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Heterocycle synthesis via radical reactions*

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Abstract: A novel synthetic method for the preparation of nitrogen-containing heterocycles via the route involving domino-type radical addition/cyclization reaction of oxime ethers is described. Alkyl radical addition/cyclization of oxime ethers carrying an appropriate leaving group proceeded smoothly to form the alkylated nitrogen-containing heterocyclic compounds. Additionally, tin-mediated radical addition/cyclization/elimination (RACE) reaction of oxime ethers is newly found and successfully applied to an asymmetric total synthesis of (–)-martinellic acid.

Keywords: radical reaction; oxime ethers; domino reaction: bgugaine; martinellic acid.

INTRODUCTION

Free-radical cyclization reactions are recognized as powerful methods to effect carbon–carbon bond-forming reactions, including the construction of mono- and polycyclic compounds [1]. These processes usually occur with regio- and stereoselective control and can be modulated to form different-sized rings. They have been applied to the synthesis of a number of natural products, pharmaceuticals, and others which mainly include heterocyclic compounds as a core structure. We have developed efficient radical addition/cyclization reactions based on sulfanyl [2] or alkyl radicals [3] for the preparation of various types of carbocycles and heterocycles. Recently, we found two efficient synthetic methods for heterocycles via the route involving radical process as a key reaction. One is the synthesis of simple pyrrolidine and piperidine compounds, and another is the synthesis of substituted pyrrolidine and piperidine derivatives using stannyl radical addition/cyclization of the oxime ethers connected to an α,β-unsaturated carbonyl group [4,5]. Particularly, the newly found RACE (radical addition/cyclization/elimination) reaction is an efficient reaction which led to the total synthesis of a unique alkaloid, (–)-martinellic acid.

RESULTS AND DISCUSSION

Radical addition/cyclization of oxime ethers toward the synthesis of heterocycles

We designed radical addition/cyclization reactions of oxime ethers aiming at the development of a new strategy for the construction of heterocycles (Scheme 1). Substrates **A** carrying two functional groups, on an electrophilic site and the other a radical acceptor site, were expected to undergo carbon radical addition regioselectively at the oxime ether group to generate boryl amines **C**. The boryl amines **C** are also expected to undergo intramolecular ionic cyclization at the leaving group to form heterocycles **D**.

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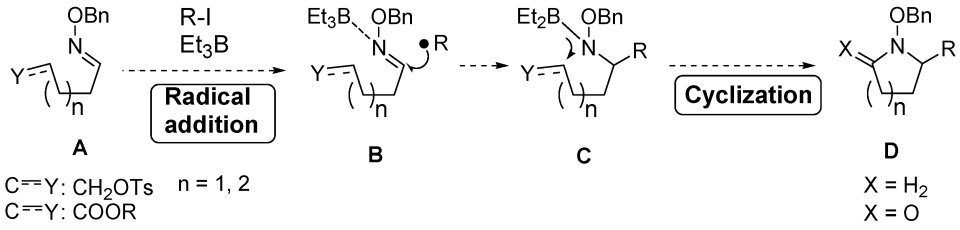
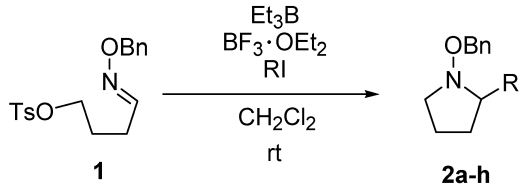


Scheme 1

If the same substrates **A** are treated with nucleophiles, two functional groups could react to form complex mixture, which is a drawback of normal ionic reactions.

First of all, we chose the oxime ether **1** carrying the tosyloxy group as a substrate (Scheme 2, Table 1). Treatment of oxime ether **1** with Et_3B in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid gave the desired product **2a** in good yield [3d]. In the presence of various types of alkyl iodides as radical precursors, the reactions also proceeded smoothly to form alkylated pyrrolidines **2b–h**, except in the cases of using sterically hindered tertiary alkyl iodides.



