **4h** was obtained in as low as 14% yield even when the reaction was conducted with 30 mol % of catalyst loading (entry 7). Simple phenyl-substituted substrate **3i** did not furnish

Table 2. Investigation of Substrate Scope[a]



entry	product		catalyst loading (mol %)	time (h)	yield (%)[b]
1		**4b**	5	48	72
2		**4c**	5	24	93
3		**4d**	5	24	90
4		**4e**	20	24	60
5		**4f**	30	24	82
6		**4g**	5	48	99
7		**4h**	30	24	14
8		**4i**	30	24	– (95)
9		**4j**	30	24	– (96)
10		**4k**	30	24	16
11		**4l**	30	72	32

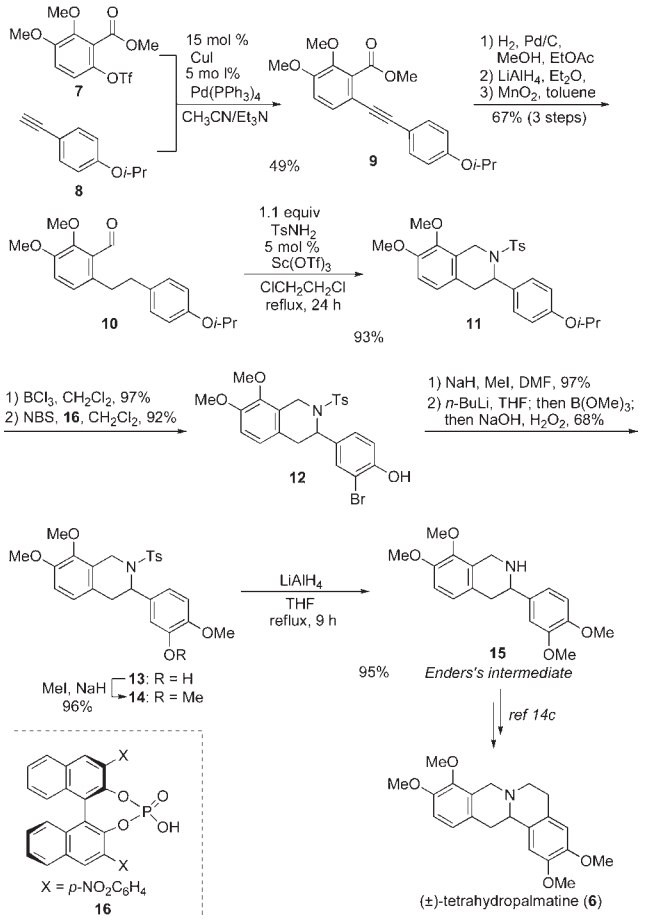
[a] Unless otherwise noted, all reactions were performed with 0.2 mmol of aldehyde **3** and 0.22 mmol of $TsNH_2$ and a catalytic amount of $Sc(OTf)_3$ in $ClCH_2CH_2Cl$ (2.0 mL) at refluxing temperature. [b] Isolated yield. The combined yield of **3** and corresponding imine **5** are indicated in parentheses.

desired product **4i**, and only corresponding imine **5i** was observed (entry 8). It is worthy of note that no desired product was obtained in the case of **3j** that had an electron-rich 2,4,6-trimethoxyphenyl group (entry 9). Furthermore, simply changing the position of the methoxy group from *para* to *ortho* dramatically lowered the reactivity. The chemical yield of **4k** was only 16% even with 30 mol % of catalyst loading (16%, entry 10, cf. entry 9 in Table 1). These results clearly show that the steric factor is

(11) One of the reviewers suggested the intermolecular hydride shift mechanism. The crossover experiment of *d*-**3a** and **3d** revealed that the hydride shift occurred intramolecularly. For more details, see Supporting Information. We thank the reviewer for the suggestion of this experiment.

(12) Attempts to extend the present method to the catalyzed, enantioselective reaction with chiral Sc-complex (with several Py-BOX ligands) were unsuccessful.

Scheme 2. Formal Synthesis of (±)-Tetrahydropalmatine



overwhelmingly important compared with the electronic factor in this reaction.

