ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

A Novel Lewis Acid Catalyzed [3 + 3]-Annulation Strategy for the Syntheses of Tetrahydro-β-Carbolines and Tetrahydroisoquinolines

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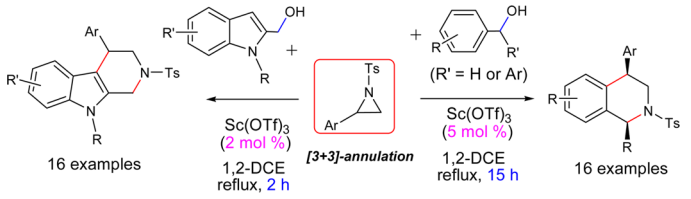
Received March 28, 2013

ABSTRACT



A novel Lewis acid catalyzed [3 + 3]-annulation process for the efficient syntheses of both tetrahydro-β-carbolines and tetrahydroisoquinolines from readily available benzylic alcohols and aziridines was developed, which would be a highly valuable complement to the widely used Pictet–Spengler reaction. A probable mechanism was proposed based on the isolation and characterization of two key intermediates. This strategy enables facile access to important alkaloid frameworks not easily available with other known methods.

Tetrahydro-β-carbolines and tetrahydroisoquinolines are highly important alkaloids with numerous valuable biological activities and pharmaceutical applications.[1] As to the construction of these two important structures (Scheme 1), the century-old one-step Pictet–Spengler reaction still stands out as one of the most direct, efficient methods using amines and aldehydes as starting materials, especially with the recent remarkable advances in the development of various asymmetric catalytic versions.[2] For the syntheses of functionalized tetrahydroisoquinolines, alternative ways have also been developed, including the oxidative dehydrogenative coupling of tetrahydroisoquinolines with various nucleophiles,[3] hydrogenation of 1-substituted 3,4-dihydroisoquinolines,[4] and others.[5] Most of these existing strategies require substrates that already have

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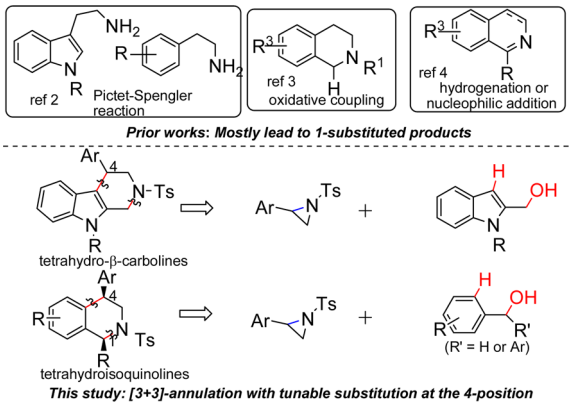
10.1021/ol4008525

the major molecular skeletons of the products or a prior installation of a relatively labile free amino functionality in one of the main starting materials. For example, the Pictet–Spengler reaction, which could be viewed as a [5 + 1]-annulation strategy, requires the prepreparation of the not-so-stable tryptamines. These limitations would inevitably erode into the product diversity of these methods. Furthermore, most current methods could only provide the corresponding products with substitutions at the 1-position, while access to the 4-substituted products is extremely limited.[2a] Consequently, a complementary method allowing more diversified syntheses of these valuable compounds would still be highly desirable. We presumed a new strategy for this purpose: the six-membered tetrahydropyridine ring in these two kinds of alkaloids might be dissected into two three-atom synthons, which could be assembled by a Friedel–Crafts alkylation and an amine-benzylation process from the corresponding benzylic alcohols and aziridines (Scheme 1).

Rare-earth metal triflates have been referred to as a type of environmentally benign efficient Lewis acid catalyst, because they are usually stable, water-compatible, recoverable, and reusable while still possessing strong catalytic activity.[6] These advantages have placed them among the most privileged Lewis acid catalysts in organic synthesis. Particularly, their unique high oxophilicity enables the use of benzylic alcohols as green electrophilic benzylation reagents, which usually generates water as the only byproduct.[7] Additionally, they have also showed high catalytic activities in the ring opening of aziridines by many nucleophiles.[8] However, the employment of these two processes in a single system is rare. We report herein the applications of rare-earth metal triflates as catalysts for a novel Lewis acid catalyzed [3 + 3]-annulation reaction, enabling accesses to both 1- and/or 4-substituted tetrahydro-β-carbolines and tetrahydroisoquinolines from simple starting materials under mild conditions.