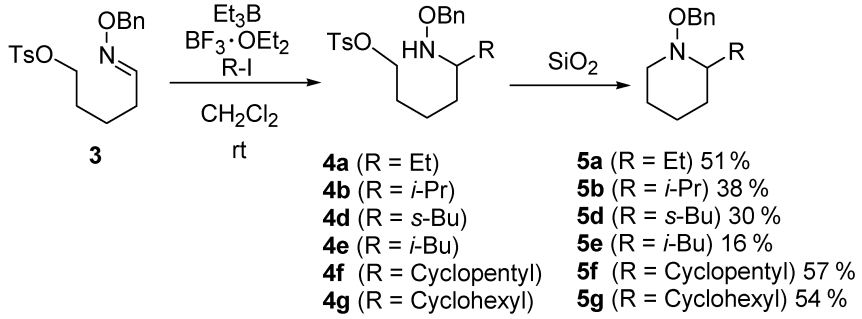
Scheme 2

Table 1 Intermolecular radical addition/cyclization reaction of oxime ether **1**.

Entry	R	Et_3B (equiv)	$BF_3{\cdot}OEt_2$ (equiv)*	Time (h)	Yield (%) **2a–h**
1	–	3	2	3.5	75
2	*i*-Pr	3	2	3	51
3	*t*-Bu	9	6	23	nr
4	*s*-Bu	6	4	22	80
5	*i*-Bu	6	4	23	13
6	Cyclopentyl	6	4	3	68
7	Cyclohexyl	6	4	4	64
8	Adamantyl	6	4	23	nr

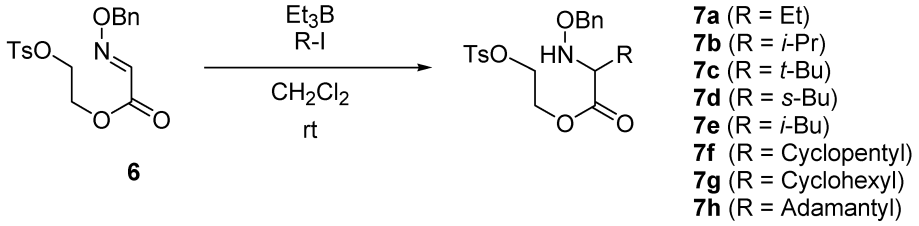
*$BF_3{\cdot}OEt_2$ was better than other Lewis acids.

Similarly, the radical reaction was extended to the homologous system **3** (Scheme 3). In this case, products **4a,b,d–g** were not cyclic compounds but easily cyclized during purification by silica gel chromatography to afford alkylated piperidines **5a,b,d–g**. Again, tertiary alkyl radical did not work well and primary alkyl radical gave the corresponding product **5e** in low yield.



Scheme 3

We then decided to use glyoxylic oxime ether **6** as a substrate expecting that more electrophilic oxime ethers may undergo the radical addition even in the absence of Lewis acid (Scheme 4, Table 2) [6]. As expected, radical addition reaction proceeded very smoothly to give adducts **7a–h**, but intramolecular cyclization did not occur even when **7a–h** were subjected to acidic conditions. Interestingly, we obtained tertiary alkyl radical addition products **7c,h** in excellent yields.

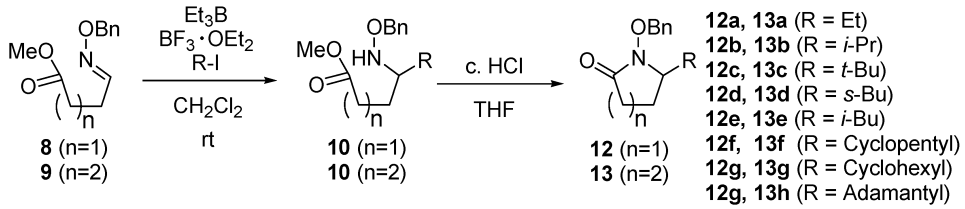


Scheme 4

Table 2 Intermolecular radical addition of oxime ether **6**.

Entry	R	Et_3B (equiv)	Time (h)	Yield (%) **7a–h**
1	–	3	2.5	79
2	*i*-Pr	3	2	81
3	*t*-Bu	6	2.3	86
4	*s*-Bu	3	5	71
5	*i*-Bu	3	3	22
6	Cyclopentyl	3	4.5	75
7	Cyclohexyl	3	4	70
8	Adamantyl	6	6	96

In our second approach, we examined the oxime ethers **8** and **9**, which carry the ester group as a functional group (Scheme 5, Table 3). In the presence of Lewis acid, two substrates **8** and **9** that have different length carbon chain underwent alkyl radical addition in all cases, but products **10** and **11** were not lactams. However, on treatment with hydrochloric acid, these adducts **10** and **11** afforded the lactams **12** and **13** in good yields.