Another interesting feature of this reaction is that the reaction proceeds even in the absence of the electronic assistance of the adjacent aromatic ring, as in the case of tetraline formation:[7a] aliphatic product **4l** was obtained in 32% yield even though 30 mol % of catalyst loading and a prolonged reaction time were required (entry 11).

The formal synthesis of (±)-tetrahydropalmatine (**6**)[13,14] was selected to showcase the synthetic potential of the present transformation. Scheme 2 illustrates the details of our synthesis. The Sonogashira coupling of triflate **7** with acetylene **8** gave adduct **9** in 49% yield. Hydrogenation, reduction of the ester group, and oxidation of the resulting alcohol afforded aldehyde **10**, which was ready for the key internal redox reaction.

Gratifyingly, the planned reaction worked well and desired product **11** was obtained in excellent chemical yield with low catalyst loading (93% with 5 mol %).[15] The selective cleavage of isopropyl ether in preference to the methyl ether by BCl_3[16] and subsequent monobromination by means of chiral phosphoric acid **16**[17] provided monobromide **12** in excellent yield (92%).[18]

After the methylation of the phenolic hydroxy group, the introduction of an oxygen function via aryl boronic ester[19] followed by methylation of the resulting phenol afforded **14**,[20] thereby setting the same oxygen function of the target compound. Finally, treatment of **14** with $LiAlH_4$ furnished free secondary amine **15**, which is the synthetic intermediate reported by Boudou and Enders.[14c] The NMR spectra of **15** coincided with those of the literature. We have achieved the formal synthesis of (±)-**6**.

In summary, a concise approach to 3-arylisoquinolines by Lewis acid catalyzed C(sp^3)–H bond functionalization was developed. Various substrates could be employed in this transformation, and the desired quinoline derivatives were obtained in good to excellent chemical yields. The application of this methodology to the formal synthesis of (±)-tetrahydropalmatine was also demonstrated. We hope this method will draw much attention as a new entry for the expeditious construction of the isoquinoline skeleton.

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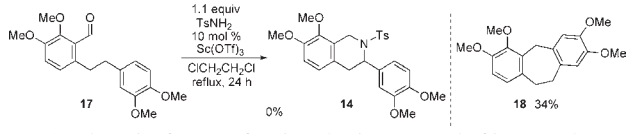
Supporting Information Available. Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra, and crystallographic data for **4a** and **14** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(13) (a) Heyl, G. *Arch. Pharm.* 1903, *241*, 318. (b) Späth, E.; Mosettig, E.; Tröthandl, O. *Chem. Ber.* **1923**, *56*, 875. (c) Miyazawa, M.; Yoshio, K.; Ishikawa, Y.; Kameoka, H. *J. Agric. Food Chem.* **1998**, *46*, 1914. (d) Ito, C.; Itoigawa, M.; Tokuda, H.; Kuchide, M.; Nishino, H.; Furukawa, H. *Planta Med.* **2001**, *67*, 473.

(14) For selected references for the total synthesis of tetrahydropalmatine, see: (a) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932. (b) Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573. (c) Boudou, M.; Enders, D. *J. Org. Chem.* **2005**, *70*, 9486 and references cited therein.

(15) Attempts with most suitable substrate **17** failed. Treatment of **17** with 10 mol % of $Sc(OTf)_3$ at refluxing $ClCH_2CH_2Cl$ for 24 h afforded seven-membered ring adduct **18** rather than desired isoquinoline **14**. This kind of side reaction was also observed in the formation of tetraline derivatives reported by Fillion. See ref 8c.



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(18) Treatment with simple Brønsted acids (such as AcOH, PPTS, etc.) led to the moderate chemical yield of monobromide **12** and a substantial amount of the dibrominated adduct was obtained (20–30%). For more details, see Supporting Information.

(19) Nicolaou, K. C.; Sasmal, P. K.; Xu, H.; Namoto, K.; Ritzen, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4225.

(20) The structure of **14** was unambiguously established by single-crystal X-ray analysis.

The authors declare no competing financial interest.