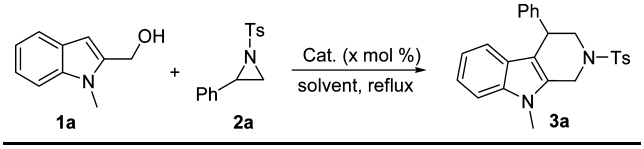
Our initial studies commenced with the reaction of *N*-methyl-2-indolylmethanol **1a** and aziridine **2a** (Table 1). In the absence of a catalyst, no reaction took place (Table 1, entry 1). It is found that $Sc(OTf)_3$ was the highly

Scheme 1. General Direct Strategies for the Syntheses of Tetrahydro-β-Carbolines and Tetrahydroisoquinolines



efficient catalyst in catalyzing this reaction among the catalysts screened. A screen of catalyst loading amounts revealed that only 2 mol % was needed to complete the reaction in 2 h in 1,2-DCE (1,2-dichloroethane), giving the desired product **3a** in 74% yield (Table 1, entries 2–4). It is worth mentioning that the reaction is tolerant of moisture and could be performed in commercial solvents under air. The use of $ScCl_3 \cdot 6H_2O$ with weaker Lewis acidicity and other rare-earth metal triflates like those of Y, La, and Yb were inferior for this reaction (Table 1, entries 6–10). Notably, the order of catalytic activity of these catalysts for this reaction is also in a good accordance with their Lewis acidity.[9] Solvents such as nitromethane and THF bearing coordinative O-atoms are highly detrimental to the reaction (Table 1, entries 10–11). Thus the optimum reaction conditions for the [3 + 3]-annulation included 2 mol % of $Sc(OTf)_3$ in 1,2-DCE for 2 h at reflux.

Table 1. Screen of the Reaction Conditions[a]



entry	cat. (*x* mol %)	solvent	time	yield[b] (%)
1	no catalyst	1,2-DCE	12 h	0
2	$Sc(OTf)_3$ (10)	1,2-DCE	0.5 h	74
3	$Sc(OTf)_3$ (5)	1,2-DCE	1 h	74
4	$Sc(OTf)_3$ (2)	1,2-DCE	2 h	74
5	$Sc(OTf)_3$ (1)	1,2-DCE	5 h	56
6	$ScCl_3 \cdot 6H_2O$ (10)	1,2-DCE	4 h	36
7	$Y(OTf)_3$ (10)	1,2-DCE	4 h	55
8	$La(OTf)_3$ (10)	1,2-DCE	12 h	46
9	$Yb(OTf)_3$ (10)	1,2-DCE	1 h	62
10	$Sc(OTf)_3$ (10)	$CHCl_3$	0.5 h	46
11	$Sc(OTf)_3$ (10)	CH_3NO_2	0.2 h	0
12	$Sc(OTf)_3$ (10)	THF	0.5 h	15

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (*x* mmol), solvent (3 mL). [b] Yield of the isolated pure product.

(4) For recent examples: (a) Berhal, F.; Wu, Z.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2012**, *14*, 3308. (b) Xie, J.-H.; Yan, P.-C.; Zhang, Q.-Q.; Yuan, K. X.; Zhou, Q.-L. *ACS Catal.* **2012**, *2*, 561. (c) Chang, M.; Li, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 10679. (d) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208.