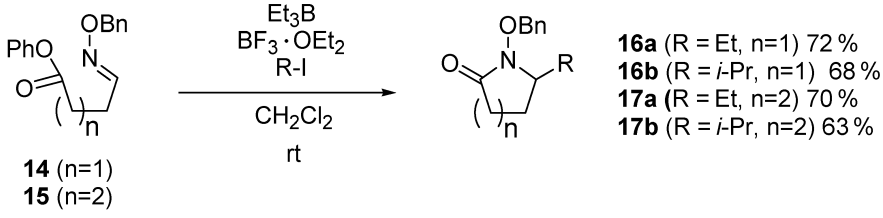


Scheme 5

Table 3 Intermolecular radical addition/cyclization reaction of oxime ethers **8** and **9**.

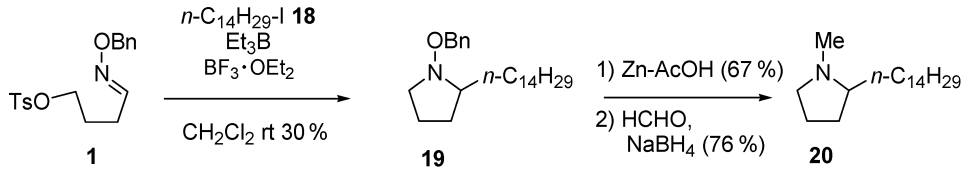
Entry	Substrate	R	Et_3B (eq.)	$BF_3{\cdot}OEt_2$ (eq.)	Time (h)		Yield (%)
1	**8**	Et	3	2	2	**10a** (79)	**12a** (78)
2	**8**	*i*-Pr	3	2	2	**10b** (78)	**12b** (79)
3	**8**	*t*-Bu	9	6	23	**10c** (39)	**12c** (65)
4	**8**	*s*-Bu	3	2	5	**10d** (83)	**12d** (95)
5	**8**	*i*-Bu	9	6	24	**10e** (26)	**12e** (85)
6	**8**	Cyclopentyl	3	2	2	**10f** (63)	**12f** (81)
7	**8**	Cyclohexyl	3	2	2	**10g** (53)	**12g** (85)
8	**8**	Adamantyl	3	6	24	**10h** (48)	**12h** (70)
9	**9**	Et	3	2	2	**11a** (70)	**13a** (85)
10	**9**	*i*-Pr	3	2	2	**11b** (67)	**13b** (78)
11	**9**	*t*-Bu	9	6	23	**11c** (24)	**13c** (70)
12	**9**	*s*-Bu	3	2	5	**11d** (55)	**13d** (77)
13	**9**	*i*-Bu	9	6	24	**11e** (11)	**13e** (83)
14	**9**	Cyclopentyl	3	2	2	**11f** (62)	**13f** (81)
15	**9**	Cyclohexyl	3	2	2	**11g** (61)	**13g** (70)
16	**9**	Adamantyl	3	6	24	**11h** (50)	**13h** (trace)

According to Landais's recent report [7], we employed the phenyl esters **14** and **15** because the phenoxy group is a better leaving group than the methoxy group. Under the standard radical conditions, **14** and **15** gave the expected lactams **16** and **17** in good yields (Scheme 6).



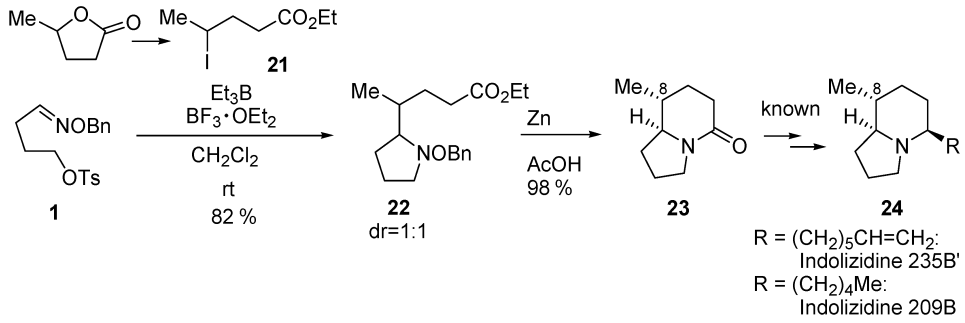
Scheme 6

Based on these results, we then applied our method to the synthesis of a few alkaloids in order to evaluate the potential of our method (Scheme 7). A simple application was the synthesis of an alkaloid, bgugaine (**20**) [8]. Radical reaction of oxime ether **1** with longer alkyl chain iodide **18** gave the alkylated and cyclized product **19** in moderate yield. Transformation of the functional groups involving reductive debenzyloxylation and reductive methylation afforded the simple alkaloid, bgugaine (**20**) [9].



Scheme 7

Another application was the formal synthesis of 5,8-disubstituted indolizidine alkaloids (Scheme 8). Addition of secondary alkyl radical generated from **21** to oxime ether **1** proceeded effectively to form the cyclized product **22**, which was a 1:1 mixture of two diastereomers. After separation of the isomers, each compound was converted into their respective bicyclic lactams, of which the lactam **23** is known as a synthetic key intermediate of the poison frog alkaloids [10,11]. Thus, we succeeded in the development of a radical addition–ionic cyclization method and its synthetic application to heterocycles.