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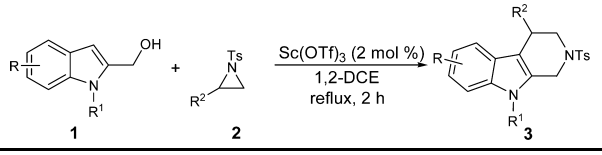
Next, a series of 2-indolyl methanols **1** and aziridines **2** were examined in the reactions to give 4-aryl-1,2,3,4-tetrahydro-β-carbolines under the optimized reaction conditions (Table 2). For aziridines derived from different substituted styrenes, substrates with electron-withdrawing substituents on the benzene ring generally gave better yields of the products than those with electron-donating ones (entries 1−7). A substituent at the *o*-position is detrimental to the yield of the product, probably due to steric reasons (entry 5). The presence of an aryl group, which might facilitate the opening of the aziridine ring, is crucial for the reaction, and aziridines derived from aliphatic alkenes failed to react in the present conditions. As to different 2-indolylmethanols **1**, functional groups such as a terminal alkene or alkyne in the substituent R^1 were well tolerated in the reaction, which allows for further elaboration of the structure (entries 9−10). However, when electron-withdrawing groups such as halogens are present at the 5-position of the indolyl ring, somewhat diminished yields were obtained (entries 11−14). Substrates **1f** and **1g** with substituents at the 7- and 8-positions of the indole ring, respectively, also participated in the reaction to give the desired products (entries 15−16). The structures of the products **3a** and **3k** were additionally confirmed by X-ray crystallographic analyses.[10]

Table 2. Scope Study for the Syntheses of 4-Aryl-1,2,3,4-tetrahydro-β-carbolines **3**[a]

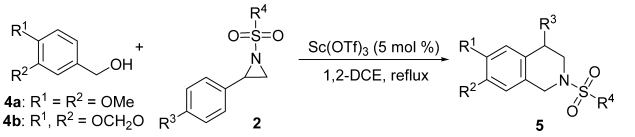


entry	R/R^1	R^2	3	yield[b](%)
1	H/CH_3 (**1a**)	Ph (**2a**)	**3a** (X-ray)	74
2	H/CH_3 (**1a**)	4-FC_6H_4 (**2b**)	**3b**	77
3	H/CH_3 (**1a**)	4-ClC_6H_4 (**2c**)	**3c**	75
4	H/CH_3 (**1a**)	4-BrC_6H_4 (**2d**)	**3d**	72
5	H/CH_3 (**1a**)	2-BrC_6H_4 (**2e**)	**3e**	46
6	H/CH_3 (**1a**)	4-$CH_3C_6H_4$ (**2f**)	**3f**	55
7	H/CH_3 (**1a**)	4-^{t}BuC_6H_4 (**2g**)	**3g**	57
8[c]	H/CH_3 (**1a**)	(**2h**)[c]	**3h**	72
9	H/allyl (**1b**)	Ph (**2a**)	**3i**	70
10	H/propargyl (**1c**)	Ph (**2a**)	**3j**	68
11	5-F/CH_3 (**1d**)	Ph (**2a**)	**3k** (X-ray)	47
12	5-Cl/CH_3 (**1e**)	Ph (**2a**)	**3l**	55
13	5-Cl/CH_3 (**1e**)	4-BrC_6H_4 (**2d**)	**3m**	68
14	5-Cl/CH_3 (**1e**)	4-$CH_3C_6H_4$ (**2f**)	**3n**	62
15	6-Cl/CH_3 (**1f**)	Ph (**2a**)	**3o**	72
16	7-CH_3/CH_3 (**1g**)	Ph (**2a**)	**3p**	46

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), $Sc(OTf)_3$ (0.01 mmol), 1,2-DCE (3.0 mL). [b] Yield of the isolated product. [c] *N*-(4-*tert*-Butylphenylsulfonyl)-2-phenylaziridine **2h** was used.

Subsequently, after some experimentation, the reaction was successfully extended to electron-rich primary benzylic alcohols, providing 4-aryl tetrahydroisoquinolines (Table 3). Generally, compared to 2-indolyl methanols, these benzylic alcohols are less reactive and a larger catalyst loading (5 mol %) and a longer reaction time (15 h) were required. The reactivity of aziridines is similar: electron-withdrawing substituents (R^3) on the benzene ring were more favorable to the annulation than electron-donating ones (entries 2−6). The use of 4-*tert*-butylphenylsulfonyl group gave a significantly improved yield (entry 7), while changing the protecting group of the N-atom of the aziridines to a more electron-deficient 4-nitrophenylsulfonyl group was deleterious to the reaction (entry 8). Notably, substrate **4b** with an acid-sensitive acetal functionality was well-tolerated in the reaction to furnish the desired products in comparable yields (entries 9−11).