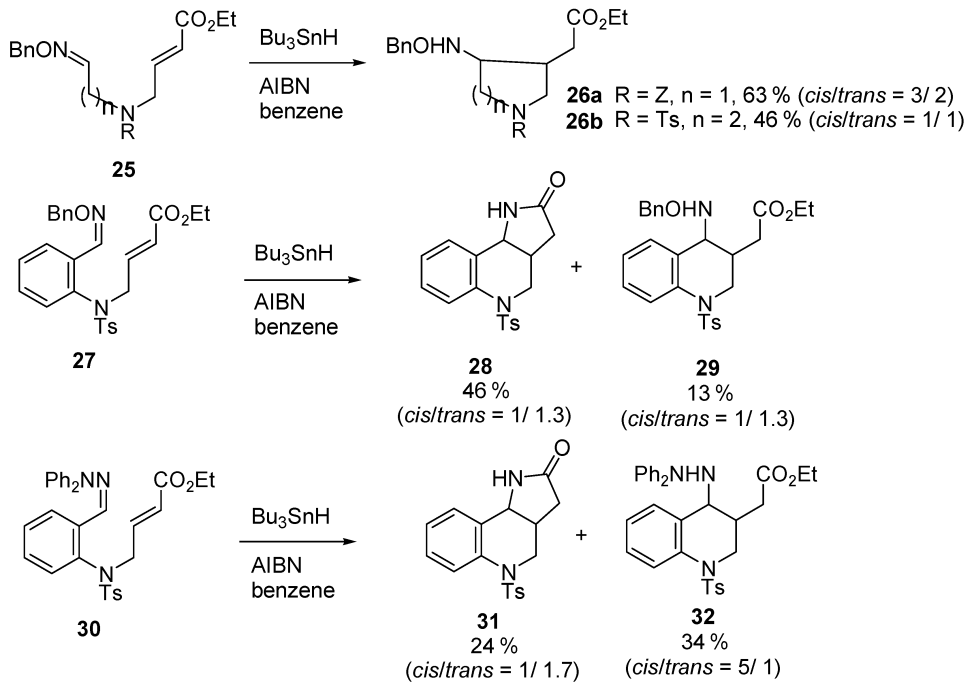


Scheme 8

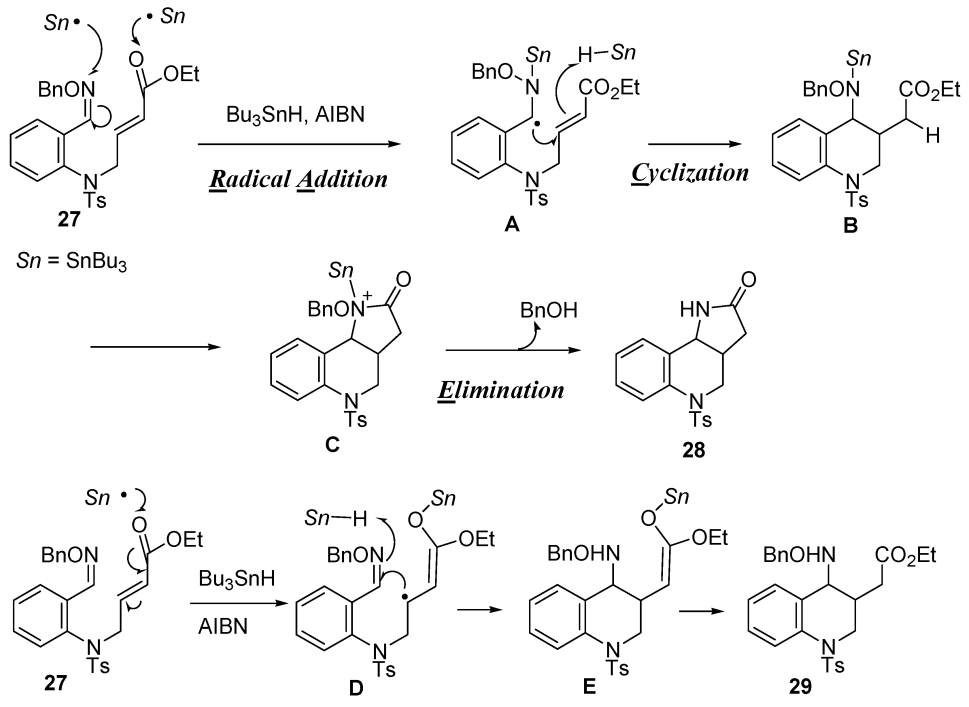
Radical addition/cyclization/elimination and total synthesis of an alkaloid, (–)-martinellic acid

During the course of our investigation on tin-mediated radical addition reactions of oxime ethers connected with carbonyl functionalities, we found an interesting reaction of conjugated systems (Scheme 9) [5]. Particularly, the α,β-unsaturated ester group exhibited a very interesting reactivity in the radical chemistry of oxime ethers. Under the standard conditions, simple substrates (**25**) involving oxime ether and conjugated ester moieties afforded the expected cyclized amino esters **26**. However, benzaldehyde oxime ether **27** gave two types of products, **28** and **29**. The major product (**28**) was a tricyclic lactam, and surprisingly the benzyloxy group was not present in the structure. Another minor product (**29**) was the bicyclic compound, which was initially our expected product. We describe this reaction leading to NH-lactam **28** as RACE. The same type of RACE reaction proceeded in the case of hydrazone **30**.

In order to find the reaction pathway of the RACE reaction, we investigated some additional reactions, including deuterium incorporation, and then proposed a tentative reaction pathway (Scheme 10). In the case of benzaldehyde oxime ether **27**, tin radical would preferably attack the oxime ether group to generate stable benzyl radical **A**, which intramolecularly cyclizes to unsaturated ester. The resulting nucleophilic aminostannane **B** cyclizes to the ester group to form NH-lactam **28** and benzyl alcohol via intermediate **C**. As a minor route, the tin radical would attack the ester carbonyl group to generate tin enolate radical **D**, which cyclizes to the oxime ether to form the bicyclic amino ester **29** via **E**. The simple oxime ether **25** would undergo radical addition/cyclization to form the cyclized amino ester **26** according to the latter route. Thus, the RACE reaction of an oxime ether car-