Table 3. Scope Study for the Syntheses of 4-Aryl-1,2,3,4-tetrahydroquinolines **5**[a]



entry	4	2 (R^3/ R^4)	5	yield[b] (%)
1	**4a**	H/4-$CH_3C_6H_4$ (**2a**)	**5a**	70
2	**4a**	F/4-$CH_3C_6H_4$ (**2b**)	**5b**	72
3	**4a**	Cl/4-$CH_3C_6H_4$ (**2c**)	**5c**	74
4	**4a**	Br/4-$CH_3C_6H_4$ (**2d**)	**5d**	74
5	**4a**	CH_3/4-$CH_3C_6H_4$ (**2f**)	**5e**	69
6	**4a**	^{t}Bu/4-$CH_3C_6H_4$ (**2g**)	**5f**	66
7	**4a**	H/4-^{t}BuC_6H_4 (**2h**)	**5g**	76
8	**4a**	H/4-$O_2NC_6H_4$ (**2i**)	**5h**	55
9	**4b**	H/4-$CH_3C_6H_4$ (**2a**)	**5i**	68
10	**4b**	Cl/4-$CH_3C_6H_4$ (**2c**)	**5j**	73
11	**4b**	CH_3/4-$CH_3C_6H_4$ (**2f**)	**5k**	67

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), $Sc(OTf)_3$ (0.025 mmol), 1,2-DCE (3.0 mL), 15 h. [b] Yield of the isolated pure product.

Then, we turned to the utilization of secondary diarylmethanols for the reaction, which provided 1,4-disubstituted tetrahydroquinolines in a single step (Table 4). Although the product yields obtained with these more sterically demanding diarylmethanols were appreciably lower, the exclusive diastereoselectivity was very remarkable: only the 1,4-*cis* diastereomer was observed. Interestingly, contrary to the above findings from the use of primary benzylic alcohols, aziridines with electron-donating groups on the benzene ring were more favored here (Table 4, entries 1−4). When the diarylmethanol has two different aryl groups, not unexpectedly, only the more electron-rich one participated in the annulation process (Table 4, entry 5).

To gain some insight into the mechanism of this cascade sequence, some controlled experiments were conducted (Scheme 2). Terminating the reaction of **4a** and aziridine

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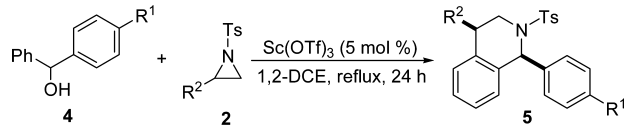
(10) CCDC 924751 (**3a**), 924752 (**3k**), 924753 (**5l**), 924754 (**5p**), and 930713 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data _request/cif.

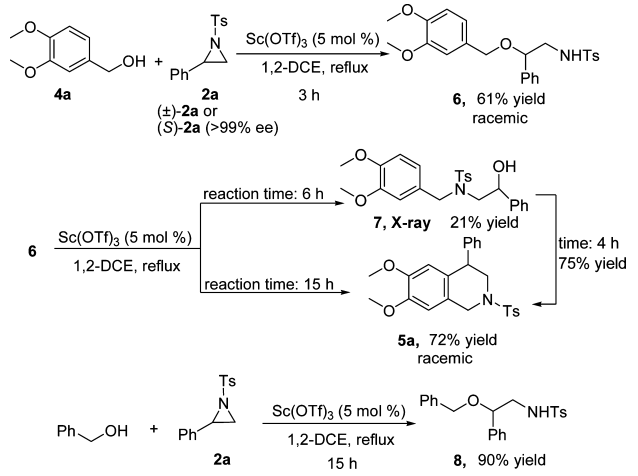
Table 4. Scope Study for the Syntheses of 1,4-Diaryl-1,2,3,4-Tetrahydroquinolines **5**[a]



entry	R^1	R^2	product	yield[b] (%)
1	H (**4c**)	Ph (**2a**)	**5l** (X-ray)	43
2	H (**4c**)	4-ClC_6H_4 (**2c**)	**5m**	38
3	H (**4c**)	4-$CH_3C_6H_4$ (**2f**)	**5n**	45
4	H (**4c**)	4-^{t}BuC_6H_4 (**2g**)	**5o**	46
5	Cl (**4d**)	Ph (**2a**)	**5p** (X-ray)	39