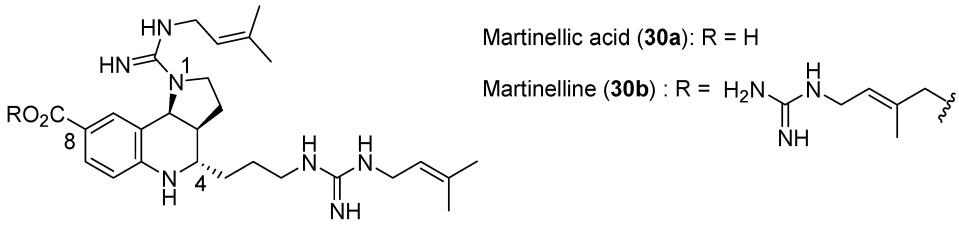
Scheme 9



Scheme 10

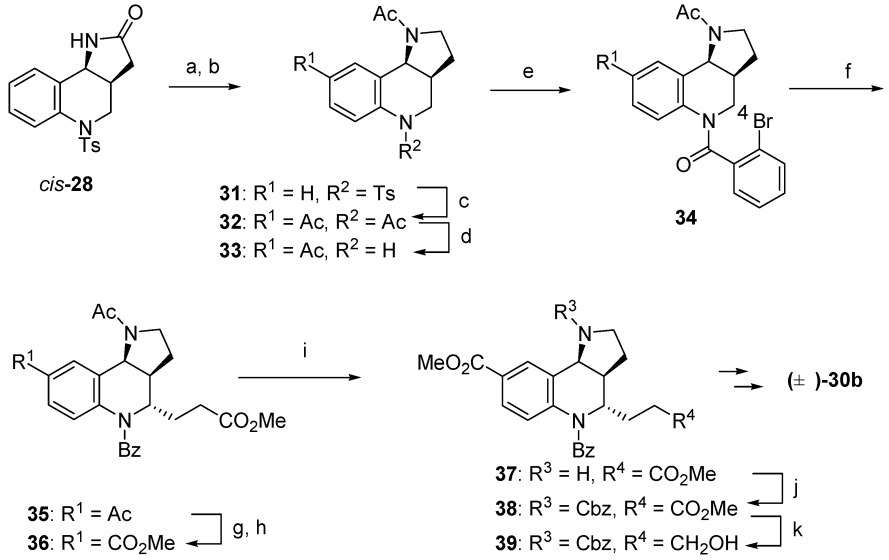
rying an unsaturated ester provides a novel method for the construction of pyrroloquinolines, which opened a new approach to total synthesis of martinelline alkaloids [5a,c].

Martinellines (**30**) are alkaloids isolated in 1995 and found to show very interesting biological activities as nonpeptidic Bradykinin receptor antagonist, which will be good candidates as lead compounds of new drug discovery (Scheme 11) [12]. The skeleton of these alkaloids is a pyrroloquinoline, which is the first example found in an alkaloid structure. The synthetic studies on martinellines have been recently reported by several groups [13], and much attention has been drawn on how to construct the pyrroloquinoline core stereoselectively. Recently, Iwabuchi [13e] and Lovely [13f] reported total synthesis of martinellines.



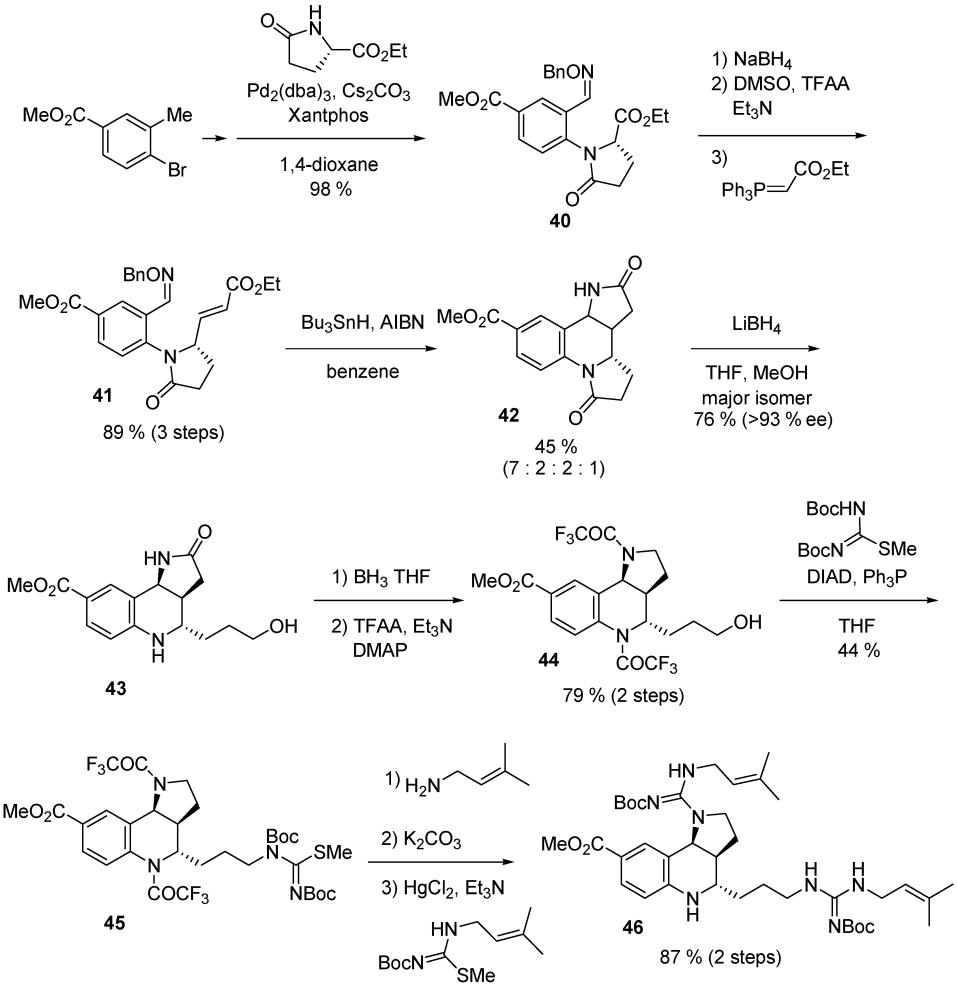
Scheme 11

Our first formal synthesis of (±)-martinellines (**30b**) was achieved by the combination of two types of radical reactions (Scheme 12) [5a,c]. One is a RACE reaction of the oxime ether **27**. From pyrroloquinoline *cis*-**28**, prepared by a RACE reaction, we prepared *o*-bromobenzoyl derivative **34** via transformation of the functional groups. The second radical reaction involved a 1,5-hydrogen radical abstraction of **34** followed by carbon–carbon bond formation with an acrylic ester to afford the propionic ester **35**. The yield of the reaction was moderate but the stereoselectivity was high. Finally, we prepared a key intermediate for the synthesis of martinelline [13d].



Scheme 12 Reagents: (a) $BH_3{\cdot}Me_2S$, THF, reflux; (b) AcCl, Et_3N, CH_2Cl_2, 0 °C; (c) AcCl, $AlCl_3$, $ClCH_2\,CH_2Cl$, reflux; (d) 10 % NaOH, MeOH, r.t.; (e) 2-bromobenzoyl chloride, Et_3N, CH_2Cl_2, r.t.; (f) methyl acrylate, Bu_3SnH, AIBN, benzene, reflux; (g) Br_2, 2.5 % NaOH, 0 °C; (h) c. H_2SO_4, MeOH, reflux; (i) $Et_3O{\cdot}BF_4$, $NaHCO_3$, r.t., then sat. $NaHCO_3$, r.t.; (j) CbzCl, Et_3N, CH_2Cl_2, 0 °C; (k) $LiBH_4$, MeOH-THF, r.t.

For our asymmetric synthesis of (–)-martinellic acid (**30a**), we employed pyroglutamate as a chiral source (Scheme 13). Commercially available bromoester and pyroglutamate were combined to give **40**, which was then converted into chiral substrate **41** for RACE reaction via the conventional transformation of the functional groups. The RACE reaction of **41** proceeded to give tetracyclic product **42**. The structure of the major product **42** was firmly established by the X-ray analysis. In order to complete the total synthesis of the alkaloid, we investigated chemoselective reduction of three carbonyl groups in **42**. Firstly, reductive opening of a lactam by lithium borohydride and then reduction of second lactam **43** with borane gave the corresponding amine, which was immediately acylated to give trifluoroacetamide **44** [13c]. We developed a new route for introduction of two guanidine groups. The Mitsunobu reaction of the hydroxyl group in **44** with isothiourea followed by replacement of the methylthio group with the alkyl amine gave the guanidine **45**. After the second guanidine was introduced by the reaction with isothiourea, the protective groups were removed to afford (–)-martinellic acid (**30a**) which was identical with the authentic sample by comparisons with their spectral data [13]. However, there remain some problems about the optical rotation of the natural alkaloid and the synthetic samples. Our synthetic sample and Iwabuchi's sample exhibited almost identical optical rotations, not the natural alkaloid which shows very low value. Thus, we assume that natural alkaloid mar-



Scheme 13

tinellic acid is racemic compound. Our synthetic route involves 17 steps and is shorter than those reported by other groups [13].

In summary, we have established two types of domino reactions which are radical addition/cyclization reactions of oxime ethers and RACE reactions of oxime ethers carrying a conjugated ester group. Both domino reactions were successfully applied to the synthesis of alkaloids.

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