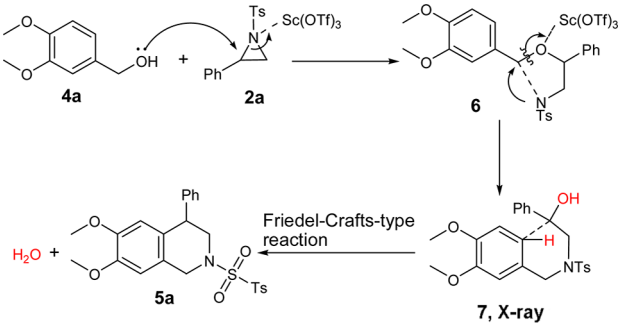
[a] Reaction conditions: **4** (0.6 mmol), **2** (0.5 mmol), $Sc(OTf)_3$ (0.025 mmol), 1,2-DCE (3.0 mL), 24 h. [b] Yield of the isolated pure product.

Scheme 2. Controlled Experiments for Mechanistic Study of the [3 + 3]-Annulation



2a at an early stage (3 h) gave compound **6** as the major product, which could be transformed into the final product **5a** in fairly good yield under the same reaction conditions after 15 h. In this process, another intermediate **7** (X-ray) could be isolated (plus **5a**) when the reaction was intercepted at 6 h, and the isolated **7** underwent a fast conversion (4 h) to **5a** in good yield under the reaction conditions. Based on these experimental findings and previous related reports, a probable mechanism for the [3 + 3]-annulation was

Scheme 3. A Mechanistic Proposal for the [3 + 3]-Annulation



proposed, as illustrated by the formation of **5a** in Scheme 3. It is assumed that the reaction was initiated by a nucleophilic ring-opening reaction of the aziridine by the benzylic alcohol to give the intermediate **6**.[11] In the presence of the rare-earth metal catalysts, **6** would then undergo an intramolecular amination of the benzylic ether to give **7**, which would undergo an intramolecular Friedel–Crafts-type alkylation to furnish the final product with one molecule of H_2O as the only byproduct. Two points of this process are noteworthy. First, probably due to the rapid racemization of the aziridine in the presence of a Lewis acid,[12] the use of enantiomerically enriched aziridine (*S*)-**2a** (> 99% ee) led to racemic **6**, which was also transformed into racemic **5a** in the same yield under these reaction conditions. Second, the occurrence of the intramolecular amination of the benzylic ether step from **6** to **7** is highly dependent on the electron nature of the benzene ring, and electron-rich substituents are necessary: using the simple electron-neutral benzyl alcohol only provided the ring-opening product **8** in high yield.[13]

In summary, a novel Lewis acid catalyzed [3 + 3]-annulation strategy was developed for the construction of tetrahydro-β-carbolines and tetrahydroisoquinolines. This efficient practical method features readily available starting materials, a wide substrate scope, environmental benignity, easy operation, and mild reaction conditions. Such a new strategy provides an excellent complement to other methods such as the Pictet–Spengler reaction using a [5 + 1]-annulation strategy. Efforts toward the development of an enantioselective version of the [3 + 3] annulation are underway.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20832001, 21072004, 21202001), the National Basic Research Program of China (2012CB821600), Natural Science Foundation of Anhui Province (1308085QB25, 1308085MB17), and grants from the Ministry of Education (20103424110001).

Supporting Information Available. Spectral and X-ray data and experimental procedures; CIF files for compounds **3a**, **3k**, **5l**, **5p**, and **7**; ^{1}H and ^{13}C NMR copies of all new compounds; and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) An alternate initiation step involving an intermolecular Friedel–Crafts-type reaction between the electron-rich aromatic ring of the benzylic alcohol and the aziridine could not be ruled out at present, though no corresponding product was isolated from the reaction system. A control experiment with the *O*-methylated analog of **4a** also gave **5a** in 52% yield after 5 h.

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(13) The use of several other benzylic alcohols such as 4-bromobenzyl alcohol, 4-methoxybenzyl alcohol, and naphthalen-2-ylmethanol all led to similar